

# Hormonal Changes and Sexual Dysfunction



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## KEYWORDS

- Sexual dysfunction • Hormone changes • Cancer survivorship
- Cancer treatment side effects

## KEY POINTS

- Sexual health is integral to the overall well-being of a patient with cancer and is often impacted by cancer treatment.
- Cancer treatment may interrupt, suppress, or permanently deplete hormonal function in both men and women.
- Physical and psychological interventions are available and can improve sexual health, and/or assist with coping with the dysfunction that results from hormonal changes.
- Patients are interested in receiving further information about their sexual health, but there are barriers that can reduce the likelihood that they will have this conversation with their oncology team.
- Well-designed intervention trials are needed to better understand the impact of systematic approaches to helping patients manage sexual dysfunction.

## SEXUALITY AND CANCER

Most patients newly diagnosed with cancer are now likely to survive their disease.<sup>1</sup> With patients with cancer living longer lives following treatment, there is a clear need to address common survivorship challenges faced by the estimated 15 million cancer survivors currently living in the United States.<sup>2</sup> In particular, a survivor's sexuality is a fundamental, life-affirming experience that can be profoundly affected by cancer treatment. There are increasing efforts to understand the complex matter of

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The authors have nothing to disclose.

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Med Clin N Am 101 (2017) 1135–1150

<http://dx.doi.org/10.1016/j.mcna.2017.06.008>

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human sexuality from an integrative perspective, rather than focusing solely on physical function and disruptions to organ function.

A number of recent models have been proposed to understand sexual health in the context of cancer care. The Neo-theoretical Framework of Sexuality describes key factors, including sexual self-concept (concerns relevant to body image), sexual relationships (concerns relevant to communication and intimacy), and sexual functioning (concerns relevant to desire, arousal, and excitement).<sup>3</sup> Others have proposed an Integrative Biopsychosocial Model for Intervention, suggesting that a broad approach is necessary to capture the psychological (eg, emotional responses to cancer, body perception, and motivation), interpersonal (eg, changes to couple dynamics, fear of intimacy, and communication barriers), biological (eg, hormonal alterations, body changes, pain, and fatigue), and cultural (eg, religious beliefs, and sexual values and norms) elements that comprise a patient's experience of sexuality.<sup>4</sup> Consistent across these models is the importance that clinicians recognize that sexuality must be seen as more than simply a mechanical event, with proper intervention often requiring a multidisciplinary approach that addresses the multiple facets that can affect sexual health.

## TREATMENT-RELATED SEXUAL DYSFUNCTION AND HORMONAL THERAPY

Providers should avoid making the assumption that all patients with cancer will present with the same types of sexual dysfunction, even if they have the same diagnoses and treatments. Generally speaking, estimates of the prevalence of sexual dysfunction after cancer range from 40% to 100%, affecting both sexes.<sup>5-7</sup> It is broadly acknowledged that all major treatment modalities have potential to significantly disrupt male and female sexual function.<sup>8</sup> Common treatment-related side effects include disorders of sexual response, desire, and motivation. Both men and women may experience difficulty with arousal, orgasmic dysfunction, hypoactive sexual desire, body image disturbances, and lowered sexual self-esteem. Men may experience erectile dysfunction, and ejaculatory dysfunction. Women may suffer from reduced lubrication, and chronic dyspareunia.<sup>9</sup> Please refer to [Table 1](#) for a summary of possible sexual health consequences of cancer treatment.

Hormonal therapies that interrupt, suppress, or permanently deplete hormonal function have profound impact on sexual function.<sup>10</sup> However, distressing sexual problems related to hormonal therapy are not consistently identified by clinicians and may be overlooked entirely.<sup>11,12</sup> This is of particular significance because both frequency and duration of use of hormonal therapies with both male and female patients is steadily increasing.<sup>13,14</sup> The following sections overview common issues around sexual dysfunction related to hormonal therapy for men and women. We also make note of several subpopulations of patients who experience significant treatment-related sexual dysfunction related to hormonal interruption/dysfunction that are often overlooked.

### **Breast Cancer**

Treatment for breast cancer can involve a combination of surgery, chemotherapy, radiation therapy, and/or hormone therapy. Women's sexual health is potentially impacted by all of these treatments,<sup>15,16</sup> and distressing sexual concerns commonly affect 30% to 100% of survivors.<sup>17</sup> The negative sexual side effects of chemotherapy treatment that depletes circulating reproductive hormones are well described in the literature<sup>18</sup> and have been shown to be particularly distressing for women.<sup>19-22</sup> More specifically, chemotherapy-related hypoestrogenism results in multiple effects

on the vagina and vulva.<sup>23</sup> The epithelium thins, loses cornification and rugation, and blood flow is decreased; causing tissue to become smooth, pale, and fragile. Vaginal secretions are decreased and pH increases. There is a loss of collagen, hyalinization, and elastin, and the vagina may narrow or shorten. This vulvovaginal atrophy is often accompanied by decreased libido and adverse effects on sexual arousal and orgasm.<sup>24</sup> For young women with breast cancer, ovarian failure induced by chemotherapy may be associated with a more comprehensive loss of ovarian function than in natural menopause.<sup>25</sup> Chemotherapy results in premature ovarian failure in 30% to 96% of premenopausal women,<sup>26</sup> with the highest risk for women older than 40 years (50%–96%) and those exposed to alkylating agents such as cyclophosphamide.<sup>27</sup> Beyond these common physical side effects of estrogen-deprivation, women who undergo hormonal disruption also report distress around decreased sense of intimacy, and diminished partner function.<sup>15,28–30</sup> Loss of sexual function and satisfaction with intimacy have been associated with poorer quality of life for breast cancer survivors.<sup>31</sup>

There is now a steadily increasing use of endocrine therapies with both older and younger patients with breast cancer and survivors.<sup>10,13</sup> Endocrine therapies typically also result in a raft of menopausal symptoms that patients are often not prepared to manage.<sup>25</sup> For more than 2 decades, 5 years or more of adjuvant tamoxifen has been the standard of care for premenopausal breast cancer survivors.<sup>32</sup> Large-scale studies have generally not found sexual dysfunction to be a common treatment-related side effect of this endocrine treatment.<sup>33</sup> However, the American Society of Clinical Oncology has revised clinical practice guidelines and now recommends the use of adjuvant ovarian suppression therapy with young female survivors of estrogen-positive breast cancer.<sup>34</sup> This means there is an increasing use of treatments to suppress ovarian function in young, premenopausal women and recent evidence regarding treatment-related sexual dysfunction is striking.<sup>35</sup> Marked vulvovaginal atrophy, loss of arousal and desire, and loss of sexual satisfaction are common, and sexual problems related to ovarian suppression do not resolve over time.<sup>36</sup>

<b>Sexual Dysfunction</b>		
<b>Male</b>	<b>Female</b>	<b>Male and Female</b>
Erectile dysfunction	Dyspareunia	Reduced libido
Dry/painful orgasm	Vaginal atrophy	Pain
Ejaculatory dysfunction	Loss of nipple sensation	Chronic fatigue
		Nausea/vomiting
		Lymphedema
		Urinary incontinence
		Bowel incontinence
		Scars
		Amputations
		Ostomies
		Problems with arousal
		Reduced sexual motivation
		Decreased body image
		Loss of sexual self-esteem

For postmenopausal survivors, aromatase inhibitors remain the preferred first line of adjuvant endocrine therapy to reduce risk of cancer recurrence.<sup>34</sup> Aromatase inhibitors act as estrogen antagonists in the vagina,<sup>37</sup> which often leads to severe dyspareunia.<sup>20</sup> In systematic review of prospective data from randomized trials and an observational study comparing aromatase inhibitors with tamoxifen, the prevalence and severity of vaginal dryness and dyspareunia are worse with aromatase inhibitors than with tamoxifen.<sup>38</sup> In addition to the intense menopause-related symptoms of vulvovaginal atrophy,<sup>39</sup> women on aromatase inhibitors are at significantly increased risk for lichen sclerosus, a perineal skin condition that results in itching, burning, and thin, crinkled skin prone to bruising and tearing.<sup>40</sup> If untreated, this condition can lead to scarring, ulcerations, and labial fusion, all of which make sexual activity painful and potentially unattainable.<sup>41</sup> Lichen sclerosus also raises risk for vulvar cancer. Given the potential risk of lichen sclerosus in women who are severely estrogen-depleted, it has been proposed that all women on an aromatase-inhibitor undergo yearly vulvovaginal examinations to rule out lichen sclerosus and other vulvovaginal side effects of treatment.<sup>40</sup>

### **Prostate Cancer**

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Men on hormone therapy similarly experience pronounced sexual side effects. The primary treatment for men diagnosed with late-stage prostate cancer is hormone therapy, also referred to as androgen deprivation therapy (ADT). Broader use of ADT in men has been increasing, with ADT now being used regularly for men diagnosed with localized high-risk disease.<sup>42–44</sup> The purpose of hormone therapy for men is to reduce the level of androgens to minimize their potential impact on the progression of prostate cancer cells. Men on ADT are essentially chemically castrated to manage aggressive prostate disease. When testosterone is depleted, nitric oxide levels drop and there is loss of intracavernosal pressure, which results in erectile dysfunction. In addition to erectile dysfunction, side effects of ADT also include body feminization, profound loss of libido, hot flashes, and emotional lability.<sup>45–47</sup> The severe hormone-related side effects are equally similar in men who are treated for either localized<sup>44,48</sup> or metastatic disease.<sup>49–52</sup> Today in North America, there are more than half a million men on ADT and most men are on ADT for several years.<sup>53</sup> The extreme sexual and quality-of-life side effects of ADT also negatively impact partners. It has been shown that both patients and partners feel unprepared to manage these problems.<sup>54</sup>

### **Testicular Cancer**

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Testicular cancer is typically treated with surgery, and potentially followed with radiation therapy or chemotherapy.<sup>55–57</sup> Sexual problems are reported by 12% to 40% of testicular cancer survivors regardless of type of treatment<sup>58</sup> and they include difficulties with sexual desire, ejaculatory difficulties, and erectile dysfunction.<sup>59–62</sup> Testicular cancer survivors also may be self-conscious about changes in physical/testicular appearance and a perceived loss of masculinity. Although treatment-related sexual problems are not always organic, rates of subnormal levels of testosterone range from approximately 10% to 15% in testicular cancer survivors.<sup>63</sup> As a result, testicular cancer survivors with decreased hormonal function often report reductions in sexual activity levels and general sexual dissatisfaction following treatment.<sup>64,65</sup> Thus, it is important for clinicians to also assess hormonal function in testicular cancer survivors who report having bothersome sexual problems.

### ***Impact of Risk-Reducing Surgery: BRCA Mutation Carriers***

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Women who are BRCA1/2 carriers face a high lifetime risk for breast (55%–85%) and/or ovarian cancer (15%–44%).<sup>66</sup> For these women, risk-reducing salpingo-oophorectomy (RRSO) is recommended by age 35 or after completion of child-bearing. RRSO reduces risk of ovarian cancer by more than 80% and also lowers breast cancer risk by half.<sup>67</sup> This preventive risk-reducing surgery successfully reduces cancer risk, but also can lead to a range of sexual side effects that are highly distressing. Comparable to those side effects previously discussed in the section describing ovarian suppression, women who undergo RRSO similarly are at risk for vaginal dryness, vulvovaginal atrophy, and loss of arousal and genital sensation.<sup>68</sup> The most frequently cited post-surgical concerns of mutation carriers are the sexual side effects, and women express that they wished they had received counseling about this topic.<sup>69</sup>

### ***Stem Cell Transplantation***

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Long-term posttransplant complications can cause significant quality-of-life impairments for those who underwent stem cell transplantation (SCT).<sup>70</sup> Endocrine disruptions can be caused by chemotherapy, radiation therapy, and SCT, with many issues the result of conditioning regimens with total body irradiation and/or chemotherapy.<sup>71</sup> Consequently, late-effects guidelines recommend that patients who have undergone SCT receive annual screenings for endocrine function (eg, thyroid function).<sup>70</sup> Gonadal dysfunction is commonly seen in SCT recipients, with reported rates as high as 92% for male and 99% for female patients.<sup>72–74</sup> Although rates of gonadal dysfunction will vary depending on individual variables (eg, age, conditioning regimen), women are generally more likely to experience problems than men. Notably, ovarian endocrine failure in adult women is usually irreversible,<sup>75,76</sup> although there is recent evidence to suggest that reduced-intensity condition regimens may protect ovarian function.<sup>77</sup> Women who experience ovarian failure are likely to suffer from significant sexual health consequences, including poorer body image (the result of hypertrichosis and Cushing syndrome, for example), lowered libido, and vaginal dryness. Consequently, women who undergo SCT report a greater decrement in frequency of sexual relations than men.<sup>78</sup> Men also experience sexual difficulties following SCT. Approximately 10% report difficulty with erectile function and/or ejaculation, and the conditioning regimen can cause testicular damage in men with low testosterone levels.<sup>78,79</sup> Women are encouraged to discuss the potential use of hormonal replacement therapy and vaginal lubrication, and both men and women should be openly discussing sexual health with their medical providers before transplantation has occurred.<sup>70,78</sup>

### ***Adolescent and Young Adult Cancer***

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Medical advances in pediatric oncology now ensure that more than 80% of children and adolescents diagnosed with cancer will survive.<sup>80</sup> Research shows that disruption of psychosexual development and sexual dysfunction are profoundly distressing long-term side effects of pediatric cancer treatment.<sup>81,82</sup> Almost half of young adult survivors of childhood cancer struggle with at least 1 major sexual problem,<sup>12,83</sup> and 30% report 2 or more problems.<sup>12</sup> Such problems include pain, difficulty with orgasm, lack of desire, and arousal difficulties. Additionally, research focusing on patients treated between the ages of 15 and 39 years found that 49% of Adolescent and young adult (AYA) reported negative effects on sexual function 1 year after cancer diagnosis and 70% of those persisted with negative perceptions at 2 years after diagnosis.<sup>84</sup> These stand in contrast to reports of sexual dysfunction in the general adolescent and young

adult population, where rates fall between 10% and 15% for women and men, respectively.<sup>85</sup> The age at which a child is diagnosed with cancer can be important with respect to their later life sexual health. For example, girls who received SCT before puberty are more likely to avoid ovarian failure, and subsequent sexual side effects, that is far more common in adults who undergo SCT. These younger patients often require sex hormone replacement therapy post-SCT.<sup>86</sup> Similarly, girls who undergo SCT at a younger age (<13 years) are more likely to maintain fertility. In contrast, boys who underwent SCT before puberty were at greater risk for infertility.<sup>87</sup>

Research focused on adult cancer survivors shows clear relationships between cancer treatments, such as chemotherapy, and hormonal therapy, with direct damage to sexual organs and/or hormonal systems resulting in sexual dysfunction.<sup>24,88–92</sup> In contrast, studies in childhood cancer survivors have shown that in addition to disruptions in endocrine function among other physical late effects, psychosocial factors, such as anxiety, fear of partner rejection, fear of being pitied, and poor self-esteem, also play a significant role in the development of sexual problems.<sup>11,12,83</sup> For example, negative body image can develop secondary to the physical changes incurred by cancer treatment and plays a prominent role in social and sexual interactions during treatment, potentially contributing to delayed physical and emotional intimacy, and continues well into survivorship.<sup>84,93</sup> Given that negative body image in adolescence can impede the development of a healthy sexual identity,<sup>94</sup> and that body image issues often remain after active treatment, it is critical for clinicians to routinely address body image concerns in addition to acknowledging and assessing changes in hormonal function.

## MANAGING SEXUAL DYSFUNCTION

### *Evaluation*

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Effective interventions can be delivered only if an adequate assessment about the patient's sexuality has occurred. The use of screening tools can be helpful as a brief, preliminary approach to assessing sexual function in cancer survivors, and to determine which patients may benefit from further discussion about their symptoms. The use of screening instruments can help with starting conversations with patients and their families.

In women, the Female Sexual Function Index (FSFI) is a measure of sexual function that has been validated in female cancer populations.<sup>95</sup> This is a 19-item self-report measure that assesses function "over the past 4 weeks" in the following specific domains relevant to female sexuality: desire, arousal, lubrication, orgasm, satisfaction, and pain.<sup>96</sup> The FSFI has been used in research conducted with patients with cancer and survivor studies,<sup>97,98</sup> and is able to differentiate between clinical and nonclinical populations.<sup>95</sup> The scale, along with instructions for use and scoring, are available at [www.FSFIquestionnaire.com](http://www.FSFIquestionnaire.com).<sup>95</sup> For providers who are working with men, the International Index of Erectile Function (IIEF) can be a valuable tool.<sup>99</sup> The IIEF is a 15-item self-report measure that is available in multiple languages.<sup>99</sup> It has been used in studies with patients with prostate cancer<sup>97</sup> and asks about sexual function "over the past 4 weeks." The IIEF asks about the following domains relevant to male sexuality: erectile function, orgasm, desire, intercourse satisfaction, and overall satisfaction.

The use of screening measures should be designed to help facilitate a subsequent conversation, instead of as a replacement of a full clinical assessment. This discussion can be guided by a structured model of clinical inquiry. An example of a popular model is the BETTER model.<sup>100</sup> The model's name stands for *Bringing up the topic of sexual*

health during consults, *Explain* to the patient that sexuality is a part of cancer care, *Tell* the patient that resources are available to address sexual health, *Time* discussions and emphasize that patients can bring the topic up at any time, *Educate* the patient about the possible changes in sexuality that can result from cancer treatment, and *Record* the discussion in the patient's chart. Alternatively, the PLISSIT Model offers another framework to consider.<sup>101</sup> PLISSIT stands for asking *Permission* to talk about sexuality, offering *Limited Information* to address sexual concerns, providing *Specific Suggestions* based on the patient's presentation, and referring for *Intensive Therapy* as indicated based on symptom report.

### **Intervention**

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Without intervention, the negative impact of sexual dysfunction on patients with cancer is significant and evidence suggests that these problems often get worse over time.<sup>102,103</sup> An overarching model that can guide a provider in appreciating the intervention process is the Five A's Framework, which focuses on 5 important facets of treatment: Ask, Advise, Assess, Assist, and Arrange.<sup>104</sup> In this model, the provider makes sure that all cancer survivors are *Asked* about their sexual health using a nonjudgmental approach. Next, the provider must demonstrate willingness to *Advise* the survivor that his or her problems are normative and that treatment options exist. Third, a provider must adequately *Assess* the survivor's sexual dysfunction. Subsequently, the patient can be *Assisted* through specific therapeutic efforts, ranging from psychoeducation, to referrals, to active treatment. Finally, a provider must ensure that he or she *Arranges* follow-up so that the patient's status is routinely monitored.

It is important that a clinician who treats cancer survivors develops a multidisciplinary network of referrals to address sexual concerns from an integrative perspective. Individuals on this list are likely to include the following:

- Urologist
- Gynecologist
- Endocrinologist
- Cardiologist
- Primary care physician
- Pelvic floor physical therapist
- Psychologist

### **Women**

As described, one of the most commonly reported post-cancer treatment symptoms for women is vaginal dryness. This can be debilitating for women because of physical consequences, such as pain, chafing, and bleeding, all of which can subsequently lead to significant reductions in sexual desire. First-line treatment includes vaginal lubricants and moisturizers. Vaginal lubricants provide topical lubrication and promote comfort during sexual activity, and, if used properly, can help to prevent irritation and potentially avoid mucosal tears. Unlike lubricants, vaginal moisturizers are intended to be used consistently for overall vaginal comfort and are not used on an as-needed basis during sexual activity. Moisturizers are designed to hydrate the vaginal mucosa and should be used routinely by cancer survivors who experience regular vaginal dryness. Rather than focusing on the particular formula used for an individual vaginal moisturizer, evidence indicates that the benefit of vaginal moisturizers depends on consistent use up to 5 times per week. Further, female cancer survivors can consider the use of vaginal dilator therapy, especially if they have received pelvic radiation. Dilator therapy helps to maintain vaginal length and caliber after radiation

therapy by preventing adherence of the vaginal walls, and long-term use after pelvic radiation therapy may be important to prevent fibrosis and ensure overall vaginal health.<sup>105,106</sup> In addition, exercises designed to tense and relax the muscles around the vaginal introitus can improve pelvic muscle floor strength and tone and vaginal elasticity, which have been associated with reductions in vaginal pain<sup>107,108</sup> and better sexual functioning.<sup>109</sup>

### **Men**

Addressing the sexual health symptoms that are commonly reported by male cancer survivors may involve collaboration with medical specialists, such as urologists who treat male sexual dysfunction. The most common challenge that a male cancer survivor will report to providers is erectile dysfunction. To treat erectile dysfunction, oral phosphodiesterase type 5 (PDE-5) inhibitors are often used at the initial therapy, as they are effective and minimally invasive.<sup>110</sup> It is noted that discontinuation of PDE-5 inhibitors can occur due to both physical (eg, headache, muscle pain, dyspepsia, facial flushing) and psychological issues (eg, anxiety about medication use, having to plan/schedule romantic activity).<sup>111,112</sup> Moreover, PDE-5 inhibitors may not be effective when men have nerve or vascular damage; for example, when there is trauma or permanent damage to nerves after radical prostatectomy, Alternatives to oral PDE-5 inhibitors include intracavernous injection therapy, transurethral alprostadil, and vacuum erection devices, all of which can be very effective for these men.<sup>113–115</sup> Specific to men who have undergone hormonal therapy, decrements to their libido are a common concern that also must be addressed. This is a difficult issue to treat, as medical options (eg, increasing testosterone levels) directly oppose the efforts at cancer therapy. There are behavioral and psychological interventions designed to facilitate improved couple's communication, reduce relationship distress, identify novel nonpenetrative intercourse sexually stimulating activities, and improve coping skills that can be helpful for the patient and his partner.<sup>116–121</sup>

### **Relationship function**

Physical sexual dysfunction due to cancer treatment can often be the precipitant that causes partners to reevaluate other issues in that particular relationship. For example, it is possible that the cancer survivor and his or her partner are facing general relationship distress,<sup>122,123</sup> or struggling with poor overall communication<sup>124</sup> instead of a specific sexual side effect. Incorporating the "cancer dyad" into any discussion that involves sexual functioning could be crucial to the success of an intervention effort.<sup>125</sup> Evidence suggests that having both partners present is helpful for both individuals during the cancer recovery process.<sup>126,127</sup>

### **Challenges**

Despite the awareness that sexual function is often affected significantly by cancer treatment and subsequent hormonal disruptions, most cancer survivors are not adequately evaluated and treated for their symptoms. Patients with cancer want information about how they can cope with sexual health changes,<sup>128</sup> but find themselves disappointed by the lack of information, support, and practical strategies provided by their clinicians to help manage the sexual changes secondary to cancer and cancer treatments.<sup>129–131</sup> By not adequately discussing sexual health during routine medical visits, clinicians may be mistakenly providing patients with the message that their sexual dysfunction cannot be adequately treated. The discomfort that medical providers experience when addressing sexual problems<sup>132</sup> appears to fall into 3 categories: issues related to patient characteristics, provider characteristics, and systems

issues.<sup>104</sup> The patient characteristics describe the provider's assumptions about their patient's sexuality due to individual characteristics, such as age, gender, partner status, sexual orientation, prognosis, and socioeconomic status. Next, the provider characteristics refer to the training, experience, knowledge, and attitudes of that particular provider, with a lack of experience and knowledge often reported as the reason for why sexuality is not sufficiently addressed during routine cancer care.<sup>133,134</sup> Finally, systems issues include problems such as insufficient time during medical appointments to discuss sexual health, in the context of the multitude of other survivorship concerns.<sup>133</sup>

## SUMMARY

Now that most cancer survivors are living many years beyond diagnosis and treatment, it is imperative for medical providers to discuss a patient's sexual health after cancer treatment. Acknowledging the general lack of formal training in sexual medicine, it is important that clinicians seek out support so that they can feel comfortable in addressing this common concern for patients during survivorship. For this reason, we strongly advise providers to build a referral list of either hospital-based or community-based colleagues who can help manage these issues. We also encourage providers to maintain an awareness of sexual dysfunction in the context of seeing survivors who do not necessarily present with more obvious comorbid side effects of treatment, such as fatigue or physical pain. This is likely most readily achieved by assessing sexual function as part of a general and routine review of systems. As patients struggle to regain quality of life and a sense of healing after cancer, simply inquiring about sexual problems both acknowledges and validates an experience that is often taboo. Finally, it is reassuring that for many cancer survivors, even a limited amount of education helping the patient understand basic treatment options (eg, vaginal lubricants and moisturizers for women, and oral PDE-5 inhibitors for men) can be very helpful. Given that most cancer patients and survivors do not receive treatment targeted to this underaddressed facet of their health, it is not only helpful but also empowering for survivors when they can gain significant improvements in quality of life from specific strategies aimed at ameliorating treatment-related sexual problems.

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