SEXUAL SATISFACTION AMONG YOUNG BREAST CANCER SURVIVORS DURING THE FIRST 5 YEARS FOLLOWING DIAGNOSIS

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SEXUAL SATISFACTION AMONG YOUNG BREAST CANCER SURVIVORS DURING THE FIRST 5 YEARS FOLLOWING DIAGNOSIS

Abstract

Purpose: To examine sexual satisfaction among premenopausal women through 5 years post-diagnosis with breast cancer.

Patients and Methods: 836 women age 20 to 45 years were accrued from January 1998 to November 2005, within 8 months of diagnosis with stage I to III breast cancer. In addition to a chart review completed by clinical staff, patients completed self-report questionnaires at baseline, and at 6 month intervals through 3 years post-baseline, and yearly up to 5 years. Random coefficient models were used to investigate changes in sexual satisfaction and the association of demographic, clinical, symptom and quality of life variables with sexual satisfaction over the 5 years following diagnosis for breast cancer.

Results: There was no significant change in sexual satisfaction over time ($p=.190$). Poorer sexual satisfaction over the 5 year period was related to having a graduate or professional degree as compared to a high school diploma or less, having had any type of chemotherapy ($p=0.021$), lack of breast sensitivity ($p=0.0006$), having moderate restless sleep ($p=0.003$), lower mental health ($p<0.001$) or physical health ($p<0.001$) status, and poorer satisfaction with their appearance ($p<0.001$).

Conclusion: The prevalence of sexual dysfunction among young breast cancer survivors is significant. Management of clinical symptoms and satisfaction with appearance are important factors to address.

Chapter 1

SEXUAL SATISFACTION AFTER BREAST CANCER DIAGNOSIS AND TREATMENT

Over 200,000 new cases of breast cancer are diagnosed each year in the United States. [1] Not counting some kinds of skin cancer, it is the most common cancer in women in the United States. Breast cancer is the most common cause of death from cancer among Hispanic women, and the second most common cause of death from cancer among white, black, Asian/Pacific Islander, and American Indian/Alaska Native women. With advances in treatment, most women will be long term survivors of their disease. Survival rates of breast cancer have improved significantly. More women are living with breast cancer, and 89% of women diagnosed are alive at five years.[2] While much attention has been put on early detection, prevention and treatment, less focus has been paid to quality of life. Common women's health issues such as fertility, pregnancy, menopause, and sexual health are uniquely affected by breast cancer diagnosis and treatment.

Normal life expectancy in early stage breast cancer underscores the need to address quality of life issues in these women. The impact of treatment on quality of life is extremely important. Among survivors, the most common primary cancer type is breast cancer.[3] The challenges faced by breast cancer survivors span the medical, physical, and psychosocial realms. Physical effects may include weight gain, cardiac complications, dysfunctional uterine bleeding, bone loss, and increased risks of other

cancers. Psychological distress is also common. For women with a diagnosis of cancer and treated with chemotherapy, 30-40% experience a degree of distress, which can persist for up to twenty years following diagnosis. In some, the symptoms are great enough for them to be diagnosed with post traumatic stress disorder.[4]

Sexual problems are common during and after breast cancer treatment. Sexual dysfunction involves psychological, physical, interrelational, and physiological issues. Sexual dysfunction is highly prevalent in women in the United States without a diagnosis of breast cancer. Approximately 40% of women have sexual concerns and 12% report a distressing sexual problem.[5] Sexual dysfunctions are characterized by the disturbances in sexual desire and in the psychophysiological changes associated with the sexual response cycle in women. It is more prevalent in women (43%) as compared to men (31%), and is associated with various demographic characteristics including age, race and education.[6] Pre- and post-marital women have an elevated risk of experiencing sexual problems. Non-married women are 1 ½ times more likely to have climax problems and sexual anxiety than married women. Education is negatively associated with sexual dysfunction. Women who have graduated from college are roughly half as likely to experience low sexual desire, problems achieving orgasm, sexual pain and sexual anxiety as women who have not graduated from high school. The association between race and ethnicity and sexual dysfunction is more variable. African American women tend to have higher rates of low sexual desire and experience less pleasure compared with Caucasian women, who are more likely to have sexual pain. Hispanic women consistently report lower rates of sexual problems.

Healthy sexual functioning has been shown to be a significant factor in quality of life. Sexuality is vital to one's sense of self and to one's perceived quality of life. Sexual dysfunction is recognized as a disorder in the *Diagnostic and Statistical Manual of Mental Disorders.* The American Association of Psychiatry defines four categories of sexual dysfunction.[7] These include the unaffected group, a low sexual desire category, a category for arousal problems and finally a group with sexual pain. The experience of sexual dysfunction is more likely among women with poor physical and emotional health and it is highly associated with overall well-being.[8] Sexual well-being is an important determinant of quality of life and many medically ill patients find sexual intimacy to be an essential mode of communication with their partners.

Interestingly, in an analysis of data from the National Health and Social Life Survey, Laumann found that health problems affect men and women differently.[6] Men with poor health have an elevated risk for all categories of sexual dysfunction, whereas women associated poor health with sexual pain. Sexual dysfunction following breast cancer diagnosis is very prevalent. It affects up to 90% of women treated for breast cancer, with some reports suggesting that nearly all women have some form of sexual complaints following treatment.[9] Despite these complaints, it remains an often neglected part of a woman's treatment.

Although many physical, psychological, and social problems related to the treatment of breast cancer disappear within a few years of diagnosis, restoration of sexual

function after treatment may not return as quickly or at all. Most women treated for breast cancer are still sexually active.[10] Female sexual dysfunction may take several forms, including lack of sexual desire, impaired arousal, inability to achieve orgasm, pain with sexual activity, or a combination of these issues. Studies have documented sexual problems following breast cancer treatment since 1983.[11] More recent studies have found persistent sexual dysfunction three years after breast cancer diagnosis.[12] Although women are grateful for improved survival, sexual problems as a result of treatment have a negative impact on measures of quality of life. Sexuality and intimacy are important factors in breast cancer survivors. Healthcare specialists must expand their focus from just treating the cancer to treating the whole patient. The original goal of survival becomes now a goal of improving quality of life.

Treatment of Breast Cancer

Most breast cancer patients receive multi-modality therapy including surgery, chemotherapy, and hormonal therapy which cure the disease or prolong life. Alone or in combination, these treatments may lead to problems with sexuality and intimacy. The sexual issues identified include changes in body image, decreased libido, fatigue, vaginal dryness, and dsypareunia, difficulty with arousal and orgasm and concern over fertility.[13-17]

Surgical Treatment

Many women will undergo surgery within days to weeks of the diagnosis which may include lumpectomy, mastectomy and/or reconstruction. Breast cancer surgery has

the potential to alter body image because it results in disfigurement. Early investigations of sexual dysfunction related to breast cancer focused on the amount of breast tissue that was removed. A mastectomy was the most disfiguring and led to loss of femininity and attractiveness. Breast conserving surgery and better reconstructive options for women after a mastectomy initially were expected to improve body image, sexual satisfaction, and decrease sexual dysfunction related to breast cancer.[18] Women who undergo a lumpectomy compared to a mastectomy report a better body image, feel more comfortable in a wide range of clothing, and retain sensation in the remaining breast tissue.[19-21] Further, reconstruction of the breast after a mastectomy has the potential to improve cosmetic appeal.[22] However, it does not preserve the tactile stimulation. Higher rates of breast conservation surgery or reconstructive surgery did not improve sexual satisfaction.[19-20]

Patients receiving mastectomy report more difficulties with clothing and body image; however, it does not affect mood or quality of life.[21] Partial mastectomy is not uniformly protective against psychological distress.[23] In a retrospective study of 72 women who underwent lumpectomy and 146 women who had a mastectomy followed by reconstruction, Schover et al. found the choice of local treatment had little psychosexual impact.[20] Similarly, Wilmoth and Ross found no significant difference between women who had a mastectomy and those who had a lumpectomy.[24] Women who underwent a lumpectomy did report a better body image but did not report an effect on their sexuality. In fact, prospective studies show no difference in quality of life outcomes of sexual functioning for breast cancer survivors on the basis of surgical treatment alone.[21,23,25]

Radiation Treatment

Side effects related to radiation are often temporary, are local to the area being radiated, and include temporary alterations in body image because of skin changes such as radiation tattoos, erythema, and burns. Radiation can also cause pain twinges, burning and overall systemic fatigue. However, these side effects usually resolve within months after radiation is completed and women typically do not experience a substantial impact on overall quality of life related to the radiation.[19,20,26] The majority of women report good or excellent cosmesis following radiation treatment.[27] Rarely, the side effects related to radiation can last longer and become chronic. Chronic effects of radiation to the breast include alterations in skin pigment, retraction telangiectasias, erythema, and fibrosis.[28] The result is poor breast cosmesis and decreased arm mobility with lasting effects on sexual function.

Chemotherapy

There are a number of different regimens used to treat breast cancer. The most common chemotherapy agents include Adriamycin, Cytoxan, Taxotere, Methotrexate, and Fluorouracil. The cancer's stage at diagnosis, hormone-receptor status, HER2 status, and lymph node status will influence the chemotherapy regimen used.

Chemotherapy has multiple potential side effects, including some that resolve quickly and others that have long lasting effects on quality of life. Acute side effects of chemotherapy that may affect a woman's sense of attractiveness include alopecia of the scalp and body hair, pallor, weight gain, nausea and vomiting and fatigue. The emphasis

on physical beauty in our culture can make this highly distressing, especially in younger women. In addition, younger women are often the recipients of more aggressive chemotherapy protocols, because physicians perceive a greater potential loss of young lives.[29-30] For premenopausal women, their quality of life can be interrupted by premature ovarian failure, resulting in vasomotor symptoms, disrupted sleep, dyspareunia, and urogenital atrophy.[14-17] For postmenopausal women, the inability to use hormone replacement therapy is limited. And, treatment of breast cancer can induce or exacerbate menopausal symptoms.

In a study conducted by the Anglo Celtic Co-operative Oncology Group, both high-dose and conventional chemotherapy showed persisting negative effects on sexual health.[31] Questions on menopausal symptoms and the Sexual Activity Questionnaire demonstrated problems with discomfort and pleasure. Sexual pleasure was significantly decreased in both groups from baseline up to five years. No significant differences were seen when compared to menopausal status at time of entry. They concluded that the most persistent changes following chemotherapy appear to be the effect of treatment on menopausal symptoms and on sexual pleasure.

Approximately twenty five percent of breast cancer is diagnosed in women who are still premenopausal.[14] Younger women are particularly vulnerable to or distressed by treatment-related sexual function or fertility related adverse effects of treatment.[32] Symptoms of depression and emotional disturbance related to disease are significantly worse in younger women. Young survivors of breast cancer perceive menopausal

symptoms as having a marked negative impact on their quality of life.[33-34] The physical effects along with relationship issues contribute to a high level of sexual concerns in young women.[35] Herbenick et al. assessed survivors' sexual function in 115 women who were younger than 50 years at diagnosis. Compared to young women without cancer treatment, breast cancer survivors scored significantly lower on the overall Sexual Function Questionnaire and its subscales, with the exception of the masturbation subscale where women with breast cancer scored significantly higher.[36]

Ovarian failure after chemotherapy is related to the dose, duration and type of chemotherapy drug with alkylating agents having the most severe impact.[37] Alkylating agents are widely used in the treatment of breast cancer and ovarian toxicity is a predictable side effect. Ovarian failure, premature ovarian failure, and a sharp decrease in circulating estrogen and testosterone levels is very common following treatment with alkylating-agent based therapy, particularly in young women.[19,33] In addition, the use of multiple agents in adjuvant therapy increases the risk of premature menopause, which has been reported in the range of 53-89%.[38]

In addition to arresting follicular maturation, and in more severe cases, destroying ova and follicles, chemotherapy regimens disrupt hormone production by the ovaries. Circulating levels of estrogens are decreased, accompanied by elevated levels of follicle-stimulating hormone and luteinizing hormone.[39] Androgens produced by the ovary are also decreased. This decrease in hormonal production seen in premature ovarian failure

as a result of chemotherapy negatively impacts sexual interest, dyspareunia and sexual activity.

Testosterone levels in women decline with age, and do not change abruptly at the time of natural menopause. After natural menopause, adrenal androgens remain stable while ovarian androgens gradually decrease. Most women maintain normal levels of sexual desire after natural menopause. This is not the case in women undergoing premature menopause as a result of breast cancer treatment. The combination of surgery, chemotherapy, adjuvant and/or hormonal therapy causes an abrupt change in natural hormone levels leading to a premature and symptomatic menopause. The sudden loss of androgen production as a result of treatment induced premature ovarian failure can be severe enough to interfere with a woman's desire and arousability. In a small case series of breast cancer patients treated with chemotherapy, Kaplan found that women who presented with complaints of low sexual desire had abnormally low levels of circulating testosterone.[40] She reports that women with low androgen levels have difficulty reaching orgasm. In a case series of breast cancer patients who chose to continue testosterone therapy for improved sexual function, despite lack of safety reports, Krychman and colleagues found a beneficial effect of testosterone on libido and sexual function.[41] In a study by Alder and colleagues aimed at investigating sexual dysfunction in premenopausal breast cancer patients, they found that low levels of sex steroids reflected the medication-induced postmenopausal status independent of chemotherapy treatment.[42] On the Female Sexual Function Index (FSFI), women who underwent chemotherapy

were more affected in all domains. Chemotherapy was predictive of problems with arousal, lubrication, orgasm, and sexual pain.

Premature menopause has a negative impact on quality of life.[43] Clinical symptoms include the sudden onset of hot flashes, vaginal dryness, and atrophy. The permanence of amenorrhea is the proxy measurement of ovarian function after chemotherapy.[44] It is directly related to a woman's age, type of chemotherapy and its duration and cumulative dosage.[45-46] Women under the age of 40 are less likely to have permanent amenorrhea then women aged 40 and older.[47] Even so, younger women may experience longer menstrual irregularities and have a greater risk of experiencing menopause at an earlier age. Younger women who preserve their menses or who develop reversible amenorrhea will still experience premature menopause as a delayed effect.[48-49] Follow-up studies of women treated with alkylating agents for Hodgkin's lymphoma suggest that even those women who recover menses may be at risk of premature menopause in the future.[50]

Vasomotor Symptoms

Vasomotor symptoms related to premature menopausal are a common problem for breast cancer survivors. Many breast cancer patients have hot flashes resulting from exacerbation of vasomotor instability in postmenopausal women or as a new symptom in premenopausal patients after chemotherapy. Fifty percent or more of survivors report vasomotor-related symptoms including hot flashes, night sweats, early awakening, weight gain, forgetfulness and breast sensitivity.[51] In a follow-up of the Quality of Life in Long-

Term, Disease-Free Survivors of Breast Cancer by Ganz and colleagues, vasomotor symptoms were particularly bothersome at 5-10 years out from diagnosis.[52] Women reported excellent physical and emotional well-being and minimal changes in energy level and social functioning. Although vasomotor symptoms had decreased, symptoms remained present and bothersome.

Vasomotor symptoms are particularly bothersome in very young breast cancer survivors. In a web-based study conducted by Leining and colleagues of premenopausal menstruating women, 46% women reported hot flashes, 46% reported night sweats and 39% reported dyspareunia.[53] Young women also reported difficulty sleeping, forgetfulness, distractibility and difficulty concentrating.

Vasomotor symptoms are also common in postmenopausal women following breast cancer treatment. In a survey of postmenopausal women undergoing treatment, 62.3% suffered from climacteric symptoms such as hot flashes, of which half were severe.[54] This suggests that vasomotor symptoms associated with breast cancer treatment may be more severe and more acute than those in women undergoing natural menopause.

Unfortunately, many treatment options available for vasomotor symptoms are contraindicated in women with a history of breast cancer. Estrogen replacement therapy is not recommended in breast cancer patients and non-hormonal therapies are largely ineffective. Women without cancer who experience vaginal dryness, hot flashes and related sexual problems following menopause have the option, after risk-benefit

consideration, of using systemic or locally applied estrogen products to improve those symptoms. This is usually not an option in breast cancer survivors. Recent studies in the use of selective serotonin-reuptake inhibitors in the treatment of hot flashes in postmenopausal women appear promising. [55-56] However, like all treatment modalities there are side effects, and the major side-effect of SSRIs is sexual dysfunction.

Vaginal dryness and urogenital atrophy

For women, the prevalence of sexual problems tends to decrease with increasing age except for those who report trouble with lubrication. In addition to vasomotor symptoms associated with menopause, vaginal dryness is particularly bothersome, even several years out from treatment. In a follow-up of the Quality of Life in Long-Term, Disease-Free Survivors of Breast Cancer by Ganz and colleagues, although vasomotor symptoms remained prevalent 5-10 years after treatment, women reported vaginal dryness and urinary incontinence to be the most bothersome.[52] In fact, vaginal dryness and urinary incontinence appeared to increase and sexual activity with a partner declined significantly. Chemotherapy had a negative impact on quality of life and in particular sexual comfort, despite the long interval from completion of treatment.

Dyspareunia as a result of vaginal dryness is more prevalent in young breast cancer survivors.[33] In fact, vaginal dryness is one of the most important predictors of sexual functioning for women with breast cancer.[52,57] It is associated with a lack of sexual interest, an inability to relax and enjoy sex, difficulty becoming aroused, and difficulty achieving orgasm.[57] Younger women complain of dsypareunia as a result of

vaginal dryness more often than women undergoing natural menopause. Much of this discomfort in young women with premature menopause is linked to urogenital atrophy. Gupta et al. studied the prevalence and severity of menopausal symptoms in two hundred women treated for breast cancer.[58] Sexual issues were reported by 60% of women, urinary issues by 55% and vaginal dryness by 55%. He concluded that menopausal symptoms, including symptoms related to urogenital atrophy had a significant impact on a woman's perceived sexual function and quality of life.

Sexuality following breast cancer treatment was examined in eight hundred breast cancer survivors following treatment who had been previously studied for health-related quality of life and sexuality related to their diagnosis.[59] Participants had completed surgical and adjuvant treatment for breast cancer. Vaginal dryness was noted in 52% of breast cancer survivors and had a significant negative effect on sexuality (P=0.0005). Sexually active women (38%) reported very little or no lubrication when excited, compared to 14% prior to the diagnosis. Significant genital pain (P=<0.0001) was experienced by 26% of women compared to 7% before diagnosis, and this pain interfered with sexual pleasure. Many women studied indicate that they are interested in sexual enhancement products such as personal lubricants.[36] Over the counter lubricants may compensate for lack of lubrication, but the thin and fragile vaginal mucosa may still be irritated by sexual intercourse, making treatment of sexual dysfunction in these women difficult.

Initially tolerable side effects of breast cancer treatment become unbearable as women struggle with sexual difficulties as they attempt to return to regular lives. The known physical effects of chemotherapy, vaginal dryness and early menopause, result in less sexual activity with their partners and strains on intimacy.[14,33,60] Ganz and colleagues identified women one month after surgery and followed them until they finished primary treatment.[61] At the end of primary treatment, women in all treatment groups reported decreased energy and many treatment associated symptoms. Physical functioning and particularly, sexual functioning was worse for women who received chemotherapy, regardless of surgery.

Vaginal dryness and atrophy remain the most common complaints and have the greatest impact on sexual function and intimacy for women regardless of menopausal status.[62] In a cross-sectional analysis by Greendale and colleagues on postmenopausal women affected by breast cancer, those women reporting the most negative impact of breast cancer on their sex lives were more likely to report relationship difficulties, to have experienced changes in hormonal levels due to breast cancer and to be bothered by vaginal dryness.[63] Interestingly, college education was associated with poorer sexual function, however, hot flashes were surprisingly associated with better satisfaction scores.

Vaginal atrophy is also associated with recurrent urinary tract infections or vaginal monilial infections. Episodes of these painful conditions may be triggered more frequently by sexual intercourse. Drugs that cause stomatitis often cause periodic vaginal

irritation during active treatment. Due to immunosuppression with chemotherapy, women with genital herpes virus or the human papilloma virus can experience exacerbations. Finally, loss of pubic hair may be a temporary embarrassment that inhibits many women sexually.

Adjuvant Therapy

Menopausal complaints are common among breast cancer patients, either as a result of chemotherapy or as a side effect from hormonal adjuvant therapy. Systemic adjuvant therapy includes hormonal manipulation and/or cytotoxic therapy. The aim of treatment is to treat undetectable micrometastases to reduce the likelihood of relapse and thereby improve survival. Compelling evidence indicates that adjuvant systemic therapy improves the survival of both premenopausal and postmenopausal women. The Early Breast Cancer Trialists' Collaborative Group conducted a meta-analysis of all randomized controlled trials of chemotherapy, tamoxifen, and ovarian ablation.[64] The meta-analysis reported a significant improvement in relapse-free survival and overall survival in premenopausal women following adjuvant therapy. Thus adjuvant therapy is a significant part of breast cancer treatment long term.

Ovarian Ablation

Ovarian ablation involves destroying the function of the ovaries. This may be completed through surgery or radiation. Permanent ovarian ablation by oophorectomy or radiation induces a premature menopause. In the absence of chemotherapy, ovarian ablation is associated with a significant improvement in disease free survival and overall

survival in premenopausal women.[65-66] Ovarian ablation has now largely been replaced by tamoxifen and aromatase inhibitors.

Endocrine Treatments

As survival increases, many women are maintained on adjuvant therapy for 5-10 years following diagnosis. A number of studies have documented adverse gynecological symptoms in breast cancer patients receiving adjuvant therapy. Endocrine treatments are well described for all stages of hormone-receptor positive breast cancer treatment. The goal of treatment is to induce a milieu of estrogen deprivation by blocking estrogen at the receptor level or by inhibiting estrogen biosynthesis. These treatments lead to short and long term consequences of estrogen deprivation, mainly menopausal symptoms.

Tamoxifen

Tamoxifen is a nonsteroidal, triphenylethylene antiestrogen that was first synthesized in the United Kingdom in the 1960s as a contraceptive.[39] It is a selective estrogen receptor modulator (SERM). A few years after its development, it was discovered to suppress carcinogen-induced mammary tumors in rats. Tamoxifen is associated with a highly significant improvement in relapse-free survival and overall survival in women with estrogen receptor (ER)-positive tumors.[67] Treatment effects of tamoxifen are related primarily to its antiestrogenic properties. The magnitude of benefit is dependent on the duration of treatment. Most women with ER positive tumors are advised to continue tamoxifen for five years or longer. Tamoxifen is known to induce or intensify vasomotor symptoms.[68-69] It also causes other menopausal symptoms such as

vaginal dryness, vaginal discharge and dyspareunia.[70] The effects of tamoxifen and cytotoxic chemotherapy on menopausal symptoms are independent.

Worldwide, tamoxifen is the most commonly prescribed anti-neoplastic agent. It is known to cause symptoms of climacteric, with acute symptoms of hot flashes, night sweats, vaginal discharge, itching, or dryness in up to 50% of women of all ages.[67,71-72] In premenopausal women, tamoxifen may disrupt menstruation and continuous treatment with tamoxifen is believed to suppress ovulation. It is not a contraceptive and may cause ovarian cysts and polyovulation. In fact, contraception is recommended in premenopausal tamoxifen users because of the risk of teratogenic effects on the fetus.

Tamoxifen also has estrogen agonist effects. The estrogenic actions of tamoxifen include the stimulation of progesterone receptor synthesis, an estrogen-like maintenance of bone and cardiovascular system, and estrogenic effects on the vaginal mucosa and the endometrium.[39] The vagina is lined by stratified squamous, nonkeratinizing epithelium containing estrogen receptor in pre- and postmenopausal women. The epithelium is multilayered and the cells in the middle and superficial zones contain glycogen only when stimulated by estrogen. Vaginal smears obtained before and after treatment with tamoxifen indicate that the drug has estrogen agonist effects on the vaginal mucosa. The major disturbing side effect of tamoxifen is an increase in hot flashes and vaginal discharge. Dsypareunia is also reported. Mortimer and colleagues examined the effect of tamoxifen on sexual desire, arousal, and ability to achieve orgasm in fifty-seven women treated with tamoxifen for 2 to 24 months.[70] Pain, burning, or discomfort with

intercourse was reported in 54% of patients and did not correlate with age, surgical treatment of the primary cancer, or chemotherapy. The anti-estrogen effect of chemotherapy on the vulvovaginal tissue combined with the adjuvant treatment with tamoxifen resulted in a 30% increase in pain or difficulty with intercourse. Thus, tamoxifen therapy was found to be associated with negative reactions during intercourse.

In addition to vaginal dryness, many women report an increase in vaginal discharge, irritation and recurrent infections with adjuvant treatment after chemotherapy. An increase in vulvovaginal candidiasis, otherwise rare in older women, has been reported in postmenopausal women taking tamoxifen.[73] There are also reports of benign ovarian cysts and endometriosis associated with tamoxifen therapy. It is unclear whether tamoxifen induces new endometriotic implants or exacerbates preexisting disease with its estrogen effect on the endometrium. Recurrent candidial infections, endometriosis and ovarian cysts can all impact sexual function and satisfaction.

Aromatase Inhibitors

Third-generation non-steroidal aromatase inhibitors anastrozole and letrozole, as well as the steroidal-type exemestane are increasingly being used in the management of breast cancer. Compared to tamoxifen, less is known regarding the impact of aromatase inhibitors (AIS) on menopause-associated gynecologic side-effects. Because of their greater efficacy in reducing recurrences as well as their better tolerability profile, these third-generation AIS are now an integral component in the management of postmenopausal adjuvant therapy for breast cancer in women with hormone receptor-

positive disease.[74] However, vaginal dryness and/or dyspareunia have not been included in the systemic evaluation of side-effects in studies using AIS.

Similar to the selective estrogen receptor modulator tamoxifen, treatment with aromatase inhibitors results in a reduction in circulating unbound, free estrogen levels. In contrast to tamoxifen, which acts as an estrogen agonist in some tissues (for example, bone, cardiovascular, vaginal mucosa or endometrium) and an antagonist in others (for example, breast), AIS produce profound suppression of estrogen in all tissues by blocking the cytochrome P450 aromatase complex that converts androgens to estradiol.[75-76] Drugs such as AIS that block ovarian function effectively reduce androgen levels. Female androgen deficiency is associated with a diminished sense of well-being, dysphoric mood, unexplained fatigue, decreased libido and decreased sexual receptivity and decreased sexual pleasure.

Aromatase inhibitors also have an adverse effect on sexual function through an increase in vaginal dryness, pruritis and dyspareunia. Compared with tamoxifen, AIS have been shown to result in more frequent vaginal dryness.[77] In a prospective study aimed at analyzing the effects of starting adjuvant tamoxifen and steroidal and non-steroidal aromatase inhibitors on the occurrence and severity of menopausal symptoms, vaginal dryness and result dyspareunia was most significant in those patients taking AIS.[78] One hundred and eighty one consecutive postmenopausal breast cancer patients completed a menopausal symptom questionnaire at baseline and one and three months after starting adjuvant treatment. Musculoskeletal pain and dyspareunia significantly

increased under AIS, while patients under tamoxifen had a significant decrease in sexual interest. Aromatase inhibitors were found to induce more atrophic symptoms compared to tamoxifen, consistent with high estrogen suppression on the vaginal mucosa. The effect of decreased sexual desire with tamoxifen may be multi-factorial and dependent on the selective estrogen receptors. Similar to previous studies, younger age was associated with more vasomotor symptoms and vaginal dryness.

The quality of life sub-study of the Arimidex, Tamoxifen, alone or in Combination (ATAC) adjuvant breast cancer trial found that the incidence of vaginal dryness, dyspareunia, and loss of sexual interest in women taking AIS was significant.[79] In women who experienced acute chemotherapy induced menopause, these symptoms were particularly bothersome. The subsequent mature quality of life outcomes from ATAC were consistent.[80] Although no differences were seen among the groups in the evaluation of vasomotor, gastrointestinal (except diarrhea – more frequent with anastrozole), and neuropsychiatric symptoms, at five years, vaginal dryness, dyspareunia and reduced libido remained significantly greater in those women taking anastrozole as compared to tamoxifen. Endocrine-related symptoms appear to peak with both tamoxifen and AIS at three months of treatment and remain stable thereafter without further increase.

Interestingly, a concurrent study examining the quality of life of postmenopausal women allocated to tamoxifen or an AIS, found no difference between the groups.[81] Postmenopausal women who were disease free after two to three years on tamoxifen

were randomly assigned to switch from tamoxifen to aromatase inhibitor exemestane or continue with tamoxifen until five years of treatment were completed. No significant differences were found between the groups apart from vaginal discharge, which was more prevalent in women taking tamoxifen. The prevalence of severe vasomotor symptoms and sexual dysfunction was high for both groups at trial entry which may explain the discrepancy.

Other Hormonal Adjuvant Treatments

Other hormonal treatments are currently under investigation in the adjuvant treatment of breast cancer. Doserlin, (Zoladex), a luteinizing hormone-releasing hormone agonist produces severe anti-estrogenic effects. Used more often in Europe, Doserlin, is linked to severe sexual dysfunction during treatment. In a study completed in Stockholm by Berglund and colleagues, the frequency of sexual intercourse and the ability to obtain orgasm was significantly reduced in Zoladex-treated patients.[82] Effects were found to be most prominent in patients who had also received chemotherapy. The sexual dysfunction effects were found to be reversible only in the patients who were not concomitantly receiving chemotherapy. In contrast to Zoladex, tamoxifen had a decreasing effect on sexual function and a positive effect on frequency of sexual intercourse. It was hypothesized that the week estrogenic effect of tamoxifen on the vaginal epithelium and resultant increased bioavailability of androgens explained the positive and ameliorating effect of tamoxifen on Zoladex. These studies illustrate the complex interaction of hormonal adjuvant therapy on the differing reproductive organs.

Other Side Effects from Diagnosis and Therapy

The secondary effects of fatigue, weight loss, alopecia, immunosuppression and nausea associated with chemotherapy often affect a woman's sense of femininity and sexuality regardless of pre or postmenopausal status. In a study conducted on psychosocial concerns and quality of life among breast cancer survivors, compared to women with chronic medical conditions, breast cancer survivors demonstrated higher levels of role function, social functioning, pain and general health.[12] However, survivors frequently reported problems associated with physical and recreational activities, body image, sexual interest, sexual function and problems with dating for those who were single. As physical problems subside, psychosocial problems, interpersonal relationship conflicts and poor body image may persist and linger well after successful treatment.[25]

Fatigue is likely the most prevalent symptom in patients with cancer. Impaired sleep is a common complaint of postmenopausal women. Therefore, it is no surprise that premature menopause in young women is associated with fatigue, impairments in daytime functioning, and an increase in daytime sleepiness. Breast cancer survivors report significantly reduced sleep quality, increased distractibility, forgetfulness and difficulty concentrating, and an increased use of sleep medication as a result of treatment induced premature menopause.[53,83] Fatigue is commonly found at the time of diagnosis as well as throughout treatment. It is best characterized by a persistent lack of energy and it disrupts routine daily activities resulting in a negative impact on quality of life. It may lead to depression and may have a significant impact on relationships and sexual function.

Other medical issues independent of or as a result of breast cancer treatment may exacerbate or attenuate sexual dysfunction. Medications such as commonly prescribed beta-blockers and anti-depressants are known to play a role in worsening sexual dysfunction. Younger women with breast cancer are particularly vulnerable to depression during and following treatment.[32] Many of these women are placed on anti-depressants which are known to have an impact on sexual function. Selective serotonin reuptake inhibitors (SSRIs) are one of the most commonly prescribed medications in women and are often used as mood stabilizers during and after treatment as well as for treatment of hot flashes. The incidence of sexual dysfunction with SSRIs is high ranging from 58% to 73% .[84] In a study of 610 women with previously normal sexual function, the overall incidence of sexual dysfunction was 56.9% among women being treated with antidepressants alone or with benzodiazepines. Highest rates were associated with the SSRIs including citalopram and paroxetine.

Lastly, sexual dysfunction may be the presenting sign of a larger psychological problem such as severe depression or anxiety related to breast cancer. Even if breast cancer treatment does not impair any physiological components to sexual function, problems may result from the psychological impact of a cancer diagnosis or trauma from potentially painful and difficult treatments. These effects may continue long after treatment has ended. In a multivariable regression analysis of predictors of sexual health after breast cancer diagnosis, a better relationship score was associated with greater satisfaction.[85] A better mental health score was also associated with less sexual

dysfunction and was more important than type of surgery, body image and menstruation history in predicting sexual satisfaction. The psychosocial variables may be more powerful than the biological factors.

Relationships

A breast cancer diagnosis affects patients and their partners. Treatment and diagnosis impacts personal identity, body image, sense of control and self-esteem. Living with breast cancer has the potential to disrupt all social interactions. Energy needed to fight breast cancer is superimposed on all relationships, impacting partnerships, families and friends. The perceived degree of social support and the nature of relationships prior to a cancer diagnosis are the best predictors of long-term adjustment to the illness.[86] Women who are in strong relationships or perceive their partners to be supportive do better. The quality of the relationship influences the perception of sexual satisfaction.[87] If a relationship is stable, the woman tends to adjust better and experience less disruption to emotional and physical intimacy. In a study of sexual functioning determinants in breast cancer survivors, the survivor's level of relationship distress was the most significant variable affecting arousal, orgasm, lubrication, satisfaction, and sexual pain.[88] Relationship concerns and depression were important influences in the development of breast cancer survivor sexual dysfunction. Likewise, sexual satisfaction and higher Female Sexual Function Index (FSFI), scores are associated with a better quality of partner relationship.[89]

Approximately one third of married couples experience sexual difficulties related to a breast cancer treatment and diagnosis.[90] The risk increases significantly if sexual difficulties preceded the diagnosis. For sexually active breast cancer survivors in a partnered relationship, the most important and consistent predictors of sexual health were the presence or absence of vaginal dryness, emotional well-being, body image, quality of the partnered relationship, and whether the woman's partner had sexual problems.

Conclusion

A diagnosis of breast cancer has a significant impact on a woman's sense of self and well–being. The sudden physical effects of acute and sometimes severe menopausal symptoms along with a variety of relationship issues contribute to a high level of sexual concerns for young women.[35] A breast cancer diagnosis has special meaning for young women because they may have more psychosocial concerns, be more vulnerable to the side effects of treatment, receive more aggressive protocols, and face diminished potential survival related to the diagnosis. Their self-esteem, emotional and physical well-being and sexuality are highly affected. These women are at particular risk of depression, sexual dysfunction and problems with intimacy. Unfortunately, treatment of sexual dysfunction is often neglected in the care of these women and this has a negative impact on quality of life.

All women are followed by an oncologist and a surgeon for their breast cancer diagnosis and treatment. Most are also followed by a radiation oncologist, obstetrician/gynecologist or a primary care physician. Yet, in a recent survey of young

women undergoing chemotherapy for breast cancer, only sixty-eight percent reported having a discussion with at least one physician regarding the possibility of early menopause as a result of treatment and only thirty four percent reported a discussion with a provider regarding future fertility.[91] In contrast, more than 90% of women reported having a discussion regarding the side effects of treatment and the impact on physical activities.

Specific Aims of Thesis

Given the host of challenges faced by women as a result of cancer diagnosis and treatment, the purpose of this thesis project was to examine sexual satisfaction following breast cancer diagnosis and treatment. Specifically, the aims of this project were to:

1. Determine factors associated with sexual activity or inactivity following breast cancer diagnosis and treatment.
2. Examine demographic, clinical, symptom and quality of life variables that are associated with sexual satisfaction up through 5 years post-diagnosis for breast cancer.

Data for this study are taken from a longitudinal investigation of premenopausal women for whom there is extensive clinical, symptom and quality of life data. Having longitudinal data adds a richness to the topic over other published studies in that we will be able to examine changes in sexual satisfaction over time and associations with sexual satisfaction over time.

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Chapter 2

SEXUAL SATISFACTION AMONG YOUNG BREAST CANCER SURVIVORS DURING THE FIRST 5 YEARS FOLLOWING DIAGNOSIS

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Introduction

Over 200,000 new cases of breast cancer are diagnosed each year in the United States.[1] With advances in treatment, most women will be long term survivors of their disease. As many as 89% of women diagnosed with breast cancer are alive at five years.[2] With this growing number of survivors, the long-term impact of breast cancer diagnosis and treatment on quality of life is important.

Approximately 25% of breast cancer is diagnosed in women who are still premenopausal.[3] The majority of these women will receive surgery, systemic chemotherapy and adjuvant therapy. They have a high risk of acute or transient amenorrhea and an additional long-term risk of early menopause.[3-5] Young breast cancer survivors perceive menopause symptoms to have a negative impact on their quality of life.[3,6] The acute premature menopause associated with sexual problems is often rated as the most distressing aspect of a young woman's cancer experience. [3,7]

Healthy sexual functioning has been shown to be a significant factor in quality of life.[8-9] Most women treated for breast cancer are still sexually active.[10] Although many physical, psychological, and social problems related to the treatment of breast cancer disappear within a few years of diagnosis, restoration of sexual function and satisfaction after treatment may not return as quickly, if at all. Many survivors have persistent sexual dysfunction for three years or longer after breast cancer diagnosis.[11]

Sexual issues identified in breast cancer survivors include changes in body image, decreased libido, fatigue, vaginal dryness and dyspareunia, difficulty with arousal and

orgasm and changes or strains in partner/marital realtionships.[12-16] These factors alone or in combination may reduce sexual satisfaction among young survivors

The purpose of the current study was to examine demographic, clinical, symptom and quality of life factors associated with sexual satisfaction among premenopausal women with breast cancer through 5 years post-diagnosis. It was hypothesized that women of older ages, those having had chemotherapy, menopausal symptoms, and lower satisfaction with appearance post-surgery, would have reduced levels of sexual satisfaction.

Methods

Procedures and Participants

Data were taken from the Menstrual Cycle Maintenance and Quality of Life After Treatment Study, a multi-center longitudinal study of premenopausal women with breast cancer.[17] The primary objectives of the study are to study menstrual bleeding patterns and treatment related amenorrhea to track subsequent pregnancies and outcomes among those who retain their fertility; and, to examine breast cancer survivor's quality of life longitudinally. Recruitment began in January of 1998 and ended in November of 2005. Follow-up on the study cohort is continuing.

A total of 836 participants were recruited from the following clinical centers: Memorial Sloan-Kettering Cancer Center in New York City, New York; M.D. Anderson Cancer Center in Houston, Texas; Presbyterian Hospital in Dallas, Texas; The University of Texas Southwestern in Dallas, Texas; and the Wake Forest University School of Medicine in Winston-Salem, North Carolina. Patients from these clinical centers were

identified through tumor or surgical registries or patient/physician referrals. Eligibility requirements included: ages 18-45 at the time of diagnosis; a first time diagnosis of invasive breast cancer, stages I-III; regular menstrual cycles at the time of diagnosis; and no prior or concurrent history of cancer, excluding basal cell carcinoma. Once a participant agreed to be in the study, she signed the informed consent form, a medical release, and completed the baseline study questionnaires. Participants were also instructed on how to complete monthly bleeding calendars necessary to track menstrual bleeding patterns.

Data Collection and Instruments

Patients completed questionnaires regarding their demographic characteristics, symptoms, quality of life, and lifestyle behaviors, at baseline and at 6 month intervals through 3 years post-baseline. Thereafter, questionnaires were completed once a year.

The items chosen for inclusion in this paper are described below and were focused on relating demographic, clinical/medical history, and quality of life variables that have been found in previous work to be associated with women's sexual satisfaction. The following measures were used in the current analyses:

Demographic and Clinical Variables

Demographics: Basic demographic information was collected including: age, marital status, race, and educational background.

Personal Habits Questionnaire: Information was obtained regarding the patients' smoking and alcohol use, height and weight, and exercise habits.

Medial Chart Review: Two medical chart reviews were performed on all patients by clinical staff at the respective recruiting institution. Chart Review I was completed by the clinic coordinators within 6 weeks of registering the patient to the protocol. This review included basic information, such as the date of breast cancer diagnosis, grade, location, and size of tumor(s), number of nodes examined, number of positive lymph nodes, type of surgery, whether reconstructive surgery was performed, and patients' height and weight. Chart Review II was completed 12 months post-enrollment to the study after most women had completed their cancer treatments. This review recorded the treatment prescribed (e.g., surgery, radiation, and/or chemotherapy; hormonal therapy), dose and duration of treatment, estrogen and progesterone receptors (positive and negative) test results, and whether the patient had a hysterectomy, oophorectomy or ovarian oblation as a result of her treatment.

SF-12 Health Status Questionnaire. The SF-12, a short form version of the SF-36, is a brief tool to assess one's physical and mental health status.[18] The measure contains two subscale scores: the mental health composite scale (MCS-12) and the physical health composite scale (PCS). Higher scores on both subscales indicate better levels of functioning.

Symptoms Checklist: Participants completed a 38-item symptom checklist adapted from the Women's Health Initiative Study.[19] It is comprised of items assessing cancer treatment-related symptoms (e.g., fatigue, constipation, decreased appetite) and menopausal symptoms (e.g., vaginal dryness, hot flashes, night sweats). Five items from this scale were utilized to assess their impact on sexual satisfaction: restless sleep,

vaginal dryness, hot flashes, night sweats, and breast sensitivity. These items are scored "0" (symptom does not occur), 1 (mild), 2 (moderate), and 3 (severe).

Body Appearance Scale: This 8-item scale assesses the participants' satisfaction with different areas of their body, including their hair, breast area, arms, face, waist, hips, thighs, and their overall body. Scores range from 8 to 40, with higher scores indicating greater satisfaction.

Dependent Variable

Watts Sexual Functioning Questionnaire: The satisfaction subscale of the Watts Sexual Functioning Questionnaire was used to assess the impact of treatment on the patients' sexual satisfaction.[20] The satisfaction subscale includes 3 items assessing how often the patient felt satisfied after sexual activity, satisfaction with the frequency of sexual activity, and the frequency of feeling tense or nervous following a sexual experience. Response categories for these items were: 1) Never, 2) Almost Never, 3) Sometimes, 4) Almost Always, and 5) Always. Scores range from 5-15, and higher scores on this subscale indicate better levels of sexual satisfaction.

Data Analysis

Sexually active participants were determined as those who reported being sexually active with a partner within the past month at any of the assessment points during the five years following diagnosis. Means, standard deviations, frequencies, percents and ranges were used to describe the participant's characteristics separately by those who were and were not sexually active. Statistical tests were used to distinguish differences between the sexually active and inactive participants. Demographic

characteristics coded categorically, including race/ethnicity, age, marital status, and educational status, were compared using chi-square tests while those coded continuously were compared using Kruskal-Wallis tests. The same analyses were performed on the clinical characteristics defined as months post diagnosis, stage of disease, type of surgery, type of treatment, and current use of hormone therapy. Type of surgery was categorized as either lumpectomy only or mastectomy. Those participants identified via medical chart review as having both a lumpectomy and mastectomy were included in the mastectomy group.

Linear mixed (random coefficient) models were used to assess the changes in sexual satisfaction over time and to determine which covariates were associated with satisfaction. The covariate by time interactions were initially assessed to determine if the effects of the covariates changed over time. These interactions by time were not found to be statistically significant. All analyses were conducted using SAS for Windows software (SAS Institute, Cary, NC).

Results

Sample Characteristics

Eight hundred thirty-six women were recruited to the study from January 1998 to November 2005. Of those 836 women, 88 indicated they were not sexually active at any time during the study. Approximately 23% of the participants were inactive at the baseline survey. The proportion of women who were sexually inactive at the time of each subsequent follow-up survey ranged from 15% (30 month follow-up) to 32% (60 month follow-up). Thirty percent of the participants returned 1-3 follow-up

questionnaires, 24% returned 4-6 questionnaires, and 46% returned more than 7 questionnaires.

Tables 1 - 3 summarize the characteristics of the participants by sexual active/inactive status. Significant differences were found between the two groups in terms of race/ethnicity (p=0.029), body mass index (BMI) (p=0.004) and marital status (p=<0.001) (Table 1). Those who had a race/ethnicity other than non-Hispanic White, those women who had never married or were divorced, separated or widowed, and those with a BMI outside the normal range, were less likely to be sexually active. With respect to the clinical characteristics of the participants (Table 2), only stage of disease was significantly related to sexually active/inactive status, in that those with a higher cancer stage at diagnosis were less likely to be sexually active (p=0.005). Type of surgery or treatments were not related to the women's sexual activity.

Table 3 contains the health status, quality of life and symptom measures used in the study. Those women who were sexually inactive had significantly lower satisfaction with their appearance (p=.003) and lower reported vaginal dryness (p<0.001).

Sexual Satisfaction

The stability of the sexual satisfaction subscales was examined. Means and standard deviations of the measure ranged from 11.18 (SD=2.64) to 11.69 (SD=2.33) over the 5 year assessment period. There was no significant change in sexual satisfaction scores among this group of survivors over time (p=0.190).

Random coefficient models were used to investigate changes in sexual satisfaction and the association of demographic, clinical, symptom and quality of life

variables with sexual satisfaction over the 5 years following diagnosis of breast cancer. Women who were never sexually active were excluded from these analyses.

The mixed model results are presented in Table 4. Only one demographic variable was related to the participants' sexual satisfaction. Those with a high school diploma or less reported greater sexual satisfaction compared to those women who had received a graduate or professional degree. Age, marital status, and race/ethnicity were not significant predictors of satisfaction over the 5 year period. Among the clinical variables, only having had any form of chemotherapy was related to poorer sexual satisfaction ($p=0.021$).

Several symptoms were significant predictors of sexual satisfaction. Vaginal dryness was strongly associated with lower sexual satisfaction; the greater the dryness the worse the satisfaction. Those with moderately restless sleep as compared to those with no restless sleep were also more likely to have reduced sexual satisfaction ($p=0.003$). In contrast, women with breast sensitivity as compared to no breast sensitivity had higher sexual satisfaction ($p=0.006$).

Both mental health ($p<0.001$) and physical health ($p<0.001$) status were positively associated with sexual satisfaction. The better the mental or physical health of the participants, the better their reported sexual satisfaction. Similarly, the greater the participants' satisfaction with appearance, the better was their reported level of sexual satisfaction ($p<0.001$).

Discussion

We analyzed factors associated with sexual activity or inactivity following breast cancer diagnosis among this cohort of young breast cancer survivors. Not surprisingly, sexual activity was significantly associated with marital status. Married/partnered women were more likely than never married, separated, or divorced women to be sexually active. Women of ethnic minorities were also less likely to be sexually active than non-Hispanic White women. In addition, women with a higher clinical stage of disease at diagnosis, and those with poorer perceived mental and physical functioning were less likely to be sexually active during the course of the study. With respect to treatment-related symptoms, the sexually inactive women reported significantly fewer problems with vaginal dryness than sexually active women. This may be a reflection that the women were not engaging in vaginal sexual activities and thus may not have encountered difficulties with vaginal dryness. We also examined demographic, clinical, and quality of life factors associated with sexual activity during the 5 years after breast cancer diagnosis. Education was the only demographic variable to be significantly related to a participant's sexual satisfaction. Women with a high school diploma or less reported greater sexual satisfaction as compared to women who had received a graduate or professional degree. There is conflicting information in the literature regarding education and its association with sexual satisfaction. In a study of sexual function among women in the United States without a history of cancer, education was found to be negatively associated with sexual dysfunction.[21] Women who have graduated from college are half as likely to experience low sexual desire, problems achieving orgasm, sexual pain and sexual anxiety as women who have not graduated from high school. In

contrast, several past studies indicate that education is not associated with sexual dissatisfaction or dysfunction when evaluating sexual problems specifically among women with a diagnosis of breast cancer.[8, 13] This association between less education and higher sexual satisfaction is intriguing and is worthy of further exploration. To our knowledge, a negative association between education and sexual satisfaction among young breast cancer survivors has not been documented in the literature prior to this study.

This study reaffirms the common and troubling symptoms younger breast cancer survivors experience with adjuvant chemotherapy, and their effects on sexual satisfaction.[22-26] Chemotherapy has multiple potential side effects, including some that resolve quickly and others that have long lasting effects on quality of life. Of the clinical symptoms recorded, we found vaginal dryness to be significantly associated with lower sexual satisfaction. Dyspareunia as a result of vaginal dryness is more prevalent in young breast cancer survivors and is one of the most important predictors of sexual problems.[27-29] Likewise, breast sensitivity was highly associated with sexual satisfaction. Those with breast sensitivity had higher sexual satisfaction than those women reporting no sensitivity. Problems with breast sensitivity and dyspareunia are associated with a lack of sexual interest, an inability to relax and enjoy sex, difficulty becoming aroused, difficulty achieving orgasm, and sexual satisfaction.[3,29] Menopausal symptoms are common following chemotherapy.[8,25-26] Premature ovarian failure is associated with vasomotor symptoms, disrupted sleep, dyspareunia and urogenital atrophy.[2,30-32] We found no significant association between hot flashes or night sweats and sexual satisfaction in this

study, although we did find that women experiencing moderately restless sleep as compared to no restless sleep reported reduced sexual satisfaction.

Among the clinical variables in our study, only chemotherapy was related to lower sexual satisfaction. Stage of disease, type of surgery, adjuvant hormonal therapy and radiation therapy were not associated with sexual satisfaction. The lack of a significant finding between surgical treatment (lumpectomy vs. mastectomy) and sexual satisfaction is consistent with previously reported prospective studies that showed no differences in sexual functioning on the basis of surgical treatment alone. [2,33-36]Both perceived mental and physical health were positively associated with sexual satisfaction. A woman's sexual satisfaction was highly associated with a better perceived mental ($p<0.0001$) and physical ($p<0.0001$) health. This finding is consistent with past research indicating that the experience of sexual dysfunction is more likely among women with poor physical and emotional health and it is highly associated with overall well-being.[37] Satisfaction with appearance also had a highly positive effect on sexual satisfaction ($p<0.0001$). Although type of surgery may not be a significant factor in sexual satisfaction, these findings again suggest that how a woman feels about herself and her body is strongly associated with her sexual satisfaction.[8,13,22,38]

This research study has several strengths. This research is one of the few studies investigating sexual problems specifically among young premenopausal breast cancer survivors prospectively over 5 years. All participants had extensive medical chart reviews regarding their tumor characteristics and treatments. Participant data were gathered at prescribed intervals throughout the study, so that recall bias was minimized. We have data on a variety of demographic, clinical, symptom and quality of life factors at

multiple time points. Our sample contains younger breast cancer survivors, all of whom had to be premenopausal at the time of cancer diagnosis, as an eligibility criterion. All of these factors make this study a unique contribution to the research on sexual satisfaction following breast cancer diagnosis.

There are several limitations of this study. Although collected at five different institutions, this sample is characteristic of many samples of breast cancer patients, relatively homogeneous (mostly non-Hispanic White, educated, and partnered women). Women were recruited primarily from the eastern and southern United States. In addition, aside from the medical chart review, we relied on self-reported data. Although retention of the study cohort was high during the follow-up period (75%), missing data for some measures and time points may have also been a factor in the results. Furthermore, we have no information on what the participants' sexual satisfaction was prior to the diagnosis, and how prior sexual satisfaction may predict satisfaction following breast cancer diagnosis and treatment. In addition, we also have no data on couple/partner factors that might influence the participants' sexual satisfaction. We have no information on sexual problems associated with partners, for example and/or factors in the couples' relationships that might impact their sexual satisfaction over time. These are critical factors that should be explored in future research in this area.

Overall, our results suggest that young breast cancer survivors report significant symptoms associated with lower sexual satisfaction following breast cancer diagnosis and treatment. Sexuality and intimacy are important factors among breast cancer survivors, and must be considered in the evaluation of current and future treatments.

Management of symptoms and satisfaction with appearance are important factors to address among young survivors.

Table 1. Baseline Demographic Characteristics of the Sexually Active and Sexually Inactive Study Participants

	Sexually Active	**Sexually Inactive**	
	n=748	*n=88*	*p-value*
Race/Ethnicity			0.029
White (non Hispanic)	666 (89.0%)	74 (84.1%)	
Black/African-American	34 (4.6%)	7 (8.0%)	
Hispanic	28 (3.7%)	3 (3.4%)	
Asian/American Indian	20 (2.7%)	4 (4.6%)	
Age at diagnosis			0.262
< 30 years	42 (5.6%)	5 (5.7%)	
30-34.9 years	135 (18.1%)	9 (10.2%)	
35-39.9 years	218 (29.1%)	25 (28.4%)	
≥ 40 -45 years	353 (47.2%)	49 (55.7%)	
Mean Age(SD)	38.7(4.9)	39.6 (5.2)	
Median/range	39.6/ 21-46.4	40.8 / 21.6-46.1	
BMI Group			0.004
Underweight (<19)	27 (3.6%)	6 (6.9%)	
Normal (18-24.99)	471 (63.0%)	45 (51.7%)	
Overweight (25-29.99)	148 (19.8%)	13 (14.9%)	
Obese (≥ 30)	102 (13.6%)	23 (26.4%)	
Mean BMI (SD)	24.4 (5.04)	25.7 (5.96)	

Median/range	23.0 / 17.0-52.6	24.1 /16.5-40.2	
Marital Status			<.0001
Never Married	92 (12.3%)	42 (47.7%)	
Presently Married	546 (73.0%)	30 (34.1%)	
Living in Marriage-like Relat.	45 (6.0%)	2 (2.3%)	
Divorced/Separated/Widowed	65 (8.7%)	14 (15.9%)	
Education			0.520
High school diploma or less	64 (8.6%)	10 (11.4%)	
Some College or Technical	176 (23.6%)	20 (22.7%)	
4 Year College Degree	219 (29.3%)	30 (34.1%)	
Graduate/Professional Degree	288 (38.6%)	28 (31.8%)	

Table 2. Baseline Clinical Characteristics of the Sexually Active and Sexually Inactive Breast Cancer Participants

	Sexually Active	**Sexually Inactive**	
	n=748	*n=88*	*p-value*
Stage of Disease			0.005
I	315 (42.2%)	29 (33.0%)	
II	388 (51.9%)	46 (52.3%)	
III	44 (5.9%)	13 (14.8%)	
Mastectomy			0.222
No	382 (50.5%)	39 (44.3%)	
Yes	364 (49.5%)	49 (55.7%)	
Lumpectomy			0.297
No	160 (21.5%)	23 (26.4%)	
Yes	583 (78.5%)	64 (73.6%)	
Chemotherapy			0.390
No	87 (11.6%)	13 (14.8%)	
Yes	661 (88.4%)	75 (85.2%)	
Radiation Therapy			0.143
No	223 (29.3%)	33 (37.5%)	
Yes	523 (70.1%)	55 (62.5%)	

Hormone Therapy			0.724
No	302 (40.6%)	34 (38.6%)	
Yes	442 (59.4%)	54 (61.4%)	
Number of Positive Nodes			0.603
None	409 (54.8%)	42 (47.7%)	
1-3	223 (29.9%)	32 (36.4%)	
4-9	71 (9.52%)	9 (10.2%)	
≥ 10	43 (5.8%)	5 (5.7%)	
ER/PR Status			0.456
Both Neg	213 (29.5%)	29 (33.3%)	
Either Pos	510 (70.5%)	58 (66.7%)	

Note: Not all participants answered all questions

Table 3. Baseline Symptom and Quality of Life Measures of the Sexually Active and Sexually Inactive Breast Cancer Participants

	Sexually Active n=748	**Sexually Inactive** n=88	
Psychosocial Measures:	Mean (SD)	Mean (SD)	p value
SF-12 Mental Composite Score (0-60)	42.9 (8.4)	42.6 (8.1)	0.862
SF-12 Physical Composite Score (0-60)	44.0 (8.9)	42.3 (10.3)	0.168
Satisfaction with Appearance (8-40)	25.8 (7.2)	23.5 (6.5)	0.003
Symptom Measures:	N / %	N/ %	P value
Restless Sleep			
No	140 (18.8)	19 (21.6)	0.524
Yes	606 (81.2)	69 (78.4)	
Vaginal Dryness			
No	418 (56.1)	72 (81.8)	<.001
Yes	327 (43.9)	16 (18.2)	

Hot Flashes			
No	459 (61.4)	49 (55.7)	0.295
Yes	288 (38.6)	39 (44.3)	
Night Sweats			
No	445 (59.6)	49 (55.7)	0.483
Yes	302 (40.4)	39 (44.3)	
Breast Sensitivity			
No	392 (52.6)	44 (50.0)	0.462
Yes	353 (47.4)	44 (50.0)	

Note: Not all participants answered all questions

Table 4. Mixed Model Regression of the Impact of Demographic, Clinical, Symptom and Quality of Life Variables* on Sexual Satisfaction During the First 5 Years Following Breast Cancer Diagnosis

	Parameter Estimate (SE)	**Overall P-value**	**Contrast P-value**
Time Since Surgery	-0.003 (.002)	0.190	
Age at diagnosis		0.688	
< 30 years	-0.175 (.336)		0.603
30-34.9 years	-0.109 (.204)		0.591
35-39.9 years	-0.204 (.172)		0.236
≥ 40 -45 years	reference		
Race/Ethnicity			
Non-Hispanic White	-0.124 (.247)	0.614	
Other	reference		
Marital Status		0.072	
Never Married	-0.080 (.349)		0.819
Divorced/Separated/ Widowed	0.380 (.280)		0.175
Married	Reference		
Education		0.018	
High school diploma or less	0.885 (.290)		0.002
Some College or Technical	0.294 (.189)		0.120

4 Year College Degree	0.272 (.175)		0.119
Graduate/Professional Degree	Reference		
Stage of Disease			
I	0.259 (.387)		0.503
II	0.091 (.364)		0.802
III	Reference		
Mastectomy	0.266 (.226)		0.240
Lumpectomy	0.014 (.210)		0.945
Chemotherapy	-0.547 (.238)		0.021
Radiation Therapy	0.224 (.22)		0.300
Hormone Therapy	0.235 (.152)		0.121
BMI Group		0.762	
Underweight (<18)	-0.026 (.437)		0.953
Normal (18-24.99)	0.173 (.227)		0.447
Overweight (25-29.99)	0.248 (.260)		0.340
Obese ($\geq$ 30)	reference		

Vaginal Dryness		<0.001	
None	Reference		
Mild	-0.364 (.077)		<0.001
Moderate	-0.842 (.103)		<0.001
Severe	-1.863 (.160)		<0.001
Hot Flashes		0.666	
None	Reference		
Mild	-0.082 (.096)		0.394
Moderate	-0.150 (.138)		0.279
Severe	-1.241 (.222)		0.278
Night Sweats		0.426	
None	Reference		
Mild	0.0003 (.092)		0.997
Moderate	0.117 (.142)		0.409
Severe	-0.178 (.240)		0.459
Breast Sensitivity		0.043	
None	Reference		
Mild	0.204 (.074)		0.006
Moderate	0.195 (.123)		0.113
Severe	0.282 (.257)		0.273
Restless Sleep		0.010	

None	Reference		
Mild	-0.104 (.076)		0.173
Moderate	-0.283 (.096)		0.003
Severe	0.009 (.162)		0.953
MCS-12	0.048 (.005)	<.0001	
PCS-12	0.030 (.005)	<.0001	
Satisfaction with Appearance	0.034 (.005)	<.0001	

*All variables were entered into the model simultaneously

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Chapter 3

SUMMARY AND FUTURE DIRECTIONS

The purpose of this thesis project was to: 1) examine factors associated with sexual activity and inactivity following breast cancer diagnosis and treatment, and 2) examine demographic, clinical, symptom, and quality of life factors associated with sexual satisfaction through 5 years post breast cancer diagnosis.

Regarding sexual activity following diagnosis, marital status was a significant predictor of sexual activity following diagnosis and treatment. Married women were more likely than never married, separated, or divorced women to be sexually active. Women of ethnic minorities were more likely to be sexually inactive than non-Hispanic White women, as were those women with a higher clinical stage of disease at diagnosis. In addition, women with poorer perceived satisfaction with appearance also were less likely to be sexually active. Sexually inactive women also reported significantly fewer problems with vaginal dryness than sexually active women.

In our mixed model analysis of factors associated with sexual satisfaction through 5 years after breast cancer diagnosis, education was the only demographic variable to be significantly related to a participant's sexual satisfaction. Women with less education reported greater sexual satisfaction as compared to women who had received a graduate or professional degree. Of the clinical variables in our study, only chemotherapy was related to poorer sexual satisfaction. Stage of disease, type of surgery, adjuvant hormonal therapy, radiation therapy, and hormonal therapy were not associated with sexual satisfaction. Chemotherapy has multiple potential side effects, including some that

resolve quickly and others that have long lasting effects on quality of life. Menopausal symptoms and premature ovarian failure are common following chemotherapy, and include vasomotor symptoms, disrupted sleep, dyspareunia and urogenital atrophy.[1-6] Not surprisingly, we found vaginal dryness to be a significant predictor of sexual dissatisfaction among the sexually active women. In addition, those reporting breast sensitivity reported greater sexual satisfaction than those with no breast sensitivity, a common side effect of breast surgery. Furthermore, those with a moderate degree of restless sleep reported less sexual satisfaction.

Both mental and physical health were positively associated with sexual satisfaction. A woman's sexual satisfaction was highly associated with better mental ($p<0.0001$) and physical ($p<0.0001$) health. Younger women with breast cancer are particularly vulnerable to depression during and following treatment as well as sleep disturbances reported above.[7] In addition, satisfaction with appearance had a highly positive effect on sexual satisfaction ($p<0.0001$). Although type of surgery may not be a significant factor in sexual satisfaction, these findings again indicate that how a woman feels about herself and her body is strongly associated with hersexual satisfaction.[7-8]

Future Research

More young women are survivors of breast cancer. Approximately 25% of breast cancer is diagnosed in women who are still premenopausal.[6] While much attention has been put on early detection, prevention and treatment, less focus has been paid to quality of life. Common women's health issues such as fertility, pregnancy, menopause, and sexual health are uniquely affected by breast cancer diagnosis and treatment. We have

demonstrated the symptoms related to sexual dysfunction are prevalent and bothersome in young breast cancer survivors. Future research should concentrate on the sexual side effects of treatment and investigate ways to ameliorate these side effects. Other hormonal treatments are currently under investigation in the adjuvant treatment of breast cancer. These new treatments may have improved side-effect profiles for general symptoms, however, sexual side effects may be worse. The sexual side effects of these new adjuvant therapies are as important as other physical side effects.

Relationship studies

In addition to therapeutic remedies, it is also important to track sexual functioning from the aspect of the patient/survivor and her partner(s). A breast cancer diagnosis affects both patients and their families. The energy needed to fight breast cancer is superimposed on all relationships, impacting partnerships, families and friends. Living with breast cancer has the potential to disrupt marriages and other partnerships.[9]Approximately one third of married couples experience sexual difficulties related to a breast cancer treatment and diagnosis.[10] The risk increases significantly if sexual difficulties precede the diagnosis. For sexually active breast cancer survivors in a partnered relationship, the most important and consistent predictors of sexual health have been found to be the presence or absence of vaginal dryness, emotional well-being, body image, quality of the partnered relationship, and whether the woman's partner had sexual problems.[10] Thus, a partner's impact on a young breast cancer survivor's sexual health is important in determining overall sexual health of the relationship.

Treatment of Sexual Dysfunction

Vaginal dryness was significantly associated with less sexual satisfaction in our study. This is supported in the literature. Dyspareunia as a result of vaginal dryness is more prevalent in young breast cancer survivors and is one of the most important predictors of sexual functioning.[11-13] Research in the future should investigate safe treatment options for breast cancer survivors who suffer from vaginal dryness and atrophy. Over the counter lubricants may compensate for the lack of lubrication, however, estrogen depletion creates a thin and fragile vaginal mucosa. Hormonal alternatives for women who have estrogen and progesterone positive breast cancer are needed.

In a case series of breast cancer patients who chose to continue testosterone therapy for improved sexual function, despite lack of safety reports, Krychman and colleagues found a beneficial effect of testosterone on libido and sexual function.[14] Further studies are needed to investigate the long-term effects of the use of testosterone and other hormonal therapies in women with breast cancer or at risk of developing breast cancer.

Summary

The results of our study support the need for further research on the sexual side effects of breast cancer treatment, as well as interventions to improve sexual satisfaction in survivors. For medical interventions to be effective, physicians must know the cause of sexual dysfunction, which is likely to be multi-factorial. Physical and emotional changes during a woman's life affect sexual function and satisfaction. Future research should focus on the physiologic and psychological effects of breast cancer treatment and

medical or social interventions that may ameliorate these effects. As survival rates continue to improve, clinicians must shift from the current focus of breast cancer eradication to the treatment of the whole physical, emotional, and sexual woman.

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CURRENT RESEARCH ACTIVITIES:

Prenatal Cytogenetic Diagnosis by Array-Based Copy Number Analysis. Ronald Wapner, MD, is the principle investigator.