Sexuality and Fertility after Cancer

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As more people achieve long-term survival after cancer, sexual dysfunction and infertility have increasingly been recognized as negative consequences that impact quality of life. Sexual dysfunction is a frequent long-term side effect of cancer treatment, but damage to different underlying physiological systems is salient in men versus women. Men frequently have erectile dysfunction (ED) related to damage to the autonomic nervous system and/or reduced circulation of blood to the penis. Hormonal impairment of sexual function is less common. Women, in contrast, are able to overcome damage to autonomic nerves if genital tissues remain structurally intact and estrogenized. Female sexual dysfunction is frequently associated with sudden premature ovarian failure or direct effects of radiation fibrosis or scar tissue causing pain with sexual activity. The lack of validated interventions for sexual rehabilitation after cancer is a major problem, as is finding cost-effective ways of providing services. Concerns about fertility are also a major source of distress to people treated for cancer during childhood or young adulthood, yet many young survivors do not recall any discussion about future childbearing potential with their oncology team. Since fertility preservation is becoming more practical for both men and women, producing patient and professional educational materials and developing professional practice guidelines should be high priorities for oncology societies.

As long as cancer treatments cannot be exclusively targeted to tumor cells, damage to the reproductive system will remain an important aspect of cancer morbidity. Problems with sexual function and fertility after cancer are not only ubiquitous, they are less likely to resolve with time than most other treatment side effects. Although not every cancer survivor cares about remaining sexually active, long-term sexual dysfunction has been documented in at least 50% of those treated for breast, prostate, colorectal or gynecological cancer.[1] Most available information about sexual dysfunction and fertility is from patients treated for solid tumors. Distress about cancer-related infertility is typically highest among those diagnosed in their reproductive years. Although a much smaller percentage of people treated for cancer are affected by infertility than by sexual dysfunction, 1 in 71 men and 1 in 51 women are diagnosed with a malignancy before age 39.[2] Although some cancer treatments can cause both sexual dysfunction and infertility, these two types of morbidity are frequently independent. For example, many young men treated with chemotherapy have poor semen quality, but with all but the high-dose regimens, their testosterone levels and sexual function remain normal.[3] Therefore, sexual function and fertility will be discussed in separate sections.

Sexual Function, Gender, and Damage from Cancer Treatment

The most common sexual problems after cancer treatment include loss of desire for sex in men or women, erectile dysfunction (ED) in men, and pain with sexual activity in women. Although difficulty reaching orgasm can occur, it typically is secondary to lack of desire and pleasure during sexual activity rather than a primary result of damage to sensory nerves.[1] Cancer treatments may damage one or more of the physiological systems needed for a healthy sexual response, including hormonal, vascular, neurologic, and psychological elements of sexual function. Treatment also may entail removal or direct damage to parts of the reproductive organs.

In men, radical surgery to treat cancer of the prostate, bladder, or rectum has been modified to spare nerves that direct blood flow into the penis. Nevertheless, rates of recovery of firm erections after surgery are far lower in large, long-term surveys than suggested by reports from selected cohorts in academic medical centers. For example, in a 5-year follow-up of a national sample of 901 men treated with radical prostatectomy, 79% ended up with ED.[4] Our own survey of over 1200 men treated for localized prostate cancer and followed for a mean of 4.3 years found an 85% rate of ED (see below).[5] Attempts at nerve-sparing radical cystectomy and rectal cancer surgery have also yielded disappointing rates of recovery of erections.[6,7] The benefits of nerve-sparing may be limited by fibrosis that builds in the soft tissue of the penis after surgery[8] or by concomitant injury to the vascular bed of the penis.

Radiation therapy to the pelvis begins a more gradual process of fibrosis that eventually may damage both the nerves and blood vessels involved in erection.[4,5] Despite use of newer modalities such as brachytherapy or computer-guided external beam treatment, rates of ED after radiation therapy increase over time so that by 5-year follow-up they equal those after radical surgery.[4] In a recent prospective

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study of 31,742 non-physician health professionals aged 53 to 90, the 2109 men who had been diagnosed with prostate cancer were 10 to 15 times more likely than men of comparable age to have ED.[9]

In women the autonomic nerves that direct blood flow into the genital area with sexual arousal may also be affected by pelvic surgery, but the impact on sexual function is unclear. Well-controlled studies of large populations of women have shown that benign hysterectomy, including removal of the cervix, does not impair women's sexual pleasure or capacity to reach orgasm.[10] After radical hysterectomy alone for cervical cancer, most sexual problems with pain or difficulty reaching orgasm resolve by a year after surgery. The only enduring difference between cancer survivors and matched controls is some loss of desire for sex and reduced vaginal lubrication.[11] In contrast to men, women who have radical cystectomy or surgery to remove rectal cancer have similar sexual function to healthy controls.[6,12] If pelvic surgery impairs vaginal expansion and lubrication, it seems that women can compensate by using estrogen replacement or water-based lubricants.

After radiation therapy in fields that include the genital area, women fare more poorly than men. Young women treated with radiation therapy for cervical cancer are significantly more likely to have problems with dyspareunia and other aspects of sexual function than matched controls.[13] Women treated with both hysterectomy and postoperative radiation for endometrial cancer have rates of vaginal stenosis as high as 55%, causing significant sexual problems.[14] Although less common, vaginal scarring and fibrosis due to graft-versus-host disease after allogeneic bone marrow transplant can have a devastating impact on women's ability to have intercourse or enjoy sex.[15] Even treatment with lubricants and vaginal estrogen cannot reverse these anatomical changes.

Cancer treatments that impair ovarian function, whether temporarily or permanently, also have a major impact on female sexual function. For example, breast surgery of any type is a very weak determinant of women's sexual function. Rather, treatment with adjuvant chemotherapy accounts for much of the sexual morbidity of breast cancer, especially in women who experience an abrupt transition to menopause as a result of their cancer treatment.[16,17] Other treatments that produce ovarian failure include GnRH agonists, bilateral oophorectomy, and aromatase inhibitors.[18] In contrast, selective estrogen receptor modifiers such as tamoxifen and raloxifene do not appear to decrease women's desire for sex, vaginal lubrication, or ability to enjoy intercourse without pain.[17]

Women in ovarian failure usually have reduced serum androgen levels, thought to contribute to loss of interest in sex and arousability. However, the one study to examine serum testosterone in breast cancer survivors found that those with higher levels actually had less desire for sex.[19] This unexpected finding may reflect the association in postmenopausal women between obesity and higher circulating androgen levels. Randomized trials show benefits of testosterone replacement in women presenting with low desire after bilateral oophorectomy.[20] However, a prospective study in a community sample of women undergoing hysterectomy for benign indications with versus without bilateral oophorectomy found no association between decreased androgen levels and sexual or emotional function at 1-year follow-up.[21] In fact, women who had bilateral oophorectomy had no decline in sexual function and improved in overall well-being.

Hormonal deficits related to cancer treatment are a far less frequent cause of male sexual dysfunction. It is also important to recognize that treatment outcome is variable. Men with advanced prostate cancer given anti-androgen therapy experience profound sexual changes, including loss of desire, ED, and difficulty reaching orgasm, but a significant minority under age 60 maintain reasonable sex lives, albeit with more effort to get aroused and less frequency. However, men treated with neoadjuvant anti-androgen therapy often do not recover normal sexual function, even after discontinuation of the hormones.[5] Hypogonadism is a treatable cause of sexual dysfunction in a minority of men treated for testicular cancer[22] or with full preparative regimens for bone marrow transplantation.[23] In both men and women, opiate pain medication, antidepressants, anti-anxiety drugs, and anti-emetics can frequently contribute to hypogonadism and sexual dysfunction.[1]

Sexual Rehabilitation after Cancer Treatment

Despite the fact that sexual problems in cancer survivors typically have organic causes, successful sexual rehabilitation often requires a broader approach that incorporates behavioral changes and involves both partners in a committed relationship.[1]

Despite the availability of a variety of treatments for ED and increasing rates of help-seeking for ED among prostate cancer survivors, most men are disappointed with the efficacy of prostaglandin E5-inhibiting drugs but also remain reluctant to try more invasive treatments such as penile injection therapy or penile prosthesis surgery. Drop-out rates are above 50% with any modality tried.[24] One predictor of successful sexual rehabilitation is having a sexually functional partner who still desires sex, [5] suggesting that simply being able to have firmer erections does not automatically result in more frequent and pleasurable sex. In fact, ED is just one of the common sexual problems men experience after prostate cancer treatment, so that sexual rehabilitation needs to focus also on decreased sexual desire, difficulty reaching orgasm, pain with ejaculation, and dismay at reduced penile size.[24-26] Similarly, merely replacing testosterone does not restore sexual function and satisfaction among men with abnormal hormonal profiles after bone marrow transplantation.[27]

Sexual rehabilitation after cancer in women also cannot be reduced to a simple paradigm of hormonal replacement or a mechanical device. Despite promising results

with using testosterone patches to treat low desire,[20] female cancer survivors have to consider their risk for breast cancer that may be potentiated by such therapy. High endogenous testosterone is a very strong risk factor for breast cancer in postmenopausal and premenopausal women,[28,29] and may also promote systemic breast cancer in women treated for localized disease.[30] Hormonal factors also appear to exacerbate the already highly elevated risk of breast cancer in women who received chest irradiation before puberty or were treated for childhood sarcoma.[31]

Much of the loss of desire for sex in women with ovarian failure is linked to dyspareunia from vaginal atrophy. A safer hormonal treatment may be the use of low-dose estrogens in the form of a vaginal ring or suppository to treat pain that does not respond to appropriate use of water-based lubricants or vaginal moisturizers.[32] Since little estrogen escapes into the systemic circulation, such products can often dramatically improve dyspareunia with negligible risk of promoting cancer recurrence. Randomized safety trials are needed, however.

Vaginal dilation is widely accepted as a treatment to prevent vaginal stenosis and agglutination in women who have pelvic radiation therapy. Yet dilation has not been validated by empirical research. A recent Cochrane Report on treating female sexual dysfunction after pelvic radiation therapy concluded that vaginal dilators were the only modality meeting reasonable standards for evidence-based medicine,[33] but it cited only two small cohort studies. Women's adherence in using vaginal dilators is quite low even after behavioral intervention.[34] If vaginal dilation is effective, does it prevent fibrosis in the vaginal walls by stimulating the inflow of oxygenated blood, like interventions to promote recovery of erections after radical prostatectomy in men?[8] Or does simple mechanical stretching of the tissues preserve vaginal elasticity? If oxygenated blood flow is crucial, becoming sexually aroused may be as effective as vaginal dilation without the problems of adherence. Recently 13 women were instructed to use a clitoral vacuum device designed to increase genital blood flow for three months after radiotherapy for cervical cancer.[35] Although the researchers claim no sexual education or counseling was provided to supplement the instructions, they did specifically ask the women to incorporate the device into self-stimulation and partner sex four times weekly. Their report of astonishing improvement in sexual function and vaginal appearance on examination is difficult to explain, but further research is certainly warranted. Even if the device has reproducible benefits, using a vibrator to promote sexual arousal might be as effective and far less expensive.

A recent worldwide survey of 27,500 men and women aged 40 to 80, unselected for health, found that sexual problems are very common, but that less than 20% of either gender typically seek medical help for them.[36] Sexual dysfunction has been cited as a major source of distress for cancer survivors in several surveys.[4,5,16] It is time to shift the focus from the causes and prevalence of sexual dysfunction after cancer to creating, evaluating, and disseminating practical and cost-effective programs of sexual rehabilitation. The current lack of randomized trials of such interventions is a major problem in psychosocial oncology.

Fertility Preservation: The Need for Better Communication before Cancer Treatment

Despite a variety of options to cryopreserve gametes and embryos for people about to begin cancer treatment, many do not get the information they need within the narrow window of time between diagnosis and beginning a cancer therapy with the potential to permanently impair fertility. Sperm banking has been available to men before cancer treatment for many years but became much more practical with the success in the early 1990s of in vitro fertilization with intracytoplasmic sperm injection, since only a few live sperm needed to survive freezing and thawing to be used in assisted reproductive treatments.[37-38] Cancer treatment does not need to be delayed since adequate semen samples can be collected daily. Even one stored ejaculate can often provide the man with the future chance of having biological offspring. Teens as young as 12 have the physical capacity and emotional maturity to provide semen samples and should be informed routinely of this option.[39] Yet a survey of over 200 male patients seen in major cancer centers revealed that only half recalled being told about sperm banking. The most common reason (other than having completed all family building at cancer diagnosis) for not banking sperm was not having been informed in time (25% of men who did not bank sperm).[38] A companion survey of oncology faculty and fellows revealed that despite almost universal agreement that sperm banking should be mentioned to all cancer patients whose treatment might impair fertility, 48% either never mentioned it or informed less than 10% of their eligible patients.[40] The major barriers to referring men for sperm banking, cited by half of physician respondents, included lack of time to discuss the topic in a busy clinic, the belief that most patients could not afford to bank sperm (a problem cited only by 7% of men who did not bank sperm[38]), and not knowing where to find a convenient sperm bank. Hematologist/oncologists were also less likely to discuss sperm banking with men who needed rapid cancer treatment or had a poor prognosis (which includes most patients with acute leukemia or high-grade lymphoma). As with many other aspects of cancer care, men who had a referral from a physician were significantly more likely to bank sperm than those who found out about it on their own.[38] Clearly educational materials are needed to facilitate communication between health care providers and patients on this important topic.

Fertility options for women are unfortunately even more problematic. Women who do not require urgent treatment may undergo a cycle of in vitro fertilization before cancer treatment and cryopreserve embryos, but the chance of a pregnancy with future use is still limited, and patients

without a male partner have to use donor sperm to take advantage of this option.[41] Women with breast cancer can utilize new protocols that may limit exposure of cancer cells to high estrogen levels by adding aromatase inhibitors or tamoxifen to the ovarian stimulating drugs.[42] Cryopreservation of mature, unfertilized oocytes is another experimental choice, but only around 100 children have been born worldwide from this technique, and concerns remain about the genetic integrity of the spindle and the optimal freezing technique.[41,43] Centers around the world have begun harvesting ovarian tissue for cryopreservation, in the hopes that autotransplantation or even xenotransplantation of the tissue will result in the development of healthy, mature oocytes.[41,43] For some malignancies, cancer cells could theoretically be harbored in the ovarian tissue. The one published birth from autotransplanted, cryopreserved ovarian tissue has been questioned since the patient had signs of recovered activity in her remaining ovary on the other side.[44] Further attempts at autotransplantation are ongoing, however, and cryopreservation of the entire ovary, rather than just of cortical tissue strips, has recently been suggested as an alternative.[45]

Another controversial area is whether the ovary can be protected during cancer treatment by using GnRH-agonists to create a temporary menopause.[41,43] Some promising results have been published, but methodological limitations of the studies and uncertainty about the mechanism of the protective effect remain. In the future, chemoprotection with small molecule compounds that inhibit ovarian apoptosis may become possible.

Women with very early stage or low-grade gynecologic cancer may be able to preserve fertility by having limited surgery, for example, conservation of the uterus and contralateral ovary for women with ovarian cancer or radical trachelectomy (preservation of the uterus despite removal of most of the cervix) for cervical cancer. Lateral transposition of the ovaries to remove them from the field of pelvic irradiation is an option that preserves ovarian function in about half of women treated for cervical cancer or Hodgkin disease.[46]

Given this array of experimental options, most not covered in the United States by insurance, it is no surprise women are often poorly informed about fertility preservation. Two recent studies of young women treated for breast cancer found a great deal of distress about infertility and dissatisfaction with communication with hematologist/oncologists on this issue.[47,48] In a survey of affluent, well-educated women belonging to an advocacy organization for premenopausal women with breast cancer, 72% had discussed fertility with their hematologist/oncologist, but often the topic was brought up by the patient. Only 51% felt their concerns had been adequately addressed.[47] In a more diverse sample of 166 young breast cancer patients, only 34% recalled discussing fertility with their oncology team.[48]

Not only is better communication about fertility preservation strongly needed between patient and hematologist/oncologists, but organizations need to develop practice guidelines on when it is appropriate to bring up infertility, how to discuss new modalities that remain experimental and often involve large out-of-pocket costs to the patient, and what options should be offered by cancer centers.[49] The advocacy organization Fertile Hope has made an excellent start in developing patient education materials (www.fertilehope.org).

Most importantly, reproductive health after cancer is only increasing in importance as the number of cancer survivors multiplies and the length of their survival also improves. Sexual function and fertility can no longer be regarded by hematologist/oncologists as frivolous or irrelevant issues, because our current cancer therapies damage reproductive health in ways that are profound and often permanent. Interventions that prevent or reverse these problems will greatly improve the quality of life of our patients.

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