

REVIEW

Sexual Dysfunction in Females after Cancer Treatment: an Unresolved Issue

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Abstract

Cancer besides being a leading cause of mortality also creates a myriad of morbidities in survivors whether treated or untreated. Among women surviving after gynecological malignancies sexual dysfunction is a morbidity unexplored in Indian context because of cultural barriers. With the increasing proportion of women surviving carcinoma of the cervix, quality of life has become an important clinical issue. Despite the immense distress it causes in patients, sexual dysfunction is neither screened nor treated in Indian scenario. Despite this recognition, the area is not well researched and there is a paucity of information on the impact of cancer treatment on sexual health in Indian Context. Research has shown that up to 50% of women treated for cervix cancers have sexual dysfunction as they recover and become cancer survivors. This article aims to review the phases of sexual response and how each may be affected by the physical and emotional stress of cancer diagnosis and treatment. We will then discuss existing tools for assessment of sexual function and approaches to their treatment. Finally, we will conclude with advice to health care professionals based on current research and suggest questions for future study.

Keywords: Sexual dysfunction- female- cancer treatment

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Introduction

The incidence of breast cancer has increased globally over the last decades (Hortobagay et al., 2005). Although traditionally less common, the greatest increase has occurred in Asian countries (Green and Raina 2008). Level of knowledge of breast cancer risk factors, symptoms and screening methods was high as compared to cervical cancer in teachers in different parts in India (Shankar et al, 2015). To reduce this increasing load of mortality due to breast cancer, emphasis on early detection and increased use of systemic therapy is required and that can only happen if we have a better understanding of the trend, age group involved and other risk factors (Chauhan et al., 2011).

In a study of Kowalczyk et al., (2016), they describe the patients who had underwent breast surgery, has a negative impact on female sexual function. The presences of a sexual partner and the support they provide as well as the level of state anxiety are the predictors of sexual dysfunction in breast cancer survivors. Raggio et al., examined on 83 breast cancer survivors at a median of 7 years after their diagnosis. They found that 77% of all

women and 60% of the sample who were sexually active reported sexual dysfunction based on the FSFI. Scientists currently (Hummel et al., 2017) evaluated the effect of Internet-based cognitive behavioral therapy (CBT) on sexual functioning and relationship intimacy. They concluded that Internet-based CBT has salutary effects on sexual functioning, body image, and menopausal symptoms in BCSs with a sexual dysfunction. Tat et al. in 2016 demonstrate the need of healthcare providers to discuss sexual health after breast cancer after treatment.

In India, approximately 1 million new cases were detected, and 680,000 deaths occurred due to cancer in 2012 (Ferlay et al., 2012). The majority, 70% of cervical cancers, is detected at Stage III or higher, leading to high mortality rates (Basu and Chowdhury, 2009). Globally 27% of total cervical cancer cases are from India which is home to 16-17% of world's women population (Shukla et al. 2009). Despite an annual cervical cancer incidence rate of 25/100,000 in India, there are no large scale public health surveillance programs in cervical cytological screening and human papillomavirus (HPV) typing in India. Over the years, due to effective screening program and National Cancer Control Program, patients

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started presenting in early stage and rate of hysterectomy increased from 5% in 1977 to 20% in 2006 but adding more morbidity to patients (Shankar et al, 2017).

The incidence of endometrial cancer cases are very low in India; the highest being observed in Bangalore (ASR=4.2) and in Delhi (ASR=4.3), while in Mumbai it was 2.8 per 100,000 (Balasubramaniam et al., 2013). Ovarian cancers account for total 3% of all cancers in women and 30% of all cancers of the female genital system (Ellenson et al., 2010; Tavassoli and Devilee, 2003). Among cancers of the female genital tract, the incidence of ovarian cancer ranks below only carcinoma of the cervix and the endometrium.

With the advent of synergistic surgical, radiotherapy and chemotherapy based management, the mortality rates in cancer patients have declined. This has led to increase in morbidities associated with malignancy survivors. Medical understanding of sexuality is based on the work of Masters and Johnson who defined the physiology of the sexual response into the arousal, plateau, climax, and resolution phases (Masters and Johnson, 1966). This model was later refined by Kaplan and Horwith to include desire, and also condensed into 3 phases: desire, arousal, and orgasm (Kaplan and Horwith, 1983). However, this model did not account for motivational drivers that may lead to the seeking and ultimately the fulfillment of desire. In 2001, Basson constructed a circular model to help define female sexual function in which the physiological parameters of Kaplan were placed in the context of psychosocial needs, particularly emotional intimacy as a driver towards sexual activity (Basson, 2001). In Basson's model, the complexity of biology and psychology was conceptualized to bring together a more comprehensive model of what we call female sexual function index. Currently Basson's model correlates well with the sexual function in women (Sands and Fisher, 2007).

Assessment of overall sexual health

To determine the etiology of female sexual dysfunction different facets of emotional, physical and other comorbid diseases and drugs intake has to be taken into consideration. As important, prior history and experience with sex, cultural issues, and religious beliefs can influence sexual function in the face of a cancer diagnosis. Hypertension, diabetes, metabolic syndrome, thyroid disorders are well known diseases associated with sexual dysfunction (Manolis and Doulas, 2008; Enzlin et al., 2003). Antihypertensives like beta-blockers as well as diuretics are well known for sexual side effects (Ko et al., 2002). Emotional disorders such as anxiety and depression are associated with reductions in sexual desire, sexual arousal, and orgasm (Krychman et al., 2006). Specific psychological issues for cancer patients may include fear of recurrence and concern over spouses and children depending on the age of children at the time of diagnosis. Additionally, women may suffer unnecessarily if they are self-blaming or feel some past behavior or transgression was a contributing factor to the development of their cancer. Relationship discord may also be exacerbated during cancer care and treatment. Further complicating these cases are the effects of antidepressant medications,

specifically selective serotonin reuptake inhibitors (SSRIs), which may further suppress sexual desire and commonly inhibit arousal and orgasms (Montejo et al., 2001).

How does cancer treatment affect sexual health?

Surgery, radiotherapy and chemotherapy all have an impact on sexual health in several ways. Oophorectomy either surgical or after radiotherapy or chemotherapy leads to acute decrease in levels of estrogen, progesterone and testosterone in women leading to irreversible menopause. With the change in this endocrine axis there is emergence of menopausal symptoms such as vulvovaginal and clitoral atrophic changes coupled with vaginal thinning, decreased elasticity with resulting dryness and onset of dyspareunia (Johansen et al., 2016). In patients undergoing hysterectomy there are both long term as well as short term sexual morbidity. Short-term patients can experience orgasmic difficulty, dyspareunia, sexual dissatisfaction, and distress by a reduced vaginal size during intercourse. Long-term effects (for as long as 2 years) tend to include a negative impact on libido and vaginal lubrication. These morbidities are more frequent with radical hysterectomies (Jensen et al., 2004; Bergmark et al., 1999).

Many have researched the impact of breast surgery on sexual health. Yet, although body image has been found to be significantly better in those receiving breast-conserving surgery, overall quality of life and sexual function have not been found to be significantly different (Ganz, 1997).

Cytotoxic chemotherapy in women not only create poor self-esteem due to alopecia and generalized weakness but also lead to decrease in sexual interest owing to side effects such as anemia, leucocytopenia, diarrhea and fatigue (Ganz et al., 2002). Antiestrogen therapies, of which the selective estrogen receptor modulator tamoxifen has been the most studied, are commonly used in hormone-positive cancers, most notably breast cancer. Tamoxifen has been reported to affect sexual function in some patients, leading to physiological consequences of impaired venous congestion and lack of vaginal lubrication, all of which result in both arousal and pain issues (Kaplan, 1992; Mourits et al., 2002).

Like surgery, radiation therapy may cause scarring and nerve damage. Radiation causes damage to the vaginal mucosa, causing stenosis and fibrosis that may lead to sexual dysfunction as well as infertility and poor pregnancy outcomes (Lamb, 1996). In situations where the ovaries are irradiated, there is also risk of sterilization and early menopause. This can sometimes be avoided with surgery to move the ovaries out of the field of radiation, but not in all cases. Radiation has both short-term and long-term effects. In the treatment of cervical cancer, women receiving radiation with or without surgery have similar sexual practices and satisfaction compared with women who have undergone radical hysterectomy 6 months after treatment, but by 1 year they have much higher rates of dyspareunia. Sexual desire and arousal also tend to be affected to a greater degree in women receiving radiation therapy, compared with those receiving surgery alone (Schover et al., 1989).

Methods of assessment of sexual function

One of the major challenges in the management of sexual dysfunction is lack of proper methodology for proper screening and diagnosis. A survey of gynecologic oncologists in New England found that less than half gather sexual history of new patients (Wiggins et al., 2007). The problem lies both among clinicians as well as the patients. Screening patients can be challenging and may be considered time consuming for oncologists focused on diagnosis, management, and the urgent medical complications of disease and treatment. Moreover, to effectively address dysfunction, health care professionals may need to establish baseline sexual function in healthy patients or at least a pretreatment baseline (Quirk et al., 2005). The basic problem being lack of time and others being personal discomfort with the topic, inadequate training and understanding of safe, effective available treatments. Patients, however, have different reasons for not discussing sexual concerns. According to a survey of 500 adults over the age of 25, the most common reasons for not bringing up sexual issues were fear of the concern being dismissed (71%), fear that the physician would be uncomfortable (68%), and fear of a lack of treatment options (76%) (Marwick, 1999).

Several scales for objective assessment of sexual dysfunction have been developed over the years. Quality-of-life questionnaires vary in their content and coverage. Some are broadly relevant to any population regardless of health or disease status (generic questionnaire), whereas others focus on particular concerns in specific disease such as cervical cancer (disease-specific questionnaire). Besides, dimension-specific questionnaires may focus on sexual dysfunction, anxiety, depression, or adverse effects after treatment.

The European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Cervix Module 24 was designed to supplement the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 as a disease-specific and treatment specific measure tool. It has been validated in patients with cervical cancer with internal consistency (Cronbach > range, 0.72-0.86 in multi-item scales) and fewer scaling errors. Female Sexual Function Index (FSFI), the Leiden Questionnaire, and Sexual Function-Vaginal Changes Questionnaire (SVQ) are dimension specific measurements concentrated on sexual function. The Female Sexual Function Index, the most commonly used instrument to measure sexual dysfunction with initial excellent reliability for total score (Cronbach >, 0.97) and subscales (Cronbach >, 0.89-0.96), has been recently validated in cervical cancer survivors.

The Leiden Questionnaire, designed to measure sexual function and vaginal changes for patients with gynecological cancer, was proven to be reliable, with (Cronbach > of 0.73 to 0.80). The Sexual Function-Vaginal Changes Questionnaire has high patient-observer agreement. The Short Form-36, Spitzer Quality of Life Index, Cancer Rehabilitation Evaluation System, European Organization

for Research and Treatment of Cancer-Quality of Life Questionnaire-C30, Rotterdam Symptom Checklist, Brief Symptom Index-18, Sexual Activity Questionnaire, and Sexual Function-Vaginal Changes Questionnaire were all validated in cancer survivors (Ye et al. 2014).

The publication of the Late Effects Normal Tissues (LENT)-Subjective, Objective, Management, Analytic (SOMA) scales by the joint efforts of the EORTC and RTOG in 1995 was an attempt to produce a universal system for measuring and recording the late effects of radiotherapy (RT).

LENT SOMA (Late effects in normal tissues subjective, objective, management and analytic) scales is a tool for radiotherapy morbidity. This scale is used to assess the use of questionnaires to score treatment effects in carcinoma of uterine cervix. LENT SOMA scales are used prospectively to study the effect of radiotherapy for carcinoma cervix. The questionnaire approach is a practical method for obtaining reliable and consistent data. In the scales each answer is scored depending on the severity of the symptoms, higher the score the more severe the symptom.

The perception of morbidity may be quite different by the doctor and the patient, particularly if the morbidity is protracted, irreversible, uncontrollable, and painful or socially disabling (Pavy et al., 1995). Therefore the LENT SOMA scale uses both the objective and subjective elements to evaluate the injury. This will allow a comparison within each set of data of the local perception of Injury and the patient's view of the treatment efficacy. This may focus attention on symptoms that can be alleviated, but which have not received sufficiently serious attention so far.

Female sexual dysfunction, the therapeutic approach

The pre text of management of sexual dysfunctions lies on three tier approach of open communication, medical understanding, and education (Krychman, 2006). The understanding that sexual dysfunctions may arise during treatment must be clearly discussed and screened for during treatment and follow-up. Regular and routine screening also may assist in identifying new or evolving concerns regarding dysfunction and may afford the opportunity to address and ultimately help guide prognosis for recovery.

Drugs affecting the desire component of sexual dysfunction are anti-depressants often prescribed in cancer survivors. Paroxetine has worst sexual side-effect profile, with increased rates of delayed orgasm and impotence. So it may be replaced with other SSRI such as fluoxetine, fluvoxamine, and sertraline. Bupropion is another worthy option (Croft et al., 1999). Endocrine causes of decreased desire, such as early menopause after oophorectomy or chemical alteration of the estrogen response with agents like tamoxifen, present a unique challenge. In many cases, hormone supplementation is strictly contraindicated on the basis of the nature of the tumor. Testosterone supplementation has been studied for libido-enhancing effects in women and used for women under other circumstances. However, testosterone is an off-label use

in women with cancer and has not been approved by the Food and Drug Administration (FDA). Given that it has not been adequately studied in female cancer survivors, it cannot be recommended for use (Barton et al., 2007).

Survivors in long-term relationships have their own challenges that may impact desire. A well-meaning partner may relinquish his or her role as initiator of sexual activity, which may undermine the survivor's confidence. A partner may also have his or her own difficulty coping with the stress of their loved one's disease or overcoming the physical and/or emotional changes the survivor has undergone. It is important that the partner be involved in the counseling, the initial setting of expectations, and in screening for dysfunction, provided the patient is comfortable with this. Also, open communication should be encouraged and a referral to an appropriate therapist may be warranted in difficult situations.

Whether it is from the hormonal effects of surgical or endocrine therapy or damage done by radiation or cytotoxic chemotherapy, vaginal dryness, irritation, and vulvo vaginal atrophy are common impediments to normal sexual function in women with cancer. Inadequate or failure of lubrication and vasocongestion as a part of normal physiological arousal or the increased sensitivity of fragile mucosa can make vaginal penetration painful and difficult or even impossible. A hormonal solution, particularly a systemic estrogen treatment, can be used in many cases, although contraindications exist in hormonally sensitive cancers. Fortunately, a number of alternatives exist and can easily be prescribed or recommended by physicians encountering this complaint.

For patients with lower risk, local estrogen creams, rings, or tablets are applied directly to the vaginal mucosa, have minimal systemic effects, and may provide the most effective treatment (Simunic et al., 2003). There are also nonpharmacologic vaginal moisturizers. The nonhormonal therapy was found in a placebo-controlled clinical trial to be effective in managing vaginal atrophy (Nachtigall, 1994).

For problems related to arousal there is a prescription device that is FDA approved as an aid for female arousal. The EROS-CVD creates orgasm gentle suction over the clitoris to increase blood flow and enhance sensation. This device has shown promising role in patients with oophorectomy, hysterectomy and in patients treated with radiotherapy who had severe dyspareunia (Josefson, 2000). Patients dealing with dyspareunia that is the result of scarring or shortening of the vagina from surgery or radiation are explained regarding the use of vaginal dilators coupled with aggressive vaginal rehabilitation including vaginal lubricants, moisturizers, and minimally absorbed local vaginal estrogen products, may also be used to lengthen or widen the vagina. This tends to be a daily exercise over a long period of time with dilators of increasing size and can be a difficult process (Miles and Johnson, 2014). In general, when confronting any sexual dysfunction, providers should always consider individual and couples counseling along with any biological or medical treatment plan that includes prescription. Even when the immediate cause of dysfunction is clear, it is possible that an emotional component exists, which would

benefit from deeper exploration. Physicians should also be willing to refer patients to a specialist when more complex or intractable problems arise.

Sexual dysfunction....a domain unresolved

As more and more patients survive their cancer, increased effort is placed on improving their quality of life. Sexual health comprises an important dimension of human well-being. Among the unresolved questions is the incomplete division between sexuality and fertility, which is highly relevant for pediatric cancer survivors and young women. Is it possible to treat them as 2 sides of the same coin? If so, how can we ensure proper care of fertility-challenged women?

Women who choose not to have children or women who for any reason do not see their fertility and sexual wellness as quite so closely intertwined? Currently there is recognition that it is important to preserve fertility; however, is preservation of sexual function addressed satisfactorily? The American Society of Clinical Oncology recommends that fertility preservation be considered as part of cancer treatment planning as early in the process as possible (Lee et al., 2006). In addition, the cancer-related FSD is limited by a better understanding of baseline sexual function when newly diagnosed. This is likely attributed to the unspoken understanding among oncologists that there is a time and place to discuss issues, and that the newly diagnosed patient, overcome with a cancer diagnosis and grappling to make decisions on treatment, is not in an appropriate state of mind to discuss sexual health. Would patients and physicians perhaps benefit from the use of some standardized verbiage in intake forms, histories, examinations, and questionnaires?

Health care learning models and paradigms must be evaluated and tested to ascertain the best method for taking a time-efficient and sensitive sexual history. In the field of female sexual pharmacology, there is only 1 FDA approved medication, conjugated equine estrogen (Premarin Vaginal Cream), for the treatment of moderate to severe dyspareunia. Safe efficacious treatment options for women irrespective of a cancer diagnosis remain extremely limited. Further development of nonhormonal treatment regimens need to be further researched and developed. Finally, there is a lack of evidence-based data evaluating the role of integrative medical techniques on sexual function, especially in the female cancer patients. Brotto et al have done some research on the practice of mindfulness, demonstrating a positive impact on sexuality, albeit in small cohorts. Such data on alternative therapeutics are important to delineate treatments that go beyond the "medicalization" of sexual dysfunction and embrace a bio psychosocial model of sexual health that can be individualized and tailored to the specific cancer survivor (Brotto et al, 2008).

In Indian scenario with cultural and ethical boundaries sex and related dysfunctions are still a taboo, but the problem exists and causes harm. Ignorance is no cure so it must be a matter of introspection that this domain of life must be discussed and treated for all cancer survivors.

Conflict of Interest

We don't have any sponsorship for this research, authorship. This is review article, so data is taken from many original articles and review papers related to this topic. Although all authors completed the disclosure declaration, there is no conflict of interests.

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