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The Prevalence and Types of Sexual Dysfunction in People With Cancer

Sexuality is a complex, multidimensional phenomenon that incorporates biologic, psychologic, interpersonal, and behavioral dimensions. It is important to recognize that a wide range of normal sexual functioning exists. Ultimately, sexuality is defined by each patient and his/her partner within a context of factors such as gender, age, personal attitudes, and religious and cultural values.

Many types of cancer and cancer therapies are frequently associated with sexual dysfunction. Across sites, estimates of sexual dysfunction after various cancer treatments have ranged from 40% to 100%.[1] Most of the information relates to women who have breast or gynecologic cancer and men who have prostate cancer. Less is known about how other types of cancers—in particular, other solid tumors—affect sexuality. Research suggests that about 50% of women who have had breast cancer experience long-term sexual dysfunction,[2,3] as do a similar proportion of women who have had gynecologic cancer.[4] For men with prostate cancer, erectile dysfunction (erections inadequate for intercourse) has been the primary form of sexual dysfunction investigated. Prevalence rates of erectile dysfunction have varied. In general, those studies that have used patients' self-reports have found higher rates of erectile dysfunction ranging from 60% to 90% after radical prostatectomy and between 67% and 85% following external-beam radiation therapy.[5-8] Erectile dysfunction appears to be least prevalent with brachytherapy and most prevalent when cryotherapy is used to treat localized prostate cancer.[9] For Hodgkin lymphoma and testicular cancer, 25% of people who have had these cancers are left with long-term sexual problems.[3,10]

Several summary articles on sexuality and cancer give particular emphasis on cancer sites that have a direct impact on sexual functioning.[11-13] An individual's sexual response can be affected in a number of ways, and the causes of sexual dysfunction are often both physiological and psychological. The most common sexual problems for people with cancer are loss of desire for sexual activity in men and women, erectile dysfunction in men, and dyspareunia (pain with intercourse) in women.[3] Men may also experience anejaculation (absence of ejaculation), retrograde ejaculation (ejaculation going backward to the bladder), or the inability to reach orgasm. Women may experience changes in genital sensations due to pain or a loss of sensation and numbness, as well as a decreased ability to reach orgasm. Loss of sensation can be as distressing as painful sensation for some individuals.[14] In women, premature ovarian failure as a result of chemotherapy or pelvic radiation therapy is a frequent antecedent to sexual dysfunction, particularly when hormone replacement is contraindicated because the malignancy is hormonally sensitive.[2]

Unlike many other physiological side effects of cancer treatment, sexual problems do not tend to resolve within the first year or two of disease-free survival;[2,7,15-19] rather, they may remain constant and fairly severe or even continue to increase. Although it is unclear how much sexual problems influence a survivor's rating of overall health-related quality of life, these problems are clearly bothersome to many patients and interfere with a return to normal posttreatment life. Assessment, referral, intervention, and follow-up are important for maximizing quality of life and survival.[2,17]

In this summary, unless otherwise stated, evidence and practice issues as they relate to adults are discussed. The evidence and application to practice related to children may differ significantly from information related to adults. When specific information about the care of children is available, it is summarized under its own heading.

In a qualitative study of 48 men (130 approached) with erectile dysfunction after treatment for early prostate cancer,[20] quality of life was significantly affected in areas such as the following:

- The quality of sexual intimacy.
- Everyday interactions with women.
- Sexual fantasy life.
- Perceptions of their masculinity.

Patients who participated in a randomized trial that compared radical prostatectomy with watchful waiting were asked to complete a questionnaire regarding symptoms, psychological functioning, and quality of life.[21] Although the frequency of sexual thoughts was similar in both groups, the prevalence of erectile dysfunction (changes in voluntary erection in sexual situations, erection on awakening, and spontaneous erections) was higher in the radical prostatectomy group (80%) than in the watchful-waiting group (45%). Among men who underwent radical prostatectomy, 56% were moderately or greatly distressed by the decline in sexual function, as compared with 40% of men in the watchful-waiting group.[21]

In a different population—that of male lymphoma survivors—a cross-sectional study of 15-year survivors of both Hodgkin and non-Hodgkin lymphoma compared sexual function and hormone levels with those of age-matched

controls.[22] Overall, the authors concluded that sexual function (as measured by the Brief Sexual Function Inventory [BSFI]) was significantly worse in the lymphoma survivors than in controls. In univariate analysis, lower functioning was attributed to the following:

- Increased age.
- Lower testosterone.
- Higher luteinizing hormone.
- Greater fatigue and emotional distress.
- At least one comorbidity.

There are several cautions in interpreting these results:

- The types of comorbidities are not listed; hence, it is not known whether cardiovascular disease was prevalent.
- Multivariate analyses to look at the relative impact of the various contributing factors to lower functioning were not performed.
- Considering the overall mean scores, the BSFI subscale scores were neither that low nor that different from the scores of controls (a difference of <0.5) even though they were statistically significantly different, likely because of the large sample size.

Although the authors concluded that sexual function was worse, it was only slightly worse; however, it reached statistical significance. Therefore, it is not clear from this study how much sexual functioning contributed to distress or decreased quality of life.[22]

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Factors Affecting Sexual Function in People With Cancer

Sexual dysfunction may be multifactorial; both physical and psychological factors contribute to its development. Physical factors include functional damage secondary to cancer therapies, fatigue, and pain. In addition, cancer therapy such as surgery, chemotherapy, radiation therapy, and bone marrow transplantation may have a direct physiologic impact on sexual function.[1] Medications used to treat pain, depression, and other symptoms may contribute to sexual dysfunction. Psychological factors include misbeliefs about the origin of the cancer, guilt related to these misbeliefs, coexisting depression, changes in body image after surgery, and stresses to personal relationships that occur secondary to cancer.[2,3] Increasing age is often believed to be associated with decreased sexual desire and performance; however, in one study, elderly men reported that sex remains important to their quality of life, that performance can be maintained into the 70s and 80s, and that altered sexual function is distressing.[4]

Treatment-related Factors Secondary to Surgery

A number of cancer treatments have a direct physiologic impact on sexual function. As treatment success has improved for some sites, attempts have been made to modify treatment to reduce sexual morbidity. Several predictors of postoperative sexual functioning include patient's age, premorbid sexual and bladder functioning, tumor location, tumor size, and extent of surgical resection.

Breast cancer

Sexual function after localized treatment for breast cancer has been the subject of a good deal of research. Several reviews concur that breast conservation or reconstruction have only a minor impact in preserving sexual function compared with a mastectomy alone.[5,6] Women who have breast conservation, in particular, are more likely to continue to enjoy breast caressing, but groups typically do not differ on less subtle variables such as the frequency of sex, ease of reaching orgasm, or overall sexual satisfaction. A cross-sectional survey of younger women (aged 50 years or younger) with breast cancer found in multivariate analyses that having a mastectomy was associated with greater problems in interest in sex; chemotherapy was associated with greater sexual dysfunction.[7] Other studies confirm that sexual quality of life is disrupted more among those receiving chemotherapy, those who have undergone total mastectomies, those whose cancers were detected at later stages, and those with more depressive symptoms near the time of diagnosis.[8] A large survey of women with breast cancer who were being treated with either adjuvant tamoxifen or adjuvant exemestane (an aromatase inhibitor) was conducted to evaluate the differences in menopausal symptoms associated with these two agents. After 1 year of use, exemestane was associated with fewer hot flashes and less vaginal discharge than tamoxifen but with more vaginal dryness, bone pain, and sleep disorders.[9]

Few studies evaluate sexuality in women with breast cancer that recurs. One longitudinal study compared women who were recently diagnosed with recurrent cancer with matched patients who were disease free. The recurrence group had less frequent intercourse, although there were no differences in sexual or relationship satisfaction. As noted in other studies of women with breast cancer, sexual changes were more common among younger patients.[10]

Colorectal cancer

Changes related to sexual functioning in men and women with colorectal cancer have not been well studied, and there is scant literature to illuminate the issues and provide understanding and effective solutions. There are, however, potential changes in sexual function that can result from commonly performed surgery, particularly surgery performed on people with rectal cancer. This section will describe the possible effects on male sexual function that can occur after rectal cancer surgery.

Sexual and urinary dysfunctions are recognized complications of resection for rectal cancer. The main cause of sexual dysfunction from surgical resection appears to be injury to the autonomic nerves in the pelvis along the distal aorta from blunt pelvic resection or undefined cutting. Incidence of genitourinary dysfunction depends on the type of surgery performed (i.e., the plane of dissection, the degree of preservation of the autonomic nerves, and the extent of pelvic dissection).[11,12] Nerve injury can occur via direct injury, by vascular damage to the vasa nervosa, or where the blood supply to the nerves that enter laterally is disrupted with traction or devascularization.[13]

The neuroanatomy for sexual functioning requires an intact autonomic nervous system, which includes an interaction between the parasympathetic and sympathetic nervous systems. Erection (parasympathetic-mediated response) is governed by impulses traveling along the nervi erigentes that arise from the second, third, and fourth sacral nerves,[14] whereas ejaculation depends on sympathetic control. The sympathetic fibers originate from the lower thoracic and upper lumbar segments of the spinal cord. These fibers descend along the aorta, forming the superior hypogastric plexus near the aortic bifurcation. The plexus divides into two trunks, which enter the pelvis along its lateral walls as the hypogastric nerves. The parasympathetic fibers to the pelvis join the hypogastric nerves on each pelvic wall to form the pelvic plexuses.[14] One study provided a more extensive review of the anatomy of the pelvic autonomic nerves and the relation of these nerves to the mesorectal fascial planes.[15] Damage to the hypogastric (sympathetic) nerves or sacral splanchnic (parasympathetic) nerves, or both, during surgical resection are the most likely cause of urinary and sexual dysfunction.[16] Pelvic plexus preservation is necessary to maintain erectile functioning, and both hypogastric nerve and pelvic plexus preservation are necessary to maintain ejaculate function and orgasm.[17]

Prostate cancer

In men, there is controversy whether the newer nerve-sparing technique for radical prostatectomy is more or less successful in preserving erectile function than definitive radiation therapy for localized prostate cancer. A 1994 survey of practice patterns found that 95% of randomly-sampled urologists considered surgery the treatment of choice for clinically localized prostate cancer in men younger than 70 years.[18] As follow-up studies of large groups of men undergoing radical prostatectomy have accumulated, estimates of the number who recover functional erections (firm enough to allow penile-vaginal penetration on most occasions) range from 10% to 40%, with

estimates of functional erections following external-beam radiation therapy ranging from 15% to 33%.[19-23] Retrospective cohort studies have provided evidence indicating superior potency results with bilateral nerve-sparing surgical techniques.[24,25] One research group suggested that much of the superiority of nerve-sparing over standard surgical technique in preserving potency is an artifact of selection bias.[26] The men selected to receive nerve-sparing surgery are those with the best potential to recover adequate erections. A systematic literature review using MEDLINE and CANCERLIT from January 1997 to June 2003 concluded that patient selection and surgical technique are the major determinants of postoperative erectile function in patients receiving treatment for localized prostate cancer. For properly selected patients undergoing a nerve-sparing radical prostatectomy by an experienced surgeon, unassisted or medically assisted erections postoperatively should be achieved.[27]

Other studies suggest that three-dimensional conformational radiation therapy may be superior to radical prostatectomy in preserving erectile function.[20,28-33] Rates of potency are typically in the 30% to 60% range, with conformal therapy superior to older techniques.[20,34-36] Men who are older and in poor health, however, are often directed into radiation therapy, so that researchers often report posttreatment sexual function only for the subgroup that began with good erections. Furthermore, long-term follow-up is needed in comparing surgery with radiation therapy because recovery of erectile function typically occurs within a year or so after radical prostatectomy, whereas the damaging impact of radiation on erectile function is slow and gradual, with declines still being observed as long as 2 or 3 years after treatment. A retrospective cohort study of men treated with either radical prostatectomy or external-beam radiation therapy (EBRT) revealed significantly greater prevalence of erectile dysfunction in the surgery group at 5 years after diagnosis (79.3% vs. 63.5%).[37] The mechanism of injury to erectile function also differs between surgery and radiation therapy. Radical prostatectomy damages nerves that direct blood flow into the penis, ultimately decreasing oxygenation of these tissues and increasing collagen deposits that interfere with the penile tissue relaxation essential for firm erection.[38] Radiation therapy appears to damage the arterial system that transports blood to the penis.[39] A retrospective review of population-based data suggests that the choice of primary treatment for prostate cancer is not associated with 2-year general health-related quality-of-life outcomes.[40]

Prostate brachytherapy with permanent radioactive implants is an increasingly popular choice for the treatment of prostate cancer. Two isotopes are commonly used: iodine 125 (^{125}I) and palladium 103 (^{103}Pd).[41] With brachytherapy, ejaculation is preserved and age (91% of men younger than 50 years) correlates with return of sexual function.[42] However, a decline in potency as a function of time following treatment is expected in patients treated with brachytherapy.[41,43] One study found an actuarial preservation of potency after brachytherapy alone of 79% at 3 years and 59% at 6 years.[44] Another study found lower rates, with 57% of men fully potent or with mild erectile dysfunction at baseline and at 30 months postbrachytherapy.[45] Potency rates after brachytherapy are significantly influenced by the addition of EBRT and/or neoadjuvant hormonal deprivation. Patients who received brachytherapy alone had a 5-year potency rate of 76%, compared with a potency rate of 56% for those treated with brachytherapy and EBRT. Patients who received a combination of EBRT, neoadjuvant hormonal deprivation, and brachytherapy had a 5-year potency rate of 29%.[41]

The etiology of erectile dysfunction following brachytherapy is unknown; however, radiation damage to nerve bundles and vascular structures has been proposed as a cause.[41] One study investigated retrospectively the relationships between the dose of radiation to structures putatively involved in prostate brachytherapy–induced erectile dysfunction and incidence of postbrachytherapy erectile dysfunction. This study found no increased risk of erectile dysfunction with increasing dose to the crus or neurovascular bundle, proposing a possible dose-response relationship between the risk of erectile dysfunction and radiation dose to the bulb.[46]

Orgasm alterations

Despite advances in our understanding of the erectile mechanism, the orgasm process remains poorly understood. Although orgasm alterations receive little attention, they are not uncommon and can be categorized into three areas:

- Changes in orgasm.
- Orgasmic pain (dysorgasmia).
- Orgasm-associated incontinence.

A study of 1,236 men treated for localized prostate cancer (52% radical prostatectomy [RP], 48% radiation therapy) found that 65% of patients reported a problem with their orgasms, including 31% who no longer tried to reach orgasm, 17% who tried but were unable to reach orgasm, and 28% with orgasms that were disappointingly weak.[47]

To define the type of orgasmic dysfunction in men after RP, one group of investigators used a survey, including questions addressing the following:[48]

- Presence of orgasm.
- Absence of orgasm.
- Orgasm quality before surgery.
- Orgasm quality after surgery.
- Presence of orgasmic pain.
- Location of orgasmic pain.
- Consistency and duration of orgasmic pain.

Of the patients treated surgically:

- 22% reported no change in orgasm intensity.
- 37% reported a complete absence of orgasm.
- 37% had a decreased orgasm intensity.
- 4% reported a more intense orgasm after RP than before.

Pain during orgasm occurred in 14% of the patients, located in the penis (63%), abdomen (9%), rectum (24%), and other areas (4%). Most patients had orgasm-associated pain for less than a minute, one-third reported pain for 1 to 5 minutes, and 12% reported pain lasting more than 5 minutes.[48] No consensus on the etiology of orgasmic pain exists; however, it is thought that bladder neck/pelvic floor spasm plays a role.

Tamsulosin

A prospective, non–placebo-controlled study was conducted to assess the use of tamsulosin, an alpha-adrenergic blocking agent, in patients with orgasmic pain. In this study, 77% of patients reported significant improvement in pain, and 12% noted complete resolution of their pain with significant increase in International Index of Erectile Function (IIEF) libido score, supporting the hypothesis that orgasmic pain is related to bladder neck and/or pelvic floor muscle spasm.[49]

Climacturia

Urinary incontinence during orgasm (climacturia) is another phenomenon that may adversely affect satisfaction with sexual activity for men post-RP and for their partners. One group of investigators reported that climacturia occurred in 20% of patients after RP and that it was unrelated to the type of prostatectomy performed (open or laparoscopic).[50] Another group reported a higher prevalence of post-RP climacturia at 45%.[51] In 68% of the cases reported, climacturia occurred rarely or only occasionally, while in 21% of cases it occurred most of the time or always. Urine leakage amounted to only a few drops in 58% of patients, but 16% reported a loss of more than 1 oz. Bother was none or minimal in 52% of patients and significant in 48%.

There is no effective treatment to restore the nature of preoperative orgasm. Dysorgasmia can be managed symptomatically with alpha-blockers, and climacturia may be managed behaviorally (restricting fluid intake and emptying the bladder before sexual activity) or mechanically (using a rubber constriction ring or condoms, if the leakage amount is small).

Penile length alterations

One study has found a significant decrease in all penile dimensions after RP: decreased penile length of 8% and 9% and decreased volume of 19% to 22% in the flaccid and erect states, respectively.[52] The most substantial change occurred between the first 4 months and 8 months postsurgery. A measured decrement in penile length was found in 71% of men after RP, which was more than 1 cm in 48% of patients at 3 months postsurgery.[53] Similar findings were obtained in another study, with a decrease in the stretched penile length in 68% of patients and more than 15% decrease in 19% of patients.[54] Penile length shortening has been shown to be independently associated with nerve preservation status and with postoperative erectile function outcome.

Anatomical fibrotic changes

Anatomical fibrotic changes that showed significantly decreased elastic fibers and smooth muscle fiber content and

increased collagen content have been demonstrated in comparisons of penile biopsies preoperatively and at 2 months and 12 months postoperatively. It is thought that the chronic absence of erectile activity leads to a state of cavernosal hypoxia, low oxygen tension, which favors the secretion of fibrogenic cytokines such as transforming growth factor-beta 1 (TGF-beta 1), while during erection the corporal smooth muscle is oxygenated. This results in the secretion of endogenous prostanoids (prostaglandin E1) which, in turn, inhibit fibrogenic cytokine production.

Physiological-functional alterations

In addition to anatomical changes, there are also physiological-functional alterations. It is well recognized that even in the hands of an experienced surgeon using nerve-sparing surgery, some degree of nerve injury is likely to occur to the cavernosal nerves. Sympathetic hyperinnervation (termed by some *competitive sprouting*) refers to the concept that when autonomic nerves are injured, sympathetic fibers are biologically primed to recuperate from injury and regenerate more quickly, resulting in unantagonized sympathetic tone in the end organ. After cavernosal nerve injury, this phenomenon results in a penile hypertonic state. Any factors that result in reduced nitric oxide secretion or increased sympathetic tone, such as nerve injury after RP, may lead to decreased relaxation or distensibility of corporal smooth muscle and may lead to shortening.

Regardless of the exact mechanism of penile length alteration, the common underlying mechanism of penile shortening and long-term erectile dysfunction may be structural changes that result from a combination of neural injury–associated denervation resulting in smooth muscle degeneration and cavernosal hypoxia-induced collagen deposition.

Penile length changes can be divided into early and delayed:

- **Early changes.** Early changes occur in response to the neural injury during RP. The cavernosal nerves degenerate, and in the early phase—when sympathetic nerve function is in the ascendancy—the penis is contracted. Given that the penile smooth muscle is highly contractile in response to adrenergic tone, this results in a penis that patients often refer to as "being drawn back in the body." This hypertonic state is most pronounced within the first 3 months to 6 months postsurgery. A clinical scenario supporting this is the circumcised man whose penis, soon after surgery, appears incompletely circumcised or even uncircumcised.

- **Delayed structural changes.** Delayed structural changes are more distressing to the patient, resulting from true irreversible structural alterations in the corporal smooth muscle. These structural changes most probably result from a combination of factors (as described above). The difference between these changes and early increased tone is shown by the reduced or absent penile stretch in the group with permanent smooth muscle alterations. It is easy to appreciate how these alterations affect not only length but also girth.

Testicular cancer

Men diagnosed with testicular cancer find changes in sexual function particularly worrisome. However, limited published data describing long-term sexual function in men postorchiectomy are encouraging. A Dutch study reported a decline in sexual function, including desire, during the first 3 months postsurgery, with function improving beyond baseline at 12 months.[55] In this study, being single was the main predictor of worse sexual functioning and/or less satisfaction with functioning at all time points. The type of treatment (orchiectomy alone vs. orchiectomy plus chemotherapy or radiation therapy) had no effect on sexual function. Depression was predictive at baseline and at 3 months but not at 12 months.[55]

A French case-control study evaluated sexual outcomes in 106 men with testicular cancer who were 5 years postdiagnosis and disease free.[56] The control group was matched by age and geographic location. Both testicular cancer survivors and controls had equal rates of marriage, divorce, and separation. There was, however, a significant difference between survivors and controls with regard to sexual enjoyment, desire ($P = .04$), infertility ($P < .001$), and erectile dysfunction ($P = .05$). Loss of sexual activity and reduction of sexual intercourse did not differ between groups.[56]

Similarly, a Norwegian study of more than 1,000 men with histories of testicular cancer (diagnosed and treated 4–18 years previously) found statistically significant differences on the Brief Male Sexual Function Inventory in the areas of erection, ejaculation, and desire in both younger men (aged 20–39 years) and older men (aged 40–59 years), compared to men of similar ages in the general population.[57] However, in contrast, the authors report that these statistically significant differences were small and not clinically meaningful. Men who received chemotherapy in addition to retroperitoneal lymph node dissection reported more trouble with ejaculation but no trouble in other sexual domains. As in the Dutch study described above, being single was the most important variable with respect

to sexual problems. In addition, increasing age was associated with worse sexual scores in this study.[57]

In summary, data suggest that although men with testicular cancer may report more problems with some aspects of sexual function, negative changes are mostly short term, with long-term function and activity being comparable to function and activity in the general population.

Other pelvic tumors

Nerve-sparing approaches to surgery appear to enhance recovery of erections at least to some degree after radical cystectomy [58,59] and colorectal surgery.[59,60] Although the sexual side effects of definitive radiation therapy for pelvic malignancies other than prostate cancer have not been well researched, outcomes similar to those after prostate cancer treatment would be expected when the dosage and field affect the pelvic vascular bed.

Pelvic surgeries in women include hysterectomy/oophorectomy, cystectomy, vulvectomy, and abdominoperineal resection and often involve removal of a portion of the vagina or other parts of the female genital anatomy. Older studies indicated that few women reported dyspareunia or loss of orgasmic capacity after radical hysterectomy; [61,62] however, a newer prospective study of women with early-stage cervical carcinoma who had undergone radical hysterectomy compared with control women reported severe orgasmic problems and uncomfortable sexual intercourse due to reduced vaginal size during the first 6 months after surgery. Throughout the first 2 years after surgery, the women reported persistent lack of sexual interest and lubrication.[63] Radical cystectomy for bladder cancer is more often associated with pain from reduced vaginal depth and caliber resulting from resection of the entire anterior vaginal wall. These patients may resume pain-free intercourse, normal sensation, and orgasm with the help of counseling, hormone therapy, and use of vaginal dilators.[64] Conservation of vaginal tissue may reduce some of these problems. Decreased morbidity has been reported from sparing of vulvar tissue with a partial vulvectomy versus radical vulvectomy, yet the amount of tissue resected has not been a good predictor of postoperative sexual satisfaction.[65] Rather, it is the quality of a woman's relationship with her partner that correlates with sexual function.[66] Women who undergo abdominoperineal resection may also report pain with intercourse related to loss of cushioning from removal of the posterior vaginal wall. In addition, pelvic adhesions or scarring may contribute to dyspareunia after an anterior/posterior resection. Radical resection of recurrent pelvic tumors in women (pelvic exenteration) involves partial or complete removal of the vagina and levator muscles. Vaginal reconstruction produces satisfactory function and aesthetic results in some patients.[67]

Treatment-related Factors Secondary to Systemic Chemotherapy

Chemotherapy is associated with loss of desire and decreased frequency of intercourse for both men and women. Common side effects experienced after chemotherapy include nausea, vomiting, diarrhea, constipation, mucositis, weight changes (gain or loss), and altered sense of taste and smell.[3] These symptoms often leave individuals feeling asexual. Alopecia is often one of the most distressing side effects with associated changes in body image.[68] Loss of pubic hair can also be particularly uncomfortable, which, in turn, promotes asexual feelings.

For women, cytotoxic agents are associated with vaginal dryness, dyspareunia, reduced ability to reach orgasm, and for older women, greater risk of ovarian cancer.[3,69-71] Premature ovarian failure secondary to chemotherapy or radiation brings the sudden onset of menopausal symptoms, and women who experience sudden loss of estrogen from the ovaries experience a number of associated sexual changes. Sexual symptoms associated with estrogen deprivation include vaginal atrophy, thinning of the vulvar tissues and vagina, loss of tissue elasticity, decreased vaginal lubrication, hot flashes, increased frequency of urinary tract infections, mood swings, fatigue, and irritability. In addition, for younger women with breast cancer, menopausal symptoms as a result of therapy contribute to poorer health perception and quality of life.[72] A study of the psychosocial aspects of the transitional period between the end of primary breast cancer treatment and survivorship enrolled 558 women. They were treated with surgery (either mastectomy or lumpectomy) with and without chemotherapy, and the health outcomes examined included physical, emotional, and sexual functioning, as well as mood and symptoms. Sexual functioning was worse for women who received chemotherapy, regardless of the type of prior surgery (i.e., mastectomy or lumpectomy). These problems with sexual function were likely related to problems with vaginal lubrication and a change in menopausal status, both of which are more common in those receiving chemotherapy.[73] Because of concerns over causing recurrence of breast cancer, hormone replacement therapy is often not recommended for women who have become menopausal during treatment.[74]

In women with malignancies of other types, however, estrogen replacement therapy can usually reverse many sexual problems. Providers should discuss with women the risks and benefits of hormone replacement therapy with consideration of each women's individual risk profile. The impact of menopause on sexual functioning and the

arousal phase of the sexual response in particular are often not communicated to women who struggle to understand these changes in their sexual responsiveness. Women who have graft-versus-host disease (GVHD) after bone marrow transplantation may develop vaginal strictures and adhesions that interfere with intercourse.[75]

For men, chemotherapy agents rarely play an obvious role in erectile dysfunction.[3] Some cytotoxic agents may cause nerve damage, but few reports indicate permanent loss of erections upon completion of treatment. Sexual dysfunction, including loss of desire and erectile dysfunction, is more common after bone marrow transplant, often associated with autonomic neuropathy or GVHD.[76,77] Systemic chemotherapy in men occasionally interferes with testosterone production in the testicles.[78] For those men who have damage to the testicles from chemotherapy, testosterone replacement may be necessary to restore sexual function.[3] More rarely, neurotoxic chemotherapies have been observed to interfere with ejaculation of semen at orgasm, presumably because of damage to autonomic nerves involved in the contractions of the prostate, seminal vesicles, and bladder neck.[79]

Treatment-related Factors Secondary to Radiation

Like chemotherapy, radiation can produce side effects such as fatigue, nausea and vomiting, diarrhea, and other symptoms that can reduce feelings of sexuality. In particular, pelvic radiation often irritates the intestinal lining and may cause diarrhea. The fatigue and change in bowel habits associated with radiation likely contribute to loss of libido and decreased sexual activity reported for both men and women.

For women, pelvic radiation also causes changes in the vagina. Both external-beam radiation and implants damage the vaginal epithelium and basal layer of the mucosa, leading to vaginal stenosis and vascular fibrosis. These factors can then lead to long-term sexual dysfunction, painful pelvic examinations, dyspareunia, potential gonadal toxicity, infertility, and low-birth-weight pregnancy outcomes in survivorship.[80,81] A longitudinal prospective study of sexual function and vaginal changes after radiation therapy for cervical cancer found persistent sexual dysfunction and adverse vaginal changes throughout the 2 years after radiation therapy during which the women were followed; 85% had low or no sexual interest, 35% reported moderate to severe lack of lubrication, 55% had mild to severe dysfunction, and 30% were dissatisfied with their sexual life.[82] Women who receive radiation should be educated regarding the use of vaginal dilators. Vascular compromise can be temporary or permanent.[83] For men with rectal cancer, pelvic radiation has been associated with difficulties attaining or maintaining erection.[84,85] The exact etiology of sexual dysfunction after radiation therapy remains unknown [13] but likely relates to arterial damage of the penile arteries, limiting blood flow needed for successful erection.[39] Proposed etiologies include pudendal or sympathetic nerve injury, vascular occlusion of penile arteries, or decreased levels of testosterone. Often, sexual changes are insidious, with changes occurring from 6 months to 1 year after radiation as fibrosis develops. There is a greater risk of sexual morbidity in men who already have compromised quality of erections before cancer diagnosis. Other risk factors that contribute to greater risk of sexual morbidity include cigarette smoking, history of heart disease, hypertension, pretreatment potency, and/or diabetes.[86]

Treatment-related Factors Secondary to Hormone Therapy

Hormone therapy for prostate cancer involves reducing circulating androgens as close to zero as possible. Because androgens also act in the brain to promote sexual desire, about 80% of men report a profound decrease in sexual interest, typically accompanied by erectile dysfunction and difficulty reaching orgasm.[87-90] Younger men, however, are sometimes able to continue adequate sexual function. With an increasing number of younger men diagnosed with asymptomatic but advanced prostate cancer found through prostate specific antigen (PSA) screening, more attention has been given to preventing some of the sexual morbidity of treatment. Some centers have experimented with delaying hormone therapy until the onset of symptoms,[91] giving intermittent hormone therapy as needed to suppress PSA,[92] or using a combination of finasteride and an androgen-receptor blocker instead of hormone treatments that totally eliminate androgen production.[93] It is not yet clear, however, whether men who try these modified treatment regimens are compromising the length of their survival.

Adjuvant tamoxifen therapy can increase the rate of hot flashes, night sweats, and vaginal discharge in women older than 45 years by approximately 10%. Furthermore, though rates of sexual activity with a partner did not decline, women taking tamoxifen reported slightly increased rates of difficulty with sexual arousal and achieving orgasm.[94,95]Tamoxifen for breast cancer, described as an antiestrogenic drug, actually acts like a weak estrogen in the genital tract.[96] The medication has anecdotally been reported to be associated with vaginal dryness and excessive vaginal lubrication, soreness, as well as occasional decrease in sexual desire and orgasmic delay.[95,97] The results of the few studies to examine women's actual sexual function while taking tamoxifen are not conclusive or easily compared because each study utilized different measures and statistical analyses. One study found no difference in reported sexual problems among women taking tamoxifen and women who received no systemic therapy, when

adjusted for age.[6] Another study similarly found no significant effect of tamoxifen on sexual functioning utilizing a different measure and examining the effect only in women aged 50 years and older.[74] Another study found that use of tamoxifen did not make a significant independent contribution to the prediction of impact on sexuality.[98] Results from a study with a limited sample size of women taking tamoxifen, however, noted a differential estrogen effect by age, such that an estrogen effect was seen on the vaginal smears of 34 of 49 participants and was more common in older patients ($P = .054$). The presence of an estrogen effect was correlated with negative reactions during sex ($P = .02$) and vaginal dryness or tightness ($P = .046$). This study raised the possibility that tamoxifen may have antagonist effects on the vagina of younger women and estrogen agonist effects on postmenopausal women.[99] Prospective study of sexual functioning with evaluation of physiologic status (e.g., vaginal mucosa and hormone levels) before and after introduction of systemic therapy continues to be warranted. The impact of tamoxifen on sexuality and mood is still not clearly understood.

Psychological Factors

Loss of interest in sex is likely to be secondary to psychological factors. It is not uncommon for both men and women to believe, though incorrectly, that past sexual activity, an extramarital affair, sexually transmitted disease, or abortion has caused their cancer. Some believe, again incorrectly, that sexual activity may promote a recurrence of their tumor. This misbelief is especially common in individuals with a malignancy of the pelvic or genital area. These individuals may need reassurance that cancer is not transmissible via sexual contact. Women with squamous cell carcinoma of the cervix have often read or been told that this cancer is associated with the sexually transmitted human papillomavirus.[100] Guilt about past sexual activity or concern about potential harm to a partner are issues that should be addressed in these patients. The health care provider can clarify that it is the virus and not the cancer that is transmissible through sexual contact.

Loss of sexual desire or a decrease in sexual pleasure is a common symptom of depression. Depression is 15% to 25% more prevalent in patients with cancer than in the healthy population;[101] therefore, an assessment to rule out depression is an important part of evaluating sexual dysfunction. Sometimes people present with complaints of sexual dysfunction, feeling less stigmatized having a physical medical problem than they do by acknowledging that they are depressed. Treating depression can be helpful in alleviating sexual dysfunction. Attention should be paid to the sexual side effects of antidepressants in clinical decision making. (Refer to the PDQ summary on Depression [1] for more information.)

Changes in body image may interfere with sexual desire in some cancer survivors, but the impact of disfiguring cancer treatments, such as mastectomy, has been exaggerated. For example, breast conservation may result in better self-rated physical attractiveness in women compared with mastectomy alone, but these groups of women do not differ in their sexual activity or satisfaction. On the other hand, weight gain after chemotherapy for breast cancer may be underestimated as a factor that decreases a woman's feelings of attractiveness.[102] Having an ostomy for elimination of stool or urine can also affect a man's or woman's sense of being sexually attractive. Specific coping strategies have been suggested to overcome these problems.[103]

One study attempted to explore the relationships between several relevant factors that can affect sexual function in 175 women with gynecologic cancer.[104] These factors included the following:

- Body image.
- Mood.
- Vaginal changes.
- Fatigue.
- Partner sexual function.
- Physical symptoms.
- General demographics such as socioeconomic status.

After controlling for sociodemographic factors, the authors concluded that physical symptoms/health status, partner function, and sexual self-image (called sexual self-schema) contributed significantly to sexual behavior, responsiveness, and satisfaction. In fact, the authors found that sexual self-schema actually served as a buffer between lack of sexual satisfaction and mood—that is, women with a more positive sexual self-image had fewer depressed symptoms when their sexual satisfaction was poor. Therefore, interventions that target cognitive representations may improve certain outcomes related to sexual health and functioning.[104]

The stress of cancer diagnosis and ongoing therapy can exacerbate underlying marital tensions. This can likewise

affect the sexual relationship. Men or women who do not have a committed relationship also have to face the potential trauma of being rejected by a new partner who learns about his or her history of cancer.[3] Some avoid all dating relationships out of fear of such rejection. One premorbid personality factor that may play a role in whether a man or woman stays sexually active after cancer is the sexual self-schema (i.e., whether an individual regards his or her own sexuality in a positive light). Women with negative sexual self-schemas were less likely to resume sex or have good sexual function after treatment for gynecological cancer.[105] One of the most important factors in adjusting after cancer is the person's feelings about his or her sexuality before cancer. That does not mean, however, that this is not a good opportunity to help a person explore those issues.

Pediatric Cancer Survivors

A cross-sectional survey of 599 survivors of pediatric cancer from three U.S. institutions in Southern California and the Midwest was conducted.[106] Types of cancer included the following:

- Leukemia (38%).
- Hodgkin/non-Hodgkin lymphoma (25%).
- Central nervous system/brain tumor (13%).
- Solid and soft tissue tumors (12%).
- Wilms tumor (4%).

Respondents had to be 21 years of age or younger at diagnosis and had to be 18 to 39 years of age at the time of the study. The mean age at diagnosis for the sample was 11 years, and the mean number of years since diagnosis was 16. The mean age of the sample was 27 years. Overall, 52% of women and 32% of men reported some problems in sexual functioning, with 43% citing at least one specific symptom. Erections were reported as being somewhat or very much of a problem by 8.5% of men. Becoming sexually aroused was reported as being somewhat or very much of a problem by 17% of women and 7% of men, and a lack of interest was reported by 19% of women and 10% of men. Emotional and physical comorbidities were more strongly associated with problems in sexual functioning.

Predictors of sexual problems in women included being married and reporting health problems; in men, lower income and reporting health problems were significant predictors.[106] While more women reported problems with sexual symptoms, men reported more distress. Limitations of this study include that it was a cross-sectional survey subject to selection/response bias. Results of this study cannot directly link sexual sequelae to a cancer diagnosis or to cancer treatment. However, particularly for men, the extent of sexual dysfunction reported is not generally seen in a cohort this young.

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Assessment of Sexual Function in People With Cancer

No clear guidelines address sexuality during the stages of disease and its treatment. When therapeutic decisions are being made, providers should offer education and information to patients, ideally with the partner present, regarding known risks of sexual morbidity associated with cancer treatments. Oncology professionals should assist patients and their partners by asking specific open-ended questions to validate the importance of sexual health concerns, thus providing an environment in which the patient and couple are encouraged and feel safe to express personal concerns. Assessment should be sensitive to the subtle ways in which changes in sexual function affect men's self-image and masculine identity.[1] Providers should examine their own thoughts and feelings regarding sexuality. When providers are not comfortable addressing issues of sexuality, their patient's concerns should not be ignored or dismissed. Referrals should be offered to alternate resources. Although some patients may not want to discuss their sexual health, providers should at least offer the option, conveying that sex is an appropriate topic to cover during future visits.

Because sexual function is one important aspect of quality of life, the follow-up oncology visit is a key opportunity for health care providers to assess whether a cancer patient is experiencing sexual problems. Although it would be ideal if an oncologist carried out the sexual assessment, time constraints and lack of training or comfort in discussing sexual issues often interfere with this goal. Furthermore, many people who have finished their cancer treatment have their routine follow-up care with a primary practitioner rather than an oncology specialist. At least in oncology settings, it may be helpful to designate and train a member of the team, such as an oncology nurse or social worker, as the expert on sexuality issues. That provider can take responsibility for asking about a variety of quality-of-life issues, including relationships and sexuality. A minimal sexual assessment might consist of asking the following question: "Many cancer survivors notice changes or problems in their sex lives after cancer treatment. Do you have any problems or concerns related to sexuality?" Simple problems can be handled with immediate reassurance or advice, but the oncology team should also build a network of specialists willing to help cancer patients with sexual issues, including mental health professionals trained in sex therapy, gynecologists familiar with women's concerns about hormone replacement or dyspareunia, urologists who specialize in treating male sexual dysfunction, and infertility specialists who can treat younger patients who are interested in having children.

The literature contains a number of articles and resources that address sexual assessment,[2] with many specific to cancer patients.[2-5] The Kaplan model provides a useful interview guide to evaluate sexual problems in healthy and medically ill individuals, focusing on the chief complaint, sexual status, psychiatric status, family and psychosocial history, relationship assessment, summary, and recommendations.[6] Kaplan's model has been applied to oncology settings, with brief descriptions of the assessment for each part of the interview.[3,7] The PLISSIT

(permission, limited information, specific suggestions, and intensive therapy) model [8] is another model of assessment and intervention commonly used as a framework for sexual rehabilitation in cancer care and medical illness.[5,9-12]

General Factors Affecting Sexual Functioning Evaluated in Assessment

Once a possible sexual problem has been identified, the most important assessment tool for the oncology health provider is a clinical interview with an individual man or woman, or with a couple.[13] The following brief list of factors known to impact current sexual functioning should be included in an assessment; the patient's specific sexual concerns or needs at the time dictate the approach and content of the discussion.

Current sexual status

In the evaluation of an individual's sexual function, the initial phase of assessment serves to clarify the nature of the individual's problem and/or complaint. A variety of aspects of current sexual function should be addressed, including the frequency of experiencing spontaneous desire for sex; ease of feeling subjective pleasure with sexual stimulation; energy for sexual activity; and signs of physiological arousal, including the ability to achieve and maintain a firm erection for a man, and vaginal expansion and lubrication for a woman. The ability to reach an orgasm is another important measure of sexual function. It is helpful to ask what types of sexual stimulation can trigger an orgasm (i.e., self-touch, use of a vibrator or shower massage, partner caressing, oral stimulation, or intercourse). Pain in the genital area that occurs with sexual activity should be described in detail: "Where is the pain? What does it feel like? What kinds of sexual activity trigger it? Does it happen every time? How long does it last?" When these lines of inquiry elicit a sexual problem, the interviewer should ask when the problem began, especially whether a cancer diagnosis or particular treatment occurred close in time to onset of the problem. Because many people who have cancer take prescription medications that can interfere with sexual function, including antihypertensives, antidepressants, or psychotropic medications, the interviewer should find out whether a new medication or change of dosage was prescribed at the problem's onset.

Premorbid sexual functioning

An individual's past (pre-illness) sexual development, preferences, and experience are vital to assessment of sexual status. The level of sexual functioning before diagnosis and treatment, interest, satisfaction, and importance of sexual functioning in the relationship all influence the patient's potential distress related to current sexual status. Individuals who have already experienced sexual difficulties may be especially vulnerable to the effects of treatment.[14] Clinicians should be careful not to make assumptions regarding the patient's previous sexual experience or the importance of sexual expression.

Psychosocial Aspects of Sexuality

Relationship status

The patient may or may not have an available partner at the time of diagnosis. Sexuality should be taken no less seriously by the clinician or the patient if there is no partner. For patients with a partner, the clinician should consider and discuss the duration, quality, and stability of the relationship before diagnosis. Additionally, as many patients fear rejection and abandonment, the clinician should inquire about the partner's response to the illness and the patient's concerns about the impact of treatment on the partner.[15-17] Partners share many of the same reactions as patients in that their most significant concerns typically relate to loss and fear of death. Moreover, the partner's physical, sexual, and emotional health should be considered relative to his/her previous and current sexual status in a complete assessment. A clinician should recognize that most couples experience difficulty discussing sexual preferences, concerns, and fears even under ideal circumstances and that sexual communication problems tend to worsen with illness and threat of death.

Psychological status

The affective spectrum during cancer treatment ranges from disbelief to clinical depression and typically changes over time. Anxiety and depression are the two most common affective disruptions among patients with cancer and both have been found to have deleterious effects on sexual functioning.[3-5,7,18] A clinician should be aware of current mental status and any history of depression or other psychiatric disorder, previous psychotherapy, treatment with psychotropic medication, and/or hospitalizations. Current use of psychotropic medications should also be reviewed with respect to impact on sexual function. Cancer treatment can produce changes to the body that

negatively impact body image and self-esteem.[4,5,19] Commonly, patients have difficulty seeing themselves as sexually attractive during and after treatment. Identifying body-image disturbances is important to incorporate into goals of care and rehabilitation. Frequently, the couple experiences changes of social roles during treatment. An individual's identity and sense of worth may be threatened when role changes occur.[4,15] The partner's participation in the patient's physical care often negatively impacts feelings of sexuality. Younger couples, more than older couples, may be vulnerable to problems with playing alternative or new domestic roles and experiencing the myriad life and financial stressors associated with treatment.[4]

To better illustrate the relationship between sexual health and psychological health, numerous sexual, physical, and psychological measures were examined in a cross-sectional study of 186 partnered women who had gynecologic cancers.[20] Diagnoses included endometrial, ovarian/peritoneal, cervical, and vulvar cancers. Most women had stage I to stage III cancers and were white, college educated, and married. Their mean age was 55 years. Sexual morbidity was defined as a summed score of the following five factors:

- Appearance/desire (seven items).
- Satisfaction/activity (six items).
- Arousal (seven items).
- Lubrication (four items).
- Pain (four items).

Sexual morbidity was moderately and significantly correlated with depression ($r = 0.34$) and traumatic stress ($r = 0.30$). It was also low-moderately correlated with body image ($r = 0.25$); and with both components of the Medical Outcomes Study—Short Form 12: physical health (activity interference/general health, $r = 0.34$) and mental health (calm/downhearted, energy, emotional problems, $r = 0.25$). Sexual morbidity was moderately to strongly and significantly correlated with fatigue ($r = 0.44$). Sexual morbidity also contributed uniquely and significantly to depression, accounting for 48% of the variance; body change stress, 26% of the variance; and psychological quality of life, 31% of the variance. The authors concluded that addressing sexual morbidity may improve psychological health.[20]

Medical Aspects of Sexuality

The clinician should ascertain past medical history with a particular emphasis on other concurrent medical illness for which the patient is receiving treatment. Comorbidity contributes to risk of sexual dysfunction and additional decrease in social and role functioning, mental health, and health perceptions. Medical illnesses that impact the endocrine, vascular, and nervous systems are all known to have a potential deleterious effect on the sexual response cycle.[13,21,22] Diabetes, hypertension, vascular disease, multiple sclerosis, and many other disorders impact sexual function, particularly the quality of erections in men. Two textbooks extensively review the impact of chronic illness and disability on sexual function.[13,22] In addition, with the growing body of evidence demonstrating the severity and chronicity of fatigue in cancer survivors, the co-existence of cancer-related fatigue may be a major barrier. In a descriptive cross-sectional study, fatigue was significantly and moderately correlated with all sexual functioning and satisfaction measures in 175 women with gynecologic cancer.[23] Therefore, assessing and addressing cancer-related fatigue, even in long-term survivors, is important.

Lifestyle factors, including smoking and substantial alcohol consumption, are also risk factors for sexual morbidity. In men, cigarette smoking may induce vasoconstriction and penile venous leakage.[21] In large amounts, alcohol is a strong sedative-hypnotic, producing decreased libido and transient erectile dysfunction.[21]

Pharmacologic treatment for cancer and chronic illness in general is often a necessary and integral component of health maintenance. Some pharmacologic treatments, however, may have direct or indirect deleterious effects on sexual function through multiple physiologic and psychologic pathways. Pharmacologic agents that may negatively affect sexual response are addressed in the section on pharmacologic effects. A number of resources provide further delineation of the mechanisms for changes in sexual function associated with these agents and include listings of specific medications and known effects on sexual function.[4,24-26]

Brief questionnaires that measure sexual dysfunction may be helpful, particularly when screening larger groups of cancer patients for sexual dysfunction or when conducting research on sexuality as an aspect of quality of life. The International Index of Erectile Function (IIEF, 15 items) and the Brief Male Sexual Function Inventory (BMSFI, 11 items) are well-validated scales measuring aspects of sexual function and satisfaction in men.[27,28] Sexual problems can also be identified with a briefer five-item scale, the Sexual Health Inventory for Men (SHIM), which

is a validated self-report scale that can be used to identify erectile dysfunction in a variety of clinical settings.[28] For women, there are several brief measures with established psychometric properties that assess sexual functioning and satisfaction: the Brief Index of Sexual Functioning for Women (BISF-W, 22 items), the Sex History Form (SHF, 46 items), the Changes in Sexual Functioning Questionnaire (CSFQ, 35 items), the Derogatis Interview for Sexual Functioning (DISF/DISF-SR, 25 items), the Female Sexual Function Index (FSFI, 19 items), and the Golombok-Rusk Inventory of Sexual Satisfaction (GRISS, 28 items).[13,29,30] These scales vary in their reliability, validity, method of attainment (i.e., patient vs. clinician rates; structured vs. semistructured), type and number of symptoms assessed, and time frame of assessment. To accurately reflect changes over time, one must obtain systematic assessment of premorbid, baseline, and follow-up levels of sexual function and satisfaction.

In addition to paper-and-pencil self-report measures of sexuality, some medical evaluations of the adequacy of the physiological response are available.[31] For men, some of the more useful evaluations include the Rigiscan, a computerized electronic instrument that measures the adequacy of nocturnal erections; penile ultrasound studies to document hemodynamics of erection; and hormonal assays. In women, the use of the vaginal maturation index to measure estrogenization, a careful pelvic examination to identify sources of pain that occur during sexual activity, and hormonal assays are most common. More sophisticated measures of vaginal blood flow or sensory thresholds have been studied but have not gained wide acceptance.

Review of the literature highlights the need for prospective studies with longer-term follow-up, validated measures, and larger sample sizes. In particular, issues of sexual recovery in women have received too little clinical attention and research.

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Pharmacological Effects of Supportive Care Medications on Sexual Function

The following sections describe the effects of various commonly used medications on sexual function in people with cancer. People undergoing cancer treatment are often treated with multiple medications that can cause diminished desire or other difficulties in sexual functioning, which can add to the impact of surgery, radiation, and chemotherapy on sexuality. Medications may adversely affect one or more of the physiologic mechanisms (i.e., vascular, hormonal, neurologic) that underlie normal sexual function. Drug therapy may also affect sexual functioning indirectly through concomitant effects on mental alertness, mood state, and/or social interactions. The evaluation of sexual problems in people with cancer must, therefore, be comprehensive and attuned to the multiple etiologies of these difficulties. The following sections may be helpful in identifying some of the possible medication side effects, though more than one may play a role in an individual.

Effect of Opioids on Sexual Function

Reduced libido is a well-known phenomenon for those using heroin or participating in a methadone maintenance program. Unfortunately, this effect is poorly understood by clinicians prescribing opioids for pain. Animal studies confirm that opioids lower testosterone levels and suppress sexual function in males.[1] Early case studies of persons using heroin or methadone described diminished libido, sexual dysfunction, reduced testosterone levels in men, and amenorrhea in women.[2-7][Level of evidence: II] Two mechanisms are thought to be responsible for the reported reduction in libido associated with opioid use. Opioids inhibit the production of gonadotropin-releasing hormone, subsequently decreasing the release of luteinizing hormone (LH), thus decreasing the production of testosterone. Opioids also produce hyperprolactinemia, which causes negative feedback on the release of LH and decreases the production of testosterone.[8][Level of evidence: IV] Opioids are known to alter the normal function of the hypothalamic-pituitary-gonadal axis.[9][Level of evidence: II] These effects resolve after the opioid has been discontinued. Other case reports of patients receiving opioids for relief of chronic pain suggest these same findings.[10,11][Level of evidence: III][12][Level of evidence: II] Another case-control study examined the effects of chronic oral opioid administration in survivors of cancer and, consistent with the research on intrathecal administration, found marked central hypogonadism among the opioid users with significant symptoms of sexual dysfunction, depression, and fatigue.[12] Although the limited research that has examined the relationships among sexual functioning, chronic pain, opioid therapy, and testosterone levels has been predominantly evaluated in men, anecdotal clinical experience supports similar relationships in women. Empirical support has been documented for women in a study that examined the endocrine consequences of long-term intrathecal administration of opioids. Reduced libido was reported in 95% of the men and 68% of the women, with significant reduction in serum LH for both groups and in serum testosterone for the men. All of the premenopausal women (n = 21) developed either amenorrhea or an irregular menstrual cycle, with ovulation in only one woman.[13][Level of evidence: II]

The long-term effects of reduced testosterone and amenorrhea are not well known. Sexuality is an important component of one's quality of life, especially for cancer survivors, but also for some people with advanced disease. Patients may report a history of changes in libido and sexual dysfunction. If these changes are distressing to the patient, serum total- and free-testosterone levels and prolactin levels may be obtained.[14] Should the patient seek improvement in libido and performance, treatment is often empirical, keeping in mind that there are many potential causes of changes in sexual function. Treatment options may include using nonopioids for pain, adding adjuvant analgesics in the hope that the opioid dose may be reduced, or replacing testosterone through injections, a patch, or gel if not contraindicated.[15] More research is needed to understand the relationship between opioids and sexual function, as well as the most effective treatment strategies.

Selective Serotonin Reuptake Inhibitors

Decreased sexual desire is a frequent symptom of depression, and sexual impairment in depressed patients has been consistently confirmed in controlled studies.[16,17][Level of evidence: II] Continued recognition of the difficulty in discerning the subjective complaints that are a part of the depressive syndrome, the consequences of treatment, a pre-existing sexual dysfunction, or a combination of these factors is needed. Approximately one-third of depressed patients without medication treatment report reduced sexual desire, anorgasmia, delayed ejaculation, or erectile dysfunction.[18] Selective serotonin reuptake inhibitors (SSRIs), tricyclics, monoamine oxidase inhibitors, and lithium have all been associated with sexual dysfunction.[19,20]

Sexual desire is mediated through the central nervous system by the reception of sensory stimuli and the subsequent interpretation through the limbic system and prefrontal cortex.[21] Additionally, the hypothalamic and preoptic nuclei contribute to the mediation of this process. Serotonin inhibits hypothalamic arousal postsynaptic receptors resulting in the release of excitatory neurotransmitters. These neurotransmitters are responsible for the activation of the erectile centers of the spinal column. Upon activation of the erectile centers, subsequent erection, orgasm, and detumescence occur in males, whereas genital vasocongestion, vaginal lubrication, and clitoral enlargement occur in females.[22] Physiologically, serotonin is stored in synaptosomal vesicles awaiting another impulse for release. SSRIs inhibit this uptake mechanism, which results in the pooling of serotonin in the synaptic space.[21,23] The excess serotonin causes the postsynaptic receptors to down-regulate, resulting in decreased stimulation of the lower erectile centers. It is this action that is thought to be the principal mechanism for SSRI-induced sexual dysfunction.

There are no well-controlled studies that evaluate the effects of SSRIs on sexual function within the oncology patient population. There are several studies, however, that have examined the effects of fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft) on sexual function in patients being treated for depression or obsessive-compulsive disorder. There are few data regarding the prevalence of sexual dysfunction with the use of citalopram (Celexa) in the treatment of depression. Sexual dysfunction from SSRIs has generally been reported to affect approximately 1% to 15% of patients in clinical trials of these medications in physically healthy depressed patients. Other studies, however, report significantly higher rates of sexual dysfunction that may more accurately reflect the incidence typical of clinical practice. A large-scale retrospective nonrandomized comparison trial of 596 psychiatric outpatients (167 men, 429 women) treated for at least 6 months with sertraline (n = 170), fluoxetine (n = 298), venlafaxine (n = 36), or paroxetine (n = 265) found that symptoms of sexual dysfunction were spontaneously reported by approximately 20% of patients overall and were more common in men (23.4%) and married individuals of both genders. The rates of sexual dysfunction associated with each of the SSRIs were the following: sertraline (16%), fluoxetine (20%), paroxetine (22%), and venlafaxine (38%). For this sample, the most common sexual symptoms reported were orgasmic delay or anorgasmia, followed by decreased desire and arousal difficulties.[24][Level of evidence: III] A prospective multicenter study of 344 patients (152 men, 192 women) with mixed psychiatric disorders treated with SSRIs and systematic inquiry of sexual dysfunction by the physician found the frequency of sexual side effects was highest for paroxetine (65%), followed by fluvoxamine (59%), sertraline (56%), and fluoxetine (54%).[25][Level of evidence: II] Paroxetine produced significantly greater delay of orgasm or ejaculation (48%) and more frequent erectile dysfunction and vaginal lubrication difficulties than sertraline (37% and 16%), fluvoxamine (31% and 10%), or fluoxetine (34% and 16%). Loss of libido and anorgasmia were more severe in women, though men reported a greater frequency of sexual dysfunction. The effects of SSRIs are dose related and may vary among the group. The incidence of sexual dysfunction obtained by patient self-report does not appear to reflect the true incidence of sexual dysfunction associated with antidepressant therapy, and systematic inquiry by providers is needed as sexual dysfunction may be an unrecognized cause of noncompliance.[26] Two critical reviews of the effects of SSRIs on sexual function are available.[26,27][Level of evidence: IV]

For individuals with premature ejaculation, SSRIs provide an effective treatment. In a double-blind placebo-controlled trial of men with lifelong rapid ejaculation, paroxetine delayed ejaculation the most, and fluvoxamine delayed ejaculation the least. Daily doses of 20 mg of paroxetine and 20 mg of fluoxetine may be regarded as effective treatments for lifelong rapid ejaculation.[28][Level of evidence: I] Cancer patients treated with these medications in clinical situations may have higher rates of anorgasmia, decreased sexual desire, and other problems, possibly because these medications compound the difficulties cancer patients encounter from multiple etiologies. There are several possible interventions in the management of SSRI-induced sexual dysfunction. An obvious, though not always appropriate, possibility is to decrease the dosage of the SSRI. Altering the timing of SSRI administration, either by delaying doses until after intercourse or dosing immediately before intercourse,[29][Level of evidence: IV] may be an effective intervention. There are published data to suggest a drug-holiday intervention over the weekend can improve the sexual dysfunction induced by SSRIs.[30][Level of evidence: II] Another possibility is the addition of another medication to help in the control of SSRI-induced sexual dysfunction or consideration of another antidepressant with less known sexual side effects. In a randomized, double-blind, multicenter trial comparison of sustained-release bupropion (bupropion SR) and sertraline, both were found to be similarly efficacious in the treatment of outpatients with moderate-to-severe depression. There was a significantly greater percentage of sertraline-induced sexual dysfunction (63% and 41% of men and women, respectively), compared with bupropion SR–induced sexual dysfunction (15% and 7%, respectively).[31][Level of evidence: I]

A definitive treatment has not been established for SSRI-induced sexual dysfunction in males or females. The oncology patient population presents with significantly more obstacles in the management of sexual dysfunction, as compared with patients whose symptoms are being managed with SSRIs for depression alone. The etiology of sexual dysfunction in cancer patients is multifactorial and complex. The above data are intended to provide

practitioners and patients with possible options in the management of SSRI-induced sexual dysfunction.

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Treatment of Sexual Problems in People With Cancer

Although research is beginning to clarify the frequency and types of sexual problems people with cancer experience, few treatment programs for sexual dysfunction in cancer patients have been designed or tested. Programs that integrate medical and psychological modalities aimed at the treatment of sexual dysfunction in those who have had cancer are warranted. Additionally, these programs must be cost-effective and accessible to people with cancer.

Many patients are fearful or anxious of their first sexual experience after treatment and can often begin a pattern of sexual avoidance. If the patient is concerned about sending mixed signals to his or her partner, this can lead to avoidance of general intimacy and touch. The partner may also contribute to the generalized avoidance of intimacy through his or her reluctance to initiate any behavior that may be perceived as pressure to be more intimate or may contribute to any potential physical discomfort from greater expression of physical intimacy. Providers need to

reassure patients and their significant others that even when intercourse is difficult or impossible, their sex lives are not over. The couple can give and receive pleasure and satisfaction by expressing their love and intimacy with their hands, mouths, tongues, and lips. Providers should encourage the couple to express affection in alternative ways (e.g., hugging, kissing, nongenital touching) until they feel ready to resume sexual activity. The couple should be encouraged to communicate honest feelings, concerns, and preferences.

If a man cannot attain an erection firm enough for penetration, and/or if intercourse is painful for a woman, some couples may be willing to find alternative ways to bring each other to orgasm and express sexual intimacy. Sensate focus exercises of noncoital pleasuring,[1,2] based on principles of sensuous massage, give couples an experience of sexual expression that allows them to be physically close and intimate without pressure and anxiety that can be associated with anticipation of intercourse. The structure and ground rules of sensate focus can help bypass performance anxiety (self-consciousness and self-evaluation) and enable the couple to lose themselves in the current experience of pleasurable touch. These exercises also help the couple communicate about potentially problematic or emotionally sensitive areas of the body. Providers should determine a couple's openness to modification of their sexual technique.

As many patients will experience anticipatory anxiety about re-establishing sexual intimacy with their partner and potential uncertainty of their own sexual response, the potential advantages of self-stimulation can be explored. Self-stimulation has the advantage of allowing the individual to become comfortable with his/her sexual response and arousal without the added pressure of performance anxiety commonly heightened by concern for their partner's pleasure, reactions, concerns, and/or fears. For many individuals, a cognitive reframing of masturbation to self-stimulation or self-pleasuring allows the individual to accept this activity as part of the process in sexual rehabilitation. For others, this behavior may still be a resilient and persistent taboo for cultural and religious reasons.

For those couples who wish to have sexual intercourse, sexual positions that place no weight on a scar or ostomy and positions that allow better control of depth of penetration can be explored. The side-by-side position (spooning) in which the man is behind the woman, or the L-shaped position, with both partners lying down, torsos at right angles and legs entwined, are two possibilities. Comprehensive pamphlets on sexuality and cancer, for both men [3] and women,[4] provide illustrations of sexual positions and other self-help information.

For patients with colostomies or ileostomies, pamphlets are available from national organizations related to resuming sexual activity including topics such as sex and the female ostomate, sex and the male ostomate, and gay and lesbian ostomates. Providers can educate patients on limiting food intake before anticipated sexual activity, watching the types of food consumed, and planning times for intimacy when a bowel movement is less likely. Although the ostomy pouch is typically changed when about one-third full, patients should be taught to empty the pouch sooner when anticipating sexual intimacy. Patients may fear that the ostomy bag will interfere with sexual intimacy, become dislodged, or cause damage to the stoma. An empty and flat ostomy bag will not become dislodged from the stoma and can be rolled up or taped down so that it will not get in the way of sexual intimacy. Decorative covers may also be worn.[5,6][Level of evidence: IV] A much greater selection of products for ostomates exists today than in years past, including disposable pouches, reusable pouches that empty from the bottom or top while still attached, pouches with filters to control odors, and pouches that hang sideways instead of down for physical activity. Patients concerned about potential odor can use deodorant tablets or liquids in the bottom of the pouch or as recommended by the manufacturer.[6]

Providers can help educate couples by offering practical suggestions to overcome changes in responsiveness to sexual stimulation. Couples should allow plenty of time for sexual expression with sufficient foreplay to develop the fullest possible sexual arousal. For some couples, early morning may be a good restful time for sexual expression. Conditions that facilitate sexual pleasure should be explored and may include relaxation, dreams, fantasy, deep breathing, and recalling positive experiences with the partner.

Erection problems are the most common sexual dysfunction for which men seek help after cancer treatment. Many men with erectile dysfunction are able to have an orgasm with oral or manual stimulation; many partners are satisfied and orgasmic with noncoital stimulation. If the desire for intercourse remains, there are several treatment options available for erectile dysfunction, depending on the cause and degree of dysfunction. Only a small percentage of men with erection problems seek help.[7,8]

With the advent of sildenafil (Viagra), a phosphodiesterase-5 (PDE-5) inhibitor used to treat erection problems,[9] the percentage of men who seek treatment for erection problems has increased. Despite the publicity about the effectiveness of sildenafil, the drug works best in men with the mildest forms of erectile dysfunction. Many men will be unable to achieve adequate erections by taking this drug alone. The use of sildenafil enables about 72% of

men with nerve-sparing prostatectomy and 15% of men with non–nerve-sparing prostatectomy to achieve erections sufficient for vaginal intercourse. Radical prostatectomy can result in nerve injury, in addition to vascular and smooth muscle damage. Injury and prolonged flaccidity of the penis can result in hypo-oxygenation of the penile tissue, further complicating structural integrity and compromising future erectile function.[10] The process of healing after surgery takes approximately 3 to 6 months, and full recovery can be expected at 1 year postsurgery. However, during this time, it is important for men to continue to have erections to keep the tissue healthy with adequate blood flow and to improve their future ability to have adequate erections. Therefore, early penile rehabilitation is recommended.[11]

In one nonrandomized study, 84 men who had undergone nerve-sparing radical prostatectomy could choose whether to start early rehabilitation or to wait.[12] In this study, *early* rehabilitation was defined as beginning activities to achieve erections within 6 months of radical prostatectomy, while *delayed* rehabilitation was defined as starting such activities more than 6 months after radical prostatectomy. Rehabilitation consisted of the use of sildenafil citrate, 100 mg, on four occasions. If erection sufficient for vaginal penetration was not achieved, then men were encouraged to use penile injections to obtain erections. Those who responded well to sildenafil citrate continued using this agent. Forty-eight men chose early rehabilitation, and 36 men chose delayed rehabilitation. The men were matched for age, comorbidities, and baseline erectile function, with a mean age of 58 years. Outcomes were evaluated with the International Index of Erectile Function (IIEF) and were assessed presurgery and at 1 and 2 years postsurgery. Trends for better scores on the IIEF were seen at 1 year, but statistically significant differences were not realized until year 2, with significantly more men in the early rehabilitation arm having unassisted functional erections (48% vs. 33%) and more men in the early group having functional erections with sildenafil (76% vs. 45%). Twenty-four percent of men in the early rehabilitation group had normal erectile function scores as measured by the IIEF, compared to 8% of men in the delayed rehabilitation group.[12][Level of evidence: II] Some data suggest that about 12% of sildenafil responders lose efficacy by 3 years.[13][Level of evidence: III]

In a study of brachytherapy in the treatment of localized prostate cancer, sildenafil improved potency in 62% to 70% of patients.[14] Patients who were not being treated with androgen therapy had a significantly better response.[15] Similarly, of men who became impotent after brachytherapy for prostate cancer,[16] 85% to 88% responded with improved erectile function when taking sildenafil. Reported potency rates after prostate brachytherapy are high; a 3-year follow-up study demonstrated that 80% of patients were able to have erections adequate for satisfactory sexual activity with or without sildenafil.[17][Level of evidence: II] Sildenafil has also improved erectile function for patients with partial parasympathetic nerve disruption from rectal surgery.[18][Level of evidence: I][19][Level of evidence: II] No other treatment for erectile dysfunction has a high rate of patient acceptance. Sildenafil has been studied in a novel primary prevention modality using nightly administration after a bilateral nerve-sparing prostatectomy. This approach effected a sevenfold improvement in return of spontaneous, normal erectile function 2 months after discontinuation of the drug.[20][Level of evidence: IV] The authors state that this effect appears to be mediated by properties unique to sildenafil that include improved endothelial function and neuronal regeneration and neuroprotection.[20]

Published data also suggest that early use of sildenafil after radical retropubic prostatectomy may preserve intracorporeal smooth muscle content;[21][Level of evidence: II] although this effect on the return of potency is not known, maintaining the pro-erectile ultrastructure is integral to rehabilitating erectile function after radical retropubic prostatectomy.[21] Data on the efficacy of early postoperative erectile treatment rely on very few randomized trials. Because the natural recovery of erectile function has been reported to take as long as 2 years,[22] larger randomized trials with at least 2 years of follow-up are needed before definitive conclusions can be drawn about the true efficacy of rehabilitative sexual therapy for postoperative erectile function.

There are three PDE-5 inhibitors approved by the U.S. Food and Drug Administration (FDA) on the market: Viagra (sildenafil), Levitra (vardenafil), and Cialis (tadalafil). Although all three of these oral medications are PDE-5 inhibitors, they are not the same. No head-to-head comparison trials have been published. It appears, however, that all three agents are similar in efficacy, helping 60% to 70% of patients with erectile dysfunction.[23][Level of evidence: I][24,25] However, comparisons of the efficacy of the PDE-5 inhibitors are complicated by the heterogeneity of the populations studied, the varied primary cancer therapies employed, different timing in measuring outcomes in the clinical trials, and variance in the endpoints used to determine efficacy. Furthermore, most of these trials were industry sponsored.

The major contraindications for use of a PDE-5 inhibitor are concurrent use of nitrates or the alpha-blockers terazosin (Hytrin) and doxazosin (Cardura). The major difference in the three approved inhibitors is that tadalafil has a considerably longer serum half-life, which provides both a larger window of opportunity and potential side effects.[24,25] There is far more research on the use of sildenafil than on the use of the other PDE-5 inhibitors in

oncology patients, as it was approved in 1998; vardenafil and tadalafil were approved in 2003. Tadalafil was investigated in the treatment of erectile dysfunction following bilateral nerve-sparing radical retropubic prostatectomy. Results from this randomized, double-blind, placebo-controlled, multicenter study found that 71% of patients randomly assigned to receive tadalafil reported improved erections.[26][Level of evidence: I] Vardenafil had been investigated in the treatment of erectile dysfunction after radical retropubic prostatectomy and following nerve-sparing radical prostatectomy.[27,28][Level of evidence: I] In post–radical retropubic prostatectomy patients, the average intercourse success rate per patient receiving 20 mg of vardenafil was 74% in men with mild to moderate erectile dysfunction and 28% in men with severe erectile dysfunction, compared with 49% and 4% for placebo.[27] Patients receiving 10-mg and 20-mg doses of vardenafil following nerve-sparing radical prostatectomy reported significantly greater intercourse satisfaction, orgasmic function, and overall satisfaction rate with hardness on the IIEF, compared with those receiving placebo.[28]

Therapies such as penile injections, vacuum devices, or intraurethral medication have extremely high dropout rates, and of men who seek help at clinics for erectile dysfunction, only about one-third feel long-term satisfaction, despite trying a mean of two different treatment modalities.[29-31][Level of evidence: II][32] For men who have a suboptimal response to oral therapies after radical retropubic prostatectomy, the use of combined intracorporal injection (ICI) and a PDE-5 inhibitor has been shown to improve erectile function. One retrospective study found that among men who experienced erectile dysfunction after nerve-sparing retropubic prostatectomy, 68% who combined ICI with either sildenafil or vardenafil reported improved erectile function. On follow-up, 36% of these patients used ICI therapy only intermittently, as they reportedly felt that this was adequate for good results.[33][Level of evidence: III]

Rates of long-term satisfaction are superior for penile prosthesis surgery,[34-36] but with less invasive and permanent treatments available, fewer men choose this treatment modality, particularly after undergoing intensive cancer therapy.[37] The role of the man's partner in prompting him to try a treatment or to keep on using it is also poorly understood. When erectile functioning is impaired, counseling should initially focus on obtaining sexual pleasure and satisfaction without erections or intercourse. For men with postsurgical erectile dysfunction, there is the possibility for improved function over time as nerves may potentially regenerate for up to 2.5 years after surgery.[6] Providers should educate patients that opting to use no medical intervention to restore erections is also a valid choice. Comprehensive reviews of the current management of erectile dysfunction are available.[38-42] Also, several authors [39,43,44] provide further discussion on the management of inhibited sexual desire and other male sexual dysfunctions.

When women experience changes in arousal, most notably vaginal dryness and irritation, vaginal moisturizers (e.g., Replens) and water-based lubricants (e.g., Astroglide and K-Y Liquid) should be suggested, especially in women who cannot use estrogen replacement. The approval of the estradiol-releasing vaginal ring (Estring), containing a slow-release preparation, 2 mg of micronized 17-beta-estradiol, may also provide a less risky alternative to systemic estrogen replacement for women with postmenopausal vaginal atrophy.[45][Level of evidence: I][46] Estring has demonstrated a decreased recurrence of urinary tract infections in postmenopausal women and a significant maturing effect on vaginal and urethral mucosal cells, decreasing the urogenital symptoms of postmenopausal women.[47][Level of evidence: I] Another alternative to local estrogen replacement is the first-available 25-µg 17-beta-estradiol vaginal tablet (Vagifem). A study comparing Vagifem tablets with 1.25-mg conjugated equine estrogen vaginal cream (Premarin) found both to be equivalent in relieving symptoms of atrophic vaginitis, with patients who received Vagifem experiencing less endometrial proliferation or hyperplasia. This study also found that women rated vaginal tablets more favorably than vaginal cream.[48][Level of evidence: I] The long-term safety of the use of vaginal estrogens by women who should avoid estrogens has not been determined.

If changes in arousal are also associated with the endocrine changes of menopause, the option and evaluation of hormone replacement should be discussed. Some women may experience discomfort with penetration around the vaginal entrance and can learn to relax the pubococcygeus muscles with Kegel exercises.[38,49,50] Women who have lost vaginal depth or caliber as a result of pelvic surgery, radiation therapy, or graft-versus-host disease may also benefit from a program of inserting vaginal dilators of gradually increasing sizes, and at the same time, learning exercises to better relax the muscles surrounding the vaginal entrance.[38,51] Some women may also benefit, at least in the short term after cancer treatment, from lubricant or anesthetic gels to prevent pain in tender, dry vulvar areas.[52][Level of evidence: I] The FDA approved a nonpharmaceutical device to aid sexual arousal in women. The EROS clitoral therapy device (EROS-CTD) creates a gentle suction over the clitoris to increase blood flow and sensation. This device is only available by prescription and is clinically indicated for the treatment of female sexual dysfunction. It is expected to be particularly effective in postmenopausal women, women who have had hysterectomies, and those women who have surgically induced menopause.[53] The efficacy of EROS therapy has been supported by several small pilot studies,[54][Level of evidence: III][55,56] one of which specifically examined

its efficacy in alleviating the symptoms of sexual dysfunction among women with a history of irradiated cervical cancer.[55][Level of evidence: II] Three months posttherapy, this study found statistically significant improvements in all domains evaluated, which included increased sexual desire, arousal, lubrication, orgasm, sexual satisfaction, and reduced pain. Additionally, follow-up gynecological examinations revealed improved vaginal elasticity, mucosal color, and moisture and decreased bleeding and ulceration. Randomized controlled trials are warranted to fully assess the benefits of EROS therapy.

More specific information for the evaluation and treatment of female sexual dysfunction, including painful intercourse (i.e., dyspareunia), vaginismus, inhibited orgasm, and sexual arousal and desire disorders, is available in other resources.[39,49,57,58]

For both men and women, a persistent and complex sexual problem is loss of desire for sex after cancer treatment. In men who have not had prostate cancer and have clinically low levels of serum testosterone, replacement by injection or patch is often effective in restoring normal sexual function. Testosterone replacement tends to have little effect, however, if given to a man whose own hormone levels fall within the normal range. Safety, dosage, and delivery systems for androgen replacement in women need to be studied. Numerous studies have evaluated the use of transdermal testosterone in various populations.[59-65][Level of evidence: I] These populations include women who have hypoactive sexual desire disorder who have had oophorectomies, who are naturally postmenopausal, who are premenopausal, and who have a history of cancer. These studies used doses ranging from 150 µg to 10 mg daily. Most of the studies in women have used concomitant estradiol supplementation if estrogen levels fell outside the normal premenopausal range and found that testosterone supplementation significantly improved libido outcomes.

Only two published studies have evaluated transdermal testosterone for libido in postmenopausal women without estrogen supplementation. One of these studies was in cancer survivors,[66] and the other was in postmenopausal women who were diagnosed with hypoactive sexual desire disorder.[67][Level of evidence: I] The clinical trial in cancer survivors showed that in 150 female cancer survivors randomly assigned to receive either 10 mg of transdermal testosterone daily or placebo for 4 weeks, there was no statistically significant difference in improvement in sexual desire as measured by a validated sexual function scale, the Changes in Sexual Functioning Questionnaire, despite the fact that androgen levels improved significantly in the women receiving the testosterone but remained unchanged in the women receiving placebo. The other clinical trial randomly assigned 814 postmenopausal women to receive either 150 µg or 300 µg of transdermal testosterone versus placebo for a year (without estrogen), with an efficacy endpoint of 24 weeks looking at satisfying sexual episodes captured in activity logs. Authors reported a significant improvement of about one additional satisfying sexual episode over a 4-week period in the 300-µg group compared to placebo, but not in the 150-µg group. Upon further analysis, it was found that women who had experienced surgical menopause, having had their ovaries removed, did not benefit from this intervention. This raises the questions of whether ovarian status in women who have been treated for cancer with chemotherapy is more like surgical or natural menopause, and whether the chemotherapy-induced menopausal ovary functions with an active stroma or has no activity after chemotherapy, akin to surgical removal. Research in this area is needed to better understand the entire hormonal milieu of women after cancer treatment and how all of the hormone changes work together to impact symptoms. Therefore, it is not clear that testosterone alone, in the absence of estrogen, can positively impact libido.

For women who have breast cancer, the safety of giving androgens is unknown. Serum androgens can be aromatized to estrogen. Data from epidemiologic studies can lead one to believe there may be an increased risk of breast cancer with higher concentrations of endogenous androgens.[68,69] However, endogenous androgens present over a life span do not equal exogenous androgen supplementation for a woman with low androgen concentrations. One small study evaluating the effects of testosterone supplementation on breast tissue found that the addition of testosterone to estrogen and progesterone inhibited the breast proliferation exhibited in the group that received estrogen, progesterone, and placebo.[70][Level of evidence: I] Furthermore, one case-controlled study in more than 8,000 women found that the use of exogenous testosterone for 4 years did not result in an increased incidence of breast cancer, despite the fact that 83% of testosterone users were also using estrogen replacement compared to only 15% of the age-matched controls.[71][Level of evidence: III] Therefore, many unanswered questions remain about sufficient androgen levels for adequate sexual function as well as short- and long-term safety. To date, there are no compelling data to support the use of testosterone alone to improve libido in women who are estrogen deficient.

Because loss of desire often is multifactorial, an approach that includes psychological assessment and treatment is usually optimal. An experienced mental health professional can rule out a mood disorder as a factor in loss of desire and can explore the interactions of factors such as changes in relationship dynamics, loss of physical well-being, changes in sexual self-concept, and negative body image. The effects of prescription medications, chemical dependency, or hormonal abnormalities can be recognized and targeted for change. Unfortunately, there is no true

aphrodisiac medication that can restore sexual desire in the presence of a normal hormonal environment.

In general, a variety of treatment modalities are available for sexual dysfunction after cancer. For many problems, providing information and suggestions for behavior change in a self-help format may be sufficient. Education can be provided via books,[38] pamphlets,[3,4] CD-ROMs, videos, peer counselors,[72][Level of evidence: I] or Internet interactions. For men and women with more complex and severe problems, professional intervention will be more effective. Future research needs to explore which treatment components are most effective with particular groups of patients. A psychoeducational intervention was evaluated in women with a history of breast cancer.[73][Level of evidence: I] The intervention content addressed the following:

- Sexual anatomy.
- Body image.
- Attitudes and behavior.
- Communication.
- Ways to enhance sexual function.

The intervention was delivered in person, in groups, at 2-hour sessions over a 6-week period. The primary outcome was the Mental Health Index, providing a measure of anxiety, depression, loneliness, distress, well-being, and positive affect. Other outcomes included sexual satisfaction, self-image, and functioning, such as dyspareunia. Women were identified through a mailed survey and randomly assigned ahead of time either to the intervention or to the control group (written material only). Women randomly assigned to the intervention were then invited to participate. Of 284 women assigned to the intervention, only 83 agreed to participate; of those, only 72 attended any of the sessions. The most common reasons for declining participation were inconvenient time and/or location, being too busy, or feeling that the intervention was not needed. One hundred twenty-seven women were randomly assigned to the control group, and follow-up was reported for 98 of them.[73]

Results from this study are presented for three groups:

- Control group.
- Intervention nonparticipants.
- Intervention participants.

An intent-to-treat analysis showed no significant differences between groups for the Mental Health Index. However, there was an intervention effect for general satisfaction with sex. An as-treated analysis did suggest improvement on the Mental Health Index, with women who reported more distress at baseline experiencing more benefit.[73] This study provides data to support the idea that interventions focusing on psychosocial and cognitive factors may be an important component of interventions to improve emotional and sexual outcomes. However, more research is needed to develop psychoeducational interventions that are less time intensive, can be disseminated easily, and are more readily accepted by cancer survivors.

Sexual counseling can be provided for individuals, couples, or groups. The effectiveness of these different formats has not been compared for people with cancer. It is also not known whether brief counseling can enhance the impact of medical treatments, such as those used to overcome erectile dysfunction or dyspareunia. There is limited research about the impact of support groups on sexual outcomes for men with prostate cancer.[74][Level of evidence: II] It is likely that associations between better outcomes and participation in support groups reflect baseline sociographic and clinical differences between those who participate in support groups and those who do not.

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Fertility Issues

Adjuvant radiation therapy and/or chemotherapy introduce higher risks of infertility in patients with cancer. Sterility from these therapies may be temporary or permanent. The occurrence of this toxicity is related to a number of factors including the individual's gender, age at the time of treatment, type of therapeutic agent, radiation field, total dose, single versus multiple agents, and length of time since treatment.

When treatment-related or disease-related dysfunction is a possibility, every effort should be made to provide adequate information and education on reproduction and fertility. Conveying such information can be complicated, especially in younger pediatric cancer patients. Children may be too young to comprehend the implications of treatment on fertility. Additionally, in some instances, parents may decide to shelter children from such discussions.[1] Existing literature suggests that only about half of men and women of child-bearing age receive the information they need from their health care providers about cancer-related infertility at the time of diagnosis and treatment planning.[2] This lack of information is one of the most common reasons men give for failing to bank sperm.[2] To address this issue, a computerized interactive educational tool for patients, families, and physicians called Banking on Fatherhood after Cancer is under development and will be viewable on CD-ROM or over the Internet.[2]

Chemotherapy

With regard to chemotherapy, the extent of damage to a patient's fertility depends on the agent administered, the doses received, and the patient's age at the time of treatment. Age is an important factor, and the possibility of gonadal recovery improves with the length of time off chemotherapy. The germinal epithelium of the adult testis is more susceptible to damage than that of the prepubertal testis.[3] The evidence to date (largely from adjuvant studies) suggests that patients older than 35 to 40 years are most susceptible to the ovarian effects of chemotherapy. The ovaries of younger women can tolerate greater doses.[4] Predicting the outcome for any individual patient is difficult, as the course of ovarian functioning following chemotherapy is variable.[3] Relative risk of ovarian failure and testicular damage from cytotoxic agents has been studied, and the alkylating agents have subsequently been shown to be damaging to fertility. The following agents have been shown to be gonadotoxic: busulfan, melphalan, cyclophosphamide, nitrosoureas, cisplatin, chlorambucil, mustine, carmustine, lomustine, cytarabine, ifosfamide, and procarbazine.[3,5-8] In addition to these alkylating agents, vinblastine, cytarabine, cisplatinum, and procarbazine have also been reported to be gonadotoxic in male and female patients.[9] Chemotherapy regimens for the treatment of non-Hodgkin lymphoma are generally less gonadotoxic than those used for Hodgkin lymphoma.[3] The addition of adjuvant endocrine therapy in patients older than 40 years was more likely to result in permanent chemotherapy-related amenorrhea.[10] The effects of chemotherapy on testicular function have also been widely studied in patients with testicular cancer. One review reported that more than half of the patients with testicular germ cell cancer showed impaired spermatogenesis before undergoing cytotoxic treatment. Permanent infertility is ultimately defined by dose of cisplatin in these patients. At doses lower than 400 mg/m^2, long-term effects on endocrine function and sperm production are unlikely to occur. Higher doses would be expected to cause long-term endocrine-gonadal dysfunction.[11]

Although chemotherapy causes ovarian damage, there appears to be no risk of toxicity to future offspring of women treated with these agents before pregnancy.[9]

Radiation

When the testes are exposed to radiation, sperm count begins to decrease and, depending on the dosage, temporary or permanent sterility may result.[4] Men who receive radiation to the abdominal or pelvic region may still regain partial or full sperm production, depending on the extent of injury to the testes. Unlike the germinal epithelium, Leydig cell function may be more prone to damage from irradiation in prepubertal life than in adulthood.[3] Testicular radiation with doses higher than 20 Gy is associated with Leydig cell dysfunction in prepubertal boys, while Leydig cell function is usually preserved with doses of as much as 30 Gy in sexually mature males.[12] Exposing the testes to ionizing radiation at a dose lower than 6 Gy causes disturbances of spermatogenesis and altered spermatocytes with recovery periods dependent on dose;[4] doses higher than 6 Gy cause permanent infertility by killing off all stem cells.[13] For patients with testicular germ cell cancer, using modern radiation techniques (radiation doses to the para-aortic field <30 Gy) and testis shielding providing testis scatter radiation (<30 Gy), radiation-induced impairment of fertility is very unlikely.[11] Sperm counts are typically lowest at 4 to 6 months posttreatment; return to pretreatment levels usually occurs in 10 to 24 months, with longer periods required for recovery after higher doses.[9] Total-body irradiation (TBI) as a conditioning regimen for stem cell transplantation causes permanent gonadal failure in approximately 80% of men.[14] For men, gonadal toxicity can be evidenced by the following three measurements: testicular biopsy, serum hormone assays (levels), and semen analysis. When male infertility is the result of abnormal hormone production, the use of hormone manipulation may lead to the return of sperm production.[15]

For women, a dose of 5 Gy to 20 Gy administered to the ovary is sufficient to completely impair gonadal function, regardless of the patient’s age; a dose of 30 Gy provokes premature menopause in 60% of women younger than 26 years.[16] In a study of children and adolescents diagnosed with cancer, female 5-year survivors were significantly

less likely to have ever been pregnant when compared with their siblings. Survivors who received hypothalamic/pituitary radiation doses of 30 Gy or higher or ovarian/uterine radiation doses higher than 5 Gy and those who were treated with lomustine or cyclophosphamide were less likely to have ever been pregnant.[17] Women who are older than 40 years when undergoing treatment have a smaller pool of remaining oocytes and require only 5 to 6 Gy to produce permanent ovarian failure. TBI, when used before stem cell transplantation, is associated with more than 90% permanent gonadal failure in women overall and an incidence of pregnancy less than 3%.[9] The outlook for recovery of ovarian function before puberty is more favorable, particularly if radiation is delivered in several fractions.[14] Measurement of gonadal toxicity in women is more difficult to assess due to the relative inaccessibility of the ovary to biopsy (which would require laparoscopy). Therefore, menstrual and reproductive history, measurements of serum hormone levels, and clinical evidence of ovarian function are the criteria most commonly used to determine ovarian failure. Several authors provide reviews of gonadal dysfunction in patients receiving chemotherapy [15] and the effect of cancer therapy on gonadal function.[4]

Preventive Strategies

For women, studies [18] have shown that movement of the ovaries out of the field of radiation (ovariopexy) —laterally, toward the iliac crest, or behind the uterus—may help preserve fertility when high doses of radiation therapy are being applied. By relocating the ovaries laterally it is possible to shield them during radiation of the para-aortic and femoral lymph nodes.[4] Pelvic radiation, however, still provokes an irradiation of the ovary of 5% to 10%, even if transposed outside the irradiation area.[16] Similar prevention strategies are available for men. When possible, lead shields are used to protect the testes.[4]

Procreative Alternatives

When feasible and relative to the necessity of treatment, oncology professionals should discuss reproductive cell and tissue banking with patients, referring to a reproductive endocrinologist before chemotherapy and/or radiation. Men can store sperm from semen ejaculate, epididymal aspirate, testicular aspirate, and testicular biopsy.[19-22] Women can store ovarian tissue, ovarian follicles, and embryos.[23,24][Level of evidence: II] In oocyte cryopreservation, which is still experimental,[25] reproductive cells/tissue are cryopreserved for future use in artificial insemination for patients who wish to protect their reproductive capacity. One published case report describes a live birth after *in vitro* fertilization of thawed cryopreserved ovarian cortical tissue into the ovaries of a 28-year-old woman who experienced ovarian failure secondary to high-dose chemotherapy for non-Hodgkin lymphoma.[26][Level of evidence: III] For this case, ovarian tissue (containing many primordial follicles) was harvested after administration of a second-line conventional therapy regimen and before treatment with high-dose chemotherapy. Since this time, work has continued to advance technology related to the preservation of unfertilized eggs and ovarian tissue cryopreservation. More data have been published from clinics using preservation of unfertilized eggs, an important option for unpartnered, fertile women at the time of cancer diagnosis and treatment. The New York University (NYU) Fertility Center reported an ongoing/delivered pregnancy rate of 57% using oocyte cryopreservation.[27] The authors state that this rate is better than the U.S. rate for conventional *in vitro* fertilization using fresh (as opposed to cryopreserved) oocytes. They also report that this success rate was similar to that for age-matched controls who underwent conventional *in vitro* fertilization at the NYU Fertility Center.[27] There is likely a good deal of variability in the expertise and success rates of fertility centers using these newer strategies. When options for patients are being investigated, critical review is needed.

These options may not be appropriate for all patients. Counseling is an important part of the decision-making process for patients. Thinking through these decisions at a time when patients are struggling with issues of life and potential death are often difficult. Patients need to consider costs, stress, time, emotions, and potential inclusion of another individual in the pregnancy process (i.e., a surrogate). For many patients, the financial costs associated with *in vitro* fertilization and subsequent embryo cryopreservation is cost prohibitive. Consideration also needs to be given to the current rate of failure for *in vitro* fertilization procedures and the potential adverse effect of malignancy on sperm parameters.[25][Level of evidence: III] A retrospective analysis, with a limited sample size, reported that the oocytes from patients with malignant disorders were of a poorer quality and exhibited a significantly impaired fertilization rate compared with age-matched controls.[25] Importantly, data on the outcome of pregnancies in cancer survivors [28][Level of evidence: III] have not shown any increase in genetically mediated birth defects, birth-weight effects, and sex ratios. Based on the evidence thus far, individuals treated with cytotoxic chemotherapy who remain fertile are not at an increased risk of having children with genetic abnormalities.[3] For all patients who wish to be parents and who have permanent infertility, adoption should be presented as a choice.

Men who are treated with sterilizing chemotherapy may have semen cryopreserved, yet utilization remains low.[29] [Level of evidence: III] In a 15-year study of 776 men with a variety of malignancies, the cumulative rate of using

the cryopreserved semen for assisted conception was less than 10% up to 8 years. Younger age at cryopreservation and a diagnosis of testicular cancer were associated with lower utilization.[30][Level of evidence: III] Despite poor postthawing sperm survival rates, intracytoplasmic sperm injection (ICSI) offers the possibility of a pregnancy even if only a single motile sperm is present after thawing.[31][Level of evidence: IV] Cryopreservation of sperm should be recommended even to oncological patients younger than 15 years (provided these patients can produce a semen sample), as overall success rates (defined as the observation of at least a single motile sperm after the thawing procedure) have been found to be similar to those observed in adults.[32][Level of evidence: III] For men who experience retrograde ejaculation after treatment and remain fertile, it is often possible to retrieve live sperm cells. An infertility specialist can retrieve sperm cells from the testicles and from urine. Testis sperm extraction incorporates the removal of testicular parenchyma with processing and isolation of individual sperm cells. This allows for ICSI in azoospermic men. In a retrospective study, 15 of 23 men who were azoospermic after receiving chemotherapy had retrievable testis sperm leading to successful fertilization. Pregnancies occurred in 31% of cycles. Future research is needed to address whether the offspring produced after ICSI techniques are at increased risk of genetic or congenital malformation.[33][Level of evidence: III] Medication can sometimes be used to stimulate the remaining nerves around the prostate and seminal vesicles to convert a retrograde ejaculation to an antegrade ejaculation. In the United States, ephedrine sulfate is most often used; in Europe, imipramine is also used. Pharmacologic agents can also be used to induce an ejaculation (i.e., intrathecal neostigmine or subcutaneous physostigmine). When medication does not work, several other techniques are available and may be recommended, including vibratory stimulation, electroejaculation, direct aspiration of fluid from the vas deferens, perineal needle stimulation, and hypogastric-nerve stimulation. Further review of these treatments and information regarding treatment of infertility and assisted reproductive technology is available.[13,34]

Fertility outcomes after therapy of common cancer types (breast cancer, leukemia and lymphoma, cervical cancer, ovarian cancer, endometrial cancer, and testicular cancer) are available in a published review.[9]

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Changes to This Summary (06/30/2011)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Editorial changes were made to this summary.

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Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about sexuality and reproductive issues that cancer patients may experience during or after treatment. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Supportive and Palliative Care Editorial Board [14]. Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,

- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

Any comments or questions about the summary content should be submitted to Cancer.gov through the Web site's Contact Form [5]. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Supportive and Palliative Care Editorial Board uses a formal evidence ranking system [15] in developing its level-of-evidence designations.

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The preferred citation for this PDQ summary is:

National Cancer Institute: PDQ® Sexuality and Reproductive Issues. Bethesda, MD: National Cancer Institute. Date last modified <MM/DD/YYYY>. Available at: http://www.cancer.gov/cancertopics/pdq/supportivecare/sexuality/healthprofessional. Accessed <MM/DD/YYYY>.

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Disclaimer

The information in these summaries should not be used as a basis for insurance reimbursement determinations. More information on insurance coverage is available on Cancer.gov on the Coping with Cancer: Financial, Insurance, and Legal Information page [17] page.

Contact Us

More information about contacting us or receiving help with the Cancer.gov Web site can be found on our Contact Us for Help [18] page. Questions can also be submitted to Cancer.gov through the Web site's Contact Form [5].

Glossary Terms

Level of evidence I

> Prospective, randomized, controlled trials and meta-analyses of prospective, randomized, controlled trials. See Levels of Evidence for Supportive and Palliative Care Studies (PDQ®) for more information.

Level of evidence II

Prospective, nonrandomized, controlled trials; prospective cohort studies; prospective case series; and cross-sectional studies. See Levels of Evidence for Supportive and Palliative Care Studies (PDQ®) for more information.

Level of evidence III

Retrospective studies. See Levels of Evidence for Supportive and Palliative Care Studies (PDQ®) for more information.

Level of evidence IV

Opinions of respected authorities based on clinical experience, consensus statements from expert committees, or authoritative reviews. See Levels of Evidence for Supportive and Palliative Care Studies (PDQ®) for more information.

Table of Links

1 http://www.cancer.gov/cancertopics/pdq/supportivecare/depression/HealthProfessional
2 https://cissecure.nci.nih.gov/livehelp/welcome.asp
3 http://cancer.gov
4 https://cissecure.nci.nih.gov/ncipubs
5 http://www.cancer.gov/contact
6 http://cancer.gov/cancerinfo/pdq/cancerdatabase
7 http://cancer.gov/cancerinfo/pdq/adulttreatment
8 http://cancer.gov/cancerinfo/pdq/pediatrictreatment
9 http://cancer.gov/cancerinfo/pdq/supportivecare
10 http://cancer.gov/cancerinfo/pdq/screening
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12 http://cancer.gov/cancerinfo/pdq/genetics
13 http://cancer.gov/cancerinfo/pdq/cam
14 http://www.cancer.gov/cancertopics/pdq/supportive-care-board
15 http://www.cancer.gov/cancertopics/pdq/levels-evidence-supportive-care/HealthProfessional
16 http://visualsonline.cancer.gov
17 http://www.cancer.gov/cancertopics/coping/financial-legal
18 http://www.cancer.gov/help