CME

Sexual Health in Women Affected by Cancer

Focus on Sexual Pain

Deborah Coady, MD, and Vanessa Kennedy, MD

As cancer therapies improve, the number of women surviving or living long lives with cancer continues to increase. Treatment modalities, including surgery, chemotherapy, radiotherapy, and hormonal therapy, affect sexual function and may cause sexual pain through a variety of mechanisms, depending on treatment type. Adverse sexual effects resulting from ovarian damage, anatomic alterations, and neurologic, myofascial, or pelvic organ injury may affect more than half of women affected by cancer. Despite the fact that no specialty is better qualified to render care for this consequence of cancer treatments, many obstetrician–gynecologists (ob-gyns) feel uncomfortable or ill-equipped to address sexual pain in women affected by cancer. Asking about sexual pain and dyspareunia and performing a thorough physical examination are essential steps to guide management, which must be tailored to individual patient goals. Understanding the cancer treatment-related pathophysiology of sexual pain aids in providing this care. Effective mechanism-based treatments for sexual pain and dyspareunia are available, and by using them, knowledgeable ob-gyns can enhance the quality of life of potentially millions of women affected by cancer.

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Advances in medical science over the past decade have dramatically improved the outlook for women with cancer. Although an estimated one in three women will be diagnosed with cancer in her lifetime, the chances of surviving after or with ongoing treatment are now higher than ever. This good news is leading to a change in the composition of the patient population cared for by obstetrician–gynecologists (ob-gyns). Female patients of all ages affected by cancer are an increasingly important and visible part of their clinical practices.

From the New York University Langone Medical Center, New York, New York; and the University of California Davis Medical Center, Sacramento, California.

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Corresponding author: Vanessa Kennedy, MD, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of California Davis Medical Center, 4860 Y Street, Suite 2500, Sacramento, CA 95817; e-mail: vakennedy@ucdavis.edu.

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Women's cancer survivorship varies by cancer site. As seen in Table 1 from the American Cancer Society, approximately 3.1 million U.S. women are now alive after a breast cancer diagnosis, representing more than 40% of all women affected by cancer.[1] Uterine corpus and colorectal cancer each account for 8% of female cancer survivors. Thus, the majority of cancer survivors cared for by ob-gyns will be affected by one of these three cancers.

Contemporary cancer treatments, including surgery, chemotherapy, radiation, targeted therapy, hormonal therapy, immunotherapy, and stem cell transplantation, often result in toxicity. These toxicities are referred to as adverse effects and may negatively affect quality of life in many domains, both during treatment and for years to come. It is clear that there is room for improvement in the care of cancer survivors. The 2015 National Comprehensive Cancer Network Survivorship Guidelines emphasize the importance of attention to the lasting physical and psychologic effects of cancer and treatments.[2] Such effects include changes in sexual function, which may not be recognized or addressed while patients are under the care of oncologists.[3]

Table 1. Female Cancer* Survivorship Statistics by Site, Age, and Time Since Diagnosis as of January 1, 2014

Statistic	n (%)
Site	
Breast	3,131,440 (41)
Uterine corpus	624,890 (8)
Colon and rectum	624,340 (8)
Melanoma	528,860 (7)
Thyroid	470,020 (6)
Non-Hodgkin lymphoma	272,000 (4)
Uterine cervix	244,180 (3)
Lung and bronchus	233,510 (3)
Ovary	199,900 (3)
Kidney	159,280 (2)
All sites	7,607,230
Age (y)	
0–14	22,410 (<1)
15–19	23,750 (<1)
20–29	108,030 (1)
30–39	258,950 (3)
40–49	637,690 (8)
50–59	1,416,880 (19)
60–69	1,953,390 (26)
70–79	1,735,930 (23)
80 or older	1,450,210 (19)
All ages	7,607,230
Time since diagnosis (y)	
0 to less than 5	2,417,640 (32)
5 to less than 10	1,667,960 (22)
10 to less than 15	1,193,310 (16)
15 to less than 20	838,050 (11)
20 to less than 25	574,360 (8)
25 to less than 30	371,620 (5)
30 or mroe	544,300 (7)
Total female survivors	7,607,230

Data from American Cancer Society. Cancer treatment and survivorship facts and Figures 2014–2015. Atlanta (GA): American Cancer Society; 2014.

Percentages do not sum to 100% as a result of rounding.

* Does not include carcinoma in situ (noninvasive cancer) of any site except urinary bladder, nor does it include basal cell and squamous cell skin cancers.

Sexual health and function is important to female cancer patients of all ages, and sexual problems after cancer diagnosis and treatment are common.[3–7] In chronic illness, sexual health is a major determinant of how women rate their overall quality of life and is a reliable predictor of emotional well-being.[8] Sexual side effects may limit the acceptance and continuation of cancer treatments and of surgical and chemopreventive therapies by women at high risk for cancer.[9] Lindau et al[5] have elegantly summarized nine domains of evidence demonstrating that ethical care of women and girls affected by cancer must optimize the preservation of sexual function (Box 1).

Box 1. Nine Domains of Evidence Underlying the Assertion That Humane and Ethical Care of Women and Girls Affected by Cancer Should Optimize Preserving Sexual Function

1. Most women and girls with cancer have a cancer that directly affects the sexual organs
2. Cancer and cancer treatment can impair female sexuality
3. Women and girls with cancer value their sexuality
4. Loss of sexual function has negative health consequences for women and girls with cancer and their partners
5. Patients want to preserve their sexuality but rarely ask for help
6. Better evidence is needed to optimize sexual outcomes in women and girls with cancer
7. Research is needed to establish effectiveness of treatments for female sexual problems in the context of cancer
8. Special effort should be made to include women and girls of sexual minority groups
9. Sexuality is an essential component of physical health

Data from Lindau ST, Abramsohn EM, Matthews AC. A manifesto on the preservation of sexual function in women and girls with cancer. Am J Obstet Gynecol 2015;213:166–74.

SEXUAL PAIN IN WOMEN AFFECTED BY CANCER

Sexual pain and dyspareunia are common in the general female population. One third of women report painful sexual activity occurring for 3 or more months at some point in their lives. From 5% to 15% of women in population-based studies in the United States and Europe disclose significant sexual pain at the time of survey.[10–13] For women affected by cancer, the prevalence is much higher. (The term "women affected by cancer" is preferred by many patients and clinicians over "survivor"and is useful because it includes women living with cancer or at high risk for cancer.) In a systematic review of 171 recently published world studies on self-reported measures of sexual function in female patients with cancer, the prevalence of sexual pain ranged from 29% to 64% in approximately two thirds of studies (Jeffery et al, unpublished data).[14] Rates of dyspareunia have been reported at 45% or higher in breast cancer survivors.[15,16] In women treated for gynecologic cancer, the rates are as high as 55%, with similar rates observed with rectal cancer treated with radiotherapy.[17,18]

Ramifications of living with persistent untreated sexual pain are many. Sexual pain or its anticipation

may preempt desire, arousal, and orgasm, so other sexual dysfunctions may understandably result.[19–21] For women in relationships, intimacy and relationship quality may suffer. Women wanting an intimate relationship may mistakenly assume it to be impossible as a result of their cancer-related pain. Many report long-lasting feelings of stigma, sadness, guilt, inadequacy, and worry over their sexual pain and the role changes that often result. Anxiety and depression are common, and some women feel that an essential component of their feminine identity, their sexual self, has been lost. Intimate partners also suffer and may develop sexual dysfunction of their own.[22] Low desire, intimacy avoidance, anxiety, and depression may compound distress from having a loved one with cancer. Cultural–religious beliefs, and widespread media misinformation about normal sexuality and sexual problems, confuse patients and partners and heighten the emotional side effects of sexual pain and dyspareunia.

Women affected by cancer would like their doctors to ask about their sexuality. They often find it hard to bring up the subject themselves.[23–25] Given treatment options, they would like to know which are more likely to have an effect on sexual functioning and how to optimize outcomes; they wish this to be part of the discussion of pros and cons of each treatment.[26,27] Sexual consequences are more routinely discussed with male patients, especially those with prostate cancer.[27] Reasons for this lack of attention to women's sexual health are many and include attitudes held by both patients and clinicians. On the part of patients with a new cancer diagnosis, future sexuality may initially be ranked low on their information priority list with "likelihood of cure" ranked highest.[3,28]

On the part of clinicians, lack of training and experience result in lower comfort levels with sexual medicine, and when patients sense discomfort, they are likely to avoid discussions.[29,30] Additionally, some clinicians may have misconceptions about how important sexual function is to women after cancer.[6] On a practical level, time and resource constraints, and the complexity of cancer care at initial and follow-up visits, often prevent clinicians from addressing the potential "collateral damage" of sexual pain.[31–33] Determinations of tolerability of cancer treatments for an individual patient rarely include assessment or discussion of sexual adverse effects, perhaps because they are considered low grade in severity and may understandably need to take a back seat to higher grade effects. Unfortunately, the topic is often not addressed after treatment either.[31] Even if the topic is discussed as part of cancer care, many women are treated for sexual problems without a gynecologic examination despite the fact that physical findings are central to management.

Awareness of the importance and yet unmet need of addressing sexual health in women affected by cancer is increasing. The National Comprehensive Cancer Network, in its practice guidelines for clinicians, patients, and insurers, directs oncologists to ask their patients about sexual function and to refer them to gynecologists if they cannot provide evaluation and treatment for sexual concerns themselves, emphasizing ob-gyns' central responsibility for this care.[2] The American Cancer Society and American Society of Clinical Oncology joint breast cancer survivorship care guidelines, and those from other oncology and sexual medicine organizations, now recommend that sexual health be a standard domain to be addressed by clinicians during cancer diagnosis, treatment, and follow-up.[34–37] Clinician comfort level and communication skills can be improved by educational articles, and by brief targeted sexual health training, as reported by Wang et al.[3,30,32] Clinicians of all specialties are increasingly working with trained peer patient advocates in larger cancer centers to broach the subject of sexual pain in women affected by cancer and provide the reliable information, experience, and support patients desire as well as an important patient-centered perspective to include in research in this field.

Obstetrician–gynecologists are the most qualified and best equipped specialists to care for women with sexual pain in the context of cancer, whether the cancer is gynecologic or nongynecologic such as breast cancer. However, a recent survey revealed that, although more than 60% of ob-gyns routinely asked their regular patients about sexual activities, fewer than one third assessed sexual satisfaction or pleasure.[38] As physicians already routinely involved with sensitive, intimate aspects of patients' lives,[39] knowledgeable, motivated ob-gyns can help close the gap in sexual health care for women affected by cancer and for all patients. The goal of this article is to provide tools to evaluate, alleviate, and prevent sexual pain and thereby empower ob-gyns to fully own this role and responsibility.

TERMINOLOGY OF SEXUAL PAIN IN WOMEN AFFECTED BY CANCER

Terminology to categorize vulvar and genital pain was recently updated based on advances in knowledge since the last classification developed in 2003

by the International Society for the Study of Vulvovaginal Disease.[40] In the 2003 version, most women with sexual pain caused by cancer treatments would have been categorized as having vulvodynia with this catch-all term denoting pain without visible cause. The 2015 Consensus Terminology and Classification of Persistent Vulvar Pain was agreed on by the three international professional societies involved in clinical care and research on persistent vulvar and sexual pain (Appendix 1, available online at http://links.lww.com/AOG/A853). Chemotherapy, radiotherapy, and surgery as well as hormonal deficiencies are now specifically listed as causative etiologies, removing sexual pain and dyspareunia in women affected by cancer from the "vulvodynia" category. Utilizing the descriptors and associated factors of the new terminology assists clinicians evaluating sexual pain in women affected by cancer.

Because sexual pain is classified by the American Psychiatric Association as a type of female sexual dysfunction, it is considered a "mental disorder" and included in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.*[41] However, it is exceedingly rare that pain with sexual activity is attributable solely to a mental condition. The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* uses the term "Genitopelvic Pain/Penetration Disorder" and causes confusion by questioning the physical basis of hypoestrogen-induced dyspareunia, the most common etiology of sexual pain in women affected by cancer: "There are no reliable tools or diagnostic methods to allow clinicians to know whether the medical condition or genitopelvic pain/penetration disorder is primary…. The relationship, however, between vulvovaginal atrophy/dryness, estrogen, and pain is not well understood."[41] In actuality, hypoestrogenism is a straightforward examination finding, and a proven cause of dyspareunia, based on robust high-level evidence from interventional studies.[42,43]

BIOPSYCHOSOCIAL ASPECTS OF SEXUAL PAIN AND FUNCTION IN THE CONTEXT OF CANCER

The perspective that sexual pain and dyspareunia are mental disorders may lead to confusion and distress for women affected by cancer if their clinicians focus on psychologic rather than biologic causes of pain. Attitudes of uninformed clinicians may add to psychologic consequences of cancer treatment-related sexual dysfunction, which can then worsen biologic pain.[44,45] For instance, anxiety may contribute to overactivity of pelvic floor muscles, compounding dyspareunia.

The female sexual response is an intricate system affected by and dependent on the big picture, which includes relationship satisfaction, intimacy, communication, and trust.[20] Uncertainty about survival, roles, lifestyle, and finances as well as body image issues and feelings of loss of the "old self" wrought by changes from surgery and radiotherapy are examples of the multifaceted concerns women affected by cancer report. Some experience a sense of bodily trauma inflicted by treatments or from the perception that their breasts or other affected sexual organs have become medicalized. Psychologic and social reactions such as these constitute the biopsychosocial framework of sexual pain and dysfunction in the context of cancer and may diminish desire and sexual response. Importantly, diagnosing a purely psychosocial basis for sexual pain is only appropriate after biologic etiologies have been completely assessed and ruled out.

EVALUATION OF SEXUAL PAIN IN WOMEN AFFECTED BY CANCER

The first step in assessing sexual pain and function in patients with cancer is to ask about it.[6,25] It is essential for ob-gyns to develop their own technique of addressing sexuality comfortably and routinely in patient encounters so that patients will feel that sexual function in general and sexual pain in particular are important aspects of their well-being worthy of being addressed. Patient questionnaires are one convenient method.

Ideally, sexual function would be assessed serially, before cancer diagnosis and treatment, through the active treatment phase, and into the survivorship period. Longitudinal assessment allows an understanding of relationships between cancer treatments and sexual adverse effects and the opportunity to evaluate efficacy of sexual pain interventions. The Female Sexual Function Index is a validated 19-item self-report questionnaire aimed at assessing the domains of sexual function including pain.[46] A short cancer-specific questionnaire, ideal for screening women affected by cancer, consists of four items and may be completed by patients in 3 minutes; it is displayed in Box 2.[47] Psychosocial health and mood issues as well as changes in roles at work, home, or within intimate relationships must be also appraised. Lesbians and bisexual women may find disclosing their sexual activities difficult; always asking whether a partner is male or female enhances communication.

Box 2. Sexual Symptom Checklist for Women After Cancer

Please answer the following questions about your overall sexual function:

1. Are you satisfied with your sexual function? ☐ Yes ☐ No

2. Do you have any concerns about vaginal health? ☐ Yes ☐ No

If not satisfied with sexual function, concerns about vaginal health, or both, please continue.

2. Do you experience any of the following sexual problems or concerns?
   - ☐ Little or no interest in sex
   - ☐ Decreased sensation (or loss of sensation)
   - ☐ Decreased vaginal lubrication (dryness)
   - ☐ Difficulty reaching orgasm
   - ☐ Pain during sex
   - ☐ Vaginal or vulvar pain or discomfort (not during sex)
   - ☐ Anxiety about having sex
   - ☐ Other problem or concern: _____

[TIP: Some patients will respond that they are not having these problems or concerns because they stopped having sex altogether. The health care provider should reassure the patient, let her know that she is not alone, and ask if she can recall what kinds of problems or concerns she was having that led her to stop having sex.]

3. Would you like more information and resources, would you like to speak with someone about these issues, or both? ☐ Yes ☐ No

Reprinted from Bober SL, Reese J, Barbera L, Bradford A, Carpenter K, Goldfarb S, Carter J. How to ask and what to do: a guide for clinical inquiry and intervention regarding female sexual health after cancer. Curr Opin Support Palliat Care 2016;10:44–54.

Clinicians need to have a patient's complete cancer treatment history. Knowing which chemotherapeutic, endocrine, targeted, and immune agents were or are still being used is crucial to management, because their adverse effects vary considerably. Consult her treating oncologist(s) and the pharmaceutical literature for premarketing and postmarketing side effects. Operative and radiotherapy reports also provide needed insights into the etiologies of sexual pain.

Physical examination is the indispensable next step in evaluation. The components of a complete external and internal examination, and relevant findings by anatomic site, in women with cancer and sexual concerns have been systematically reviewed and comprehensively summarized in table form by Lindau et al (Appendix 2, available online at http://links.lww.com/AOG/A854).[48] The examination is more informative, and less painful for the patient, if she is involved with it as much as possible.[49] For instance, have her assist exposure by retracting her labia and clitoral hood herself while she views her vulva with a handheld mirror and points out painful areas. She will increase her knowledge and sense of control, which is empowering in this emotionally difficult setting.

The external examination includes systematic inspection and palpation of the groin, mons, and vulva with each of the architectural elements assessed and findings described, as outlined in Appendix 2, http://links.lww.com/AOG/A854. Women with cancer treatment-induced menopause describe a range of genital symptoms and can point out areas of sensitivity, delicacy, itching, chafing, and irritation. As the introital epithelium dries and thins, pre-existing mild prolapse that had gone unnoticed by the patient may become uncomfortable; discomfort may also accompany changes in the urethral meatus. Similarly, lichen sclerosis or lichen planus, vulvar dermatoses associated with sexual pain, may be exacerbated, and genital herpes simplex virus recurrence may accompany falls in estrogen. Careful examination may disclose specific conditions, which may be mistaken as the "vaginal dryness" extremely common in women affected by cancer and the strongest predictor of sexual dysfunction.[50] In women with breast cancer in "The Health of Women" online cohort study, an ongoing initiative of the Dr. Susan Love Research Foundation, 47% of 3,016 report "vaginal dryness" compared with 24% of 6,026 women without breast cancer.[51] Patients using aromatase inhibitors are at especially high risk for vaginal dryness and sexual side effects with more than half reporting dyspareunia.[35,52–55] Adequately evaluating vulvar symptoms is key for effective therapy.

Include in the examination an assessment for a possible nerve component to pain working with the patient to map areas that are constantly painful or provoked by touch or sexual activity. Focus on the sensory areas of the pudendal, genitofemoral, obturator, ilioinguinal, and iliohypogastric nerves using a cotton swab to touch and point out specific areas (see Appendix 3, available online at http://links.lww.com/AOG/A855). Surgery and radiotherapy for uterine, ovarian, cervical, vulvar, vaginal, bladder, colorectal, and anal cancers may cause neuropathic genital pain resulting from injury of these nerves. Pelvic autonomic nerves responsible for

aspects of sexual, bowel, and bladder function may also be damaged.[56] Mechanisms of injury include neuromata formation after transection; nerve compression or entrapment from disruption of perineural tissues, scarring, and anatomic changes; and radiation damage to the nerve's vasculature. Radiotherapy-induced entrapment of the pudendal nerve has been described; its incidence may be underappreciated.[57,58] A careful neuroanatomy-based examination will identify which pelvic nerves may be pain generators; targeted diagnostic anesthetic injections of these nerves are confirmatory when pain is temporarily relieved.[59] If burning pain, allodynia, dysesthesia, or paresthesias are generalized in the vulva, consider the possibility of chemotherapy-induced peripheral neuropathy. Taxanes, vinca alkaloids, platinum analogues, and 5-fluorouracil medications may cause this potentially disabling adverse effect as well as autonomic neuropathy.[60] Chemotherapy-induced peripheral neuropathy typically affects long peripheral nerves that end in fingers and toes, but the lengthy pudendal nerve is not immune.

A key part of the examination is specific assessment of the vulvar vestibule. In hypoestrogenic breast cancer patients with dyspareunia, the most exquisitely tender area is the vulvar vestibule.[61] The nonkeratinized squamous epithelium here is easily disturbed by hormonal change and inflammation and is the site of provoked vestibulodynia, the leading cause of painful intercourse in premenopausal women.[62] The vestibule may be the first or only genital tissue damaged in women treated for cancer. Introital pain with penetration is severe and burning in quality, and painful fissuring in the thinned posterior fourchette may bleed. Check for allodynia, a feature of vestibulodynia, with the Q-tip test. Begin at the labial skin outside the vestibule, pressing gently with a cotton swab to dent the surface 1 mm deep, noting the patient's reported pain level on a rating scale of 0–5. Repeatedly perform the test, moving inward toward the smooth vestibule surface, from lateral to medial, in organized fashion, addressing the full circle of epithelium, including hymenal remnants and urethra. Record areas and pain ratings on a diagram to aid follow-up. The Q-tip can then be used to gently collect a sample of secretions from the lower third of the vaginal canal for evaluation of pH and saline wet mount or cultures if indicated. The vaginal epithelium reacts quickly to treatment-induced hypoestrogenism with decreased moisture, collagen, glycogen, and hyaluronic acid. An alkaline pH and altered microbiome make it susceptible to bacterial overgrowth and inflammatory vaginitis with discharge that can irritate the vestibule adding to dyspareunia.[63]

The internal vaginal examination is performed after superficial portions of the examination are complete to avoid triggering pain and muscle guarding, which decrease examination accuracy. Gentle digital examination best precedes the speculum examination in patients with cancer who are likely to have vaginal or pelvic floor scarring so that such findings can be take into consideration when choosing speculum size and angle and depth of insertion. Starting with one lubricated digit for patient comfort, gently assess the caliber of the vaginal canal, and the surrounding pelvic floor myofascia, for tone, elasticity, asymmetry, connective tissue restrictions, muscle tenderness, trigger points, and the patient's ability to elicit contraction and relaxation of muscles. Pelvic floor muscle overactivity, and stiffness from hypoestrogenism, may worsen dyspareunia from other causes. Note bladder base pain to palpation. Additional important myofascial findings are obtained by digital anal examination, which needs special attention in patients after radiation and with anorectal cancer, because the anus and anorectal canal may become a source of pain with sexual activities. A bimanual assessment of pelvic organ size, shape, and mobility is then performed.

The vaginal canal is then examined carefully with a speculum, narrow or pediatric if needed, noting epithelial thickness and moisture, length, caliber, capacity, visible lesions, and radiation stigmata, which include pallor, loss of elasticity and lubrication, dryness, thinning, and fibrosis. The cervix should be inspected if present but may be obscured by scar tissue in patients who have undergone radiation for cervical or anal cancers.

Cancer treatments may negatively affect sexual function by causing pain with sexual activities involving nongenital body areas that women often consider important to their sexuality such as the breasts. Ask about and evaluate persistent postlumpectomy, postmastectomy, and postradiation pain that may occur in the breasts, chest wall, axilla, arm, and shoulder in up to 80% after breast cancer.[64–66] (See Appendix 2, http://links.lww.com/AOG/A854 for potential examination findings.) In addition to upper extremity lymphedema, women treated for breast cancer may experience range-of-motion restrictions and arm pain that inhibit intimate activities.[67] Neuroma formation or nerve compression from surgical injury to the intercostal–brachial nerve may cause pain and sensory disturbances. Radiation-induced brachial plexopathy as well as chemotherapy-induced hand and foot syndrome may make some sexual activities painful.[53,68] In the head and neck area, postoperative anatomic

changes, or chemotherapy adverse effects such as mucositis and persistent dry mouth, may alter a woman's physical and emotional comfort with kissing and oral sex. Attending to the various treatment adverse effects that make sexual activities painful for women affected by cancer validates their concerns and enhances care.

Occasionally, patients with sexual pain require additional detailed evaluations, which may or may not fall within their clinician's expertise. Vulvar and pelvic imaging studies, and guided diagnostic nerve blocks to evaluate possible nerve injury, may be needed.[59] Pain in nongenital areas such as the anorectum, urinary tract, chest wall, breast, and axilla requires consultation and treatment by appropriate specialists. Obstetrician–gynecologists can help their patients by identifying and referring to experts in vulvar pain, urology, physiatry, colorectal surgery, neurology, and peripheral nerve surgery in their communities.

TREATMENT OF SEXUAL PAIN AND DYSPAREUNIA IN WOMEN AFFECTED BY CANCER

Contemporary cancer therapies, including surgery, chemotherapy, radiation, targeted medications, hormonal therapy, immunotherapy, and stem cell transplantation, are responsible for most sexual pain in women affected by cancer through several specific mechanisms; more than one may be at work in an individual patient. Table 2 summarizes common mechanisms and mechanism-directed treatment approaches. Obstetrician–gynecologists can rely on their established knowledge base and clinical skills to treat most mechanisms causing sexual pain in women affected by cancer.

Before treatment planning, the patients' goals must be clarified through an open discussion, keeping in mind that criteria for a fulfilling sex life vary greatly between individuals.[23] For instance, the importance of penetrative sex is high for some, but other women affected by cancer may not be interested in genital sexual activity at all, not wishing to pursue therapies. However, spontaneous or provoked vulvar and pelvic pain must be evaluated and treated regardless of current desire for sexual activity. Early intervention can mitigate pain and lessen the likelihood of a persistent pain condition.

Hypoestrogenism

Damage to or suppression of ovarian function with lowering or cessation of estrogen and androgen production is the outcome of many cancer treatments and is the most common cause of sexual pain in women affected by cancer. If hypoestrogenism is expected, preemptively protect the vulvar surface consistently with semiocclusive skin protectants to prevent microabrasions, drying, contact irritation, and resulting sexual discomfort. Simple ointments such as Aquaphor or natural oils, including olive, safflower, or coconut, should be applied frequently, at least after each void or bowel movement. Other preventive strategies are in Appendix 4, available online at http://links.lww.com/AOG/A856.

Low-dose topical estrogen is by far the most effective treatment for hypoestrogenic sexual pain and, instituted early in the course of cancer treatments, will efficiently counter the effects of falling estrogen levels.[42,43] Systemic menopausal hormone therapy, in the low doses currently advised, needs to be supplemented with topical estrogen to adequately support the vulvovaginal tissues in iatrogenic menopause.[42] If the examination shows that estrogen decline has already had its effect, even if severe, dedicated topical use will still reverse the tissue damage in up to 90%.[43] Historically, the site of topical estrogen use has been the vaginal canal, but for most women with sexual pain, the introital area, including the urethra, inner labia minora, vestibule, and posterior fourchette, is a key site for application. If the vulva is very delicate, and in patients with reactions to preservatives and alcohol, custom-compounded hormones in a simple oil or ointment base are better-tolerated. Trying different bases and types of estrogen may be needed in sensitive individuals. As the tissues improve, many women can switch to usual pharmaceutical topical estrogen products. Demonstrating the application for the patient while she observes with a mirror helps individualize treatment for her specific vulvar anatomy and lessens risk of over- or underuse. Start with a small amount applied in a thin layer on a well-defined site at bedtime. Over the next several evenings, increase the application area as needed to cover affected surfaces. After 2–4 weeks, if response is deemed adequate at a follow-up visit, dosing can be decreased to two to three times a week for long-term maintenance.

Low-dose estrogen to support the vaginal canal is also crucial and best begun preemptively. Many products are available for patients to try, including tablets, creams, and rings, and a pessary is in development. Initial nightly use of creams or tablets for 2 weeks, with tapering to two to three times a week, is effective. Patients should be advised to use simple lubricants during penetrative sexual activities; the oils mentioned previously are good options. Twice-weekly vaginal moisturizers

Table 2. Management of Sexual Pain in Women Affected by Cancer

Physiologic Mechanism	Causative Cancer Treatment	Common Types of Sexual Pain	Treatment Options
Hypoestrogenism	Chemotherapy Endocrine therapy Ovarian suppression Oophorectomy Pelvic radiotherapy Stem cell transplantation (GVHD)	Generalized vulvar discomfort and dryness Vestibulodynia Dyspareunia Urethral and bladder pain	Vulvar skin protectants Vaginal lubricants Low-dose topical vulvar and vestibule estrogen Low-dose vaginal estrogen Low-dose topical DHEA or testosterone Ospemifene Hyaluronic acid or other vaginal moisturizers Vaginal and oral probiotics Topical lidocaine to vestibule before penetration Vaginal dilators and vibrators Pelvic floor physical therapy
Anatomic alterations	Surgery Radiotherapy Stem cell transplantation (GVHD)	Vaginal canal obstruction, stenosis, shortening, or absence Dyspareunia Vulvar pain Myofascial pain in pelvic floor or pelvic girdle	Skin protectants Self-massage Vaginal lubricants and moisturizers Vaginal dilators and vibrators Physical therapy Exercise Sexual and couples therapy to aid in modifying sexual activity Group therapy Mind–body therapies*
Neurologic injury to pudendal, pelvic, chest, other nerves			
Neuromata	Surgery	Localized burning pain in genital or abdominal wall surgical scars	Physical therapy with soft tissue mobilization Perineural injections Surgical excision
Nerve compression	Surgery Radiotherapy	Burning, sharp, radiating, or itching pain in vulva, buttocks, chest wall, extremities Paresthesias Vestibulodynia Clitorodynia	Physical therapy with soft tissue mobilization Exercise Perineural injections Transcutaneous electrical nerve stimulation Neuromodulation Acupuncture Mind–body therapies* Surgical decompression
Peripheral neuropathy	Chemotherapy Radiotherapy	Burning pain in feet, toes, fingers, genitals Paresthesias	Oral or topical amitriptyline or duloxetine Topical lidocaine Exercise Nutritional supplements Transcutaneous electrical nerve stimulation Acupuncture Mind–body therapies*

(*continued*)

Table 2. Management of Sexual Pain in Women Affected by Cancer (*continued*)

Physiologic Mechanism	Causative Cancer Treatment	Common Types of Sexual Pain	Treatment Options
Myofascial and musculoskeletal injury	Chemotherapy Endocrine therapy Surgery Radiotherapy Stem cell transplantation (GVHD)	Dyspareunia Myalgias, spasms, or cramping pain in vulva, pelvic floor, pelvic girdle, extremities Arthralgias	Physical therapy Exercise Electrical stimulation Biofeedback Vaginal dilators and vibrators Trigger point injections Dry needling Vaginal or rectal diazepam Botulinum toxin Acupuncture Low-dose vulvovaginal estrogen Mind–body therapies*
Lymphedema	Surgery Radiotherapy	Tight, aching, or provoked pain in involved areas: extremities, vulva, breast, axilla, chest wall	Manual lymphatic drainage Compression wraps and garments Yoga Low- to moderate-intensity exercise Acupuncture
Altered microbiome	Chemotherapy Endocrine therapy Targeted agents Radiotherapy	Irritating vaginal discharge, may result in vestibulodynia Anal irritation Intestinal cramping Diarrhea	Oral and vaginal probiotics Low-dose vaginal estrogen Dietary modifications Antidiarrheal medications
Intestinal injury	Chemotherapy Surgery Radiotherapy	Anorectal pain Anal fissures Intestinal cramping Diarrhea	Oral and vaginal probiotics Hypnosis Dietary modifications Acupuncture Exercise Antidiarrheal medications Mind–body therapies* Anal fissures: topical anesthetics, pelvic floor physical therapy, botulinum toxin
Urinary tract injury	Chemotherapy Surgery Radiotherapy	Provoked urethral pain Bladder base pain with penetration Postcoital bladder pain	Low-dose topical estrogen therapy Physical therapy Dietary modifications Acupuncture Urologic modalities such as bladder instillations Mind–body therapies*

DHEA, dehydroepiandrosterone; GVHD, graft-versus-host disease.
* Mind–body therapies include yoga, qigong, breathing practices, meditation, and mindfulness-based stress reduction.

can also supplement vaginal estrogen; use on alternate nights.

Conjugated equine estrogens and estradiol are the most commonly used topical hormones in North America, but experience in other countries shows that other estrogens such as estriol, even in ultralow doses, benefit hypoestrogenic genital changes.[69,70] A combination 0.03 mg estriol and lactobacilli vaginal suppository improves vaginal dryness without systemic absorption.[69] Promestrione has been prescribed by European gynecologists for intravaginal use for decades. It is a stable estradiol diether, unable to cross the vaginal epithelium or be converted to estradiol, making it an ideal option for women with estrogen-sensitive cancers, but it has not been available in the United States.[71]

Topical androgens can also benefit atrophic vulvar tissues, and testosterone added to estradiol helps in hormonally associated vestibulodynia.[62] Low-dose dehydroepiandrosterone improves sexual pain

and dyspareunia in menopausal women without an increase in serum dehydroepiandrosterone, estrogen, testosterone, or their metabolites.[21,72–74] It is likely to be approved by the U.S. Food and Drug Administration as "Prasterone" in 2016.

Ospemifene is a selective estrogen-receptor modulator with estrogenic activity in the vulvovagina and appears to have a neutral effect on the breast and endometrium. Experience is limited in the context of estrogen-sensitive cancers, but for women with other types of cancer, ospemifene is an option for hypoestrogenic sexual pain.[72,75] It can be supplemented initially, before it takes effect, with low-dose topical estrogen. Some women may prefer this oral approach.

Women with estrogen-sensitive cancers as well as their clinicians are apprehensive about using medications containing hormones, and their fears are heightened by nonevidence-based product labels that need revision by the U.S. Food and Drug Administration.[42,76] Women affected by cancer need accurate information, informed discussions, shared decision-making, and reassurance as part of an individualized risk–benefit assessment. Consensus is developing from the bulk of research, recently reviewed by Santen and, in the context of breast cancer, by the American College of Obstetricians and Gynecologists and Biglia et al, that contemporary low-dose estrogen vaginal products do not raise serum estrogen levels above those in untreated menopausal women.[70,77,78] They are also not associated with higher breast cancer recurrence rates or endometrial stimulation.[42,78] Systemic absorption is unlikely to occur at all if low-dose hormones are applied only to limited areas of vulvar skin and vestibular epithelium. With vaginal estrogen, the epithelium recovers and cornifies during the first weeks of treatment, and absorption becomes undetectable. Initiating treatment early during cancer therapies, before significant hypoestrogenic injury occurs, offers the least chance of systemic exposure while providing women affected by cancer the benefit many seek. The absorption of other topical low-dose hormones, including testosterone and dehydroepiandrosterone, is similarly low but has not been studied in the context of hormonally sensitive cancers.

In patients with sexual pain related to aromatase inhibitors, use of topical estrogens is limited by concerns that any amount of absorbed estrogen may interfere with this medication's effect. A clinical trial evaluating serum estrogen levels in this setting will be completed in September 2017; any benefit afforded by avoiding topical hormones is theoretical at this time.[79] More women may adhere to aromatase inhibitor treatment if their sexual pain and genital discomfort are eased with careful use of low-dose topical estrogen. Adverse effects contribute to the almost 30% early discontinuation rate, and similar noncompliance rate, with endocrine therapies for treatment and chemoprevention of breast cancer, potentially adding to increased mortality.[9,80,81] Consideration can also be given to switching endocrine agents in some cases. For instance, more women on raloxifene report dyspareunia and vaginal dryness compared with tamoxifen.[82] Some women on aromatase inhibitors with distressing sexual pain may benefit from switching to a selective estrogen-receptor modulator such as tamoxifen, even temporarily.[78,80,83] Notably, an increased risk of endometrial cancer has not been observed in women using topical estrogen with tamoxifen.[83] Newer selective estrogen-receptor modulators in development may benefit genital tissues more than those currently available.

In women with a history of endometrial cancer, use of vulvovaginal estrogen remains controversial, although evidence suggests that recurrence rates are not increased with topical use.[70,84,85] Given the available data, it is reasonable to offer endometrial cancer survivors topical estrogen after a discussion of nonhormonal options and potential risks and benefits.

Nonhormonal therapies benefit hypoestrogenism as well as other mechanisms causing sexual pain, either alone or as an adjunct to topical hormones. Consistent vaginal and oral probiotic supplementation may be helpful.[35] Hyaluronic acid vaginal tablets, often used in Europe, performed as effectively as low-dose estradiol when inserted nightly in an 8-week trial.[73,86] In patients with breast cancer, topical lidocaine applied to the vestibule for 10 minutes before penetration, and then removed and replaced with a lubricant if desired, significantly eases dyspareunia.[87] For women wanting to preserve penetrative sexual activity, strategies that allow continuing regular intercourse and orgasm are beneficial. Vaginal dilators or vibrators, with physical therapist guidance if needed, also help maintain introital elasticity and vaginal capacity.

Anatomic Alterations

Surgery and radiotherapy cause sexual pain through various effects, ranging from gross anatomic changes to more subtle adverse effects on skin, mucosa, muscle, connective tissue, nerves, and lymphatics. Self-massage mobilizes soft tissues and may decrease scar formation, introital narrowing, and superficial dyspareunia. Routine use of rehabilitative postoperative physical therapy, including exercise programs,

facilitates healing by increasing pelvic blood flow and strengthening and stretching reactive pelvic floor and girdle muscles.

Pelvic surgery may shorten, narrow, or deviate the vaginal canal, decreasing capacity for intercourse; pelvic radiation may induce a potentially devastating anatomic alteration, vaginal stenosis. Similar outcomes may result if graft-versus-host disease of the vulvovaginal epidermis develops in women treated with stem cell transplantation.[53,88] These adverse effects are challenging to prevent and treat, but committed use of physical modalities, especially dilators, is effective for most. Vaginal dilator use is especially critical for radiated patients, because clinical experience and a recent Cochrane review show that use of dilators is associated with less stenosis.[89] Most guidelines advise insertion of a lubricated dilator, dildo, or vibrator for 10–20 minutes, three times a week, starting within 2–4 weeks of completion of radiation. The goal of dilation is frequent separation of the vaginal walls to minimize formation of adhesions as tissues heal. Similar results may be achieved with regular penetrative intercourse. Stretching the vaginal tissues will also help the underlying myofascia and may prevent fibrosis in this layer. Slight bleeding or spotting with dilator use is common as a result of the fragility of the epithelial tissues, and women need to be reassured that this is expected. Vaginal lubricants, moisturizers, and hormones are important adjuncts. Guidelines regarding how long dilation should continue range from 1 year to indefinitely.

Many women affected by cancer, however, encounter technical difficulty, discomfort, and fear when initiating use of vaginal dilators on their own, leading to poor results and to published studies that do not reflect the benefit of correct use.[89–92] Radiated patients particularly struggle with maintaining a dilator program, often failing to follow the recommendations of their radiation oncologists, whom they may see infrequently after radiotherapy ends.[93] The support of ob-gyns, to assist these patients with an ongoing program, is invaluable. Several strategies help patients' motivation and success over the long-term: referral to psychoeducational groups or peer advocates; an educated office support staff; specialized nurse–educators; a reminder system; more frequently scheduled ob-gyn follow-up visits; and the involvement of an intimate partner as coach and assistant with the dilator program.[91,93]

Success with dilators is higher with the help of expert pelvic floor physical therapists who are skilled in assessing anatomic changes, which may differ significantly between patients, and in providing personal instruction. Treatments include using different types of dilators to maintain or regain vaginal length, flexibility, and capacity and strategies to overcome sexual challenges as well as the manual techniques discussed subsequently. For example, for patients unable to regain enough length, or who have persistent deep dyspareunia, a penis ring (placed around the base of the partner's penis) may be provided to reduce the depth of penetration.

Psychologic ramifications after undergoing radiotherapy directed to women's most intimate body parts appear to be frequent; counseling with a talk therapist knowledgeable about how radiation is performed can reduce distress and its effect on sexual function. Women who have undergone vaginectomies, or who have a short residual vaginal length, benefit from sexual and couples therapy to discuss expanding sexual activities away from a main focus on penetration.[23]

Neurologic Injury

Sexual pain resulting from neuromata, at sites of surgical transection of the pudendal or other pelvic nerve branches, may be eased by manual physical therapy modalities and injections that decrease surrounding myofascial tension and scarring, but surgical excision is often required. For pain from nerve compression, targeted perineural pudendal or other pelvic nerve injections, using an anesthetic and corticosteroid, may provide permanent relief. A therapeutic course of three to four injections at 3-week intervals can be performed with digital or imaging guidance. In persistent cases, surgical approaches for decompression may be needed.[59] Nerve pain resulting from radiotherapy is more difficult to manage as a result of associated vascular injury; nonsurgical and integrative strategies for neuropathic pain, as discussed subsequently, are therefore important approaches.

Prevention and management of chemotherapy-induced peripheral neuropathy in women affected by cancer living long lives after chemotherapy are difficult but essential. Controlling predisposing factors, like diabetes, is necessary before neurotoxic chemotherapy.[60] Early intervention is key, because treatments are less effective in neuropathic pain of longer duration. Most of the commonly used oral neuropathic medications such as gabapentin are of disappointingly low efficacy.[53] Opioid pain relievers do not relieve neuropathic pain and should be avoided. Some evidence supports the use of duloxetine in chemotherapy-induced peripheral neuropathy and low-dose amitriptyline in neuropathic vulvar pain.[63] Topical medications, including lidocaine,

gabapentin, and amitriptyline, applied locally to the vulva or other painful sites benefit some women and avoid systemic side effects. In refractory cases of neuropathic pain, peripheral or spinal neuromodulation may be considered.

Integrative approaches are encouraged to rehabilitate neuropathic pain. Exercise improves peripheral neuropathy, and low- to -moderate-intensity training such as swimming is recommended.[94–96] Patients are often more successful with a formal home exercise program developed by a physical therapist in addition to benefiting from manual pelvic floor therapies. Modalities such as transcutaneous electrical nerve stimulation, acupuncture, and the mind–body therapies of yoga and qigong improve pain in half of patients, a higher response rate than obtained by neuropathic medications.[97–99] Supplements beneficial to other peripheral neuropathies such as α-lipoic acid, vitamin D3, vitamin B12, and magnesium are low-risk interventions. Omega-3 fatty acids were protective in a small randomized trial.[100] High-level evidence exists for the effectiveness of mindfulness-based stress reduction and meditation for improving overall quality of life in cancer survivors; these therapies buffer the physiologic consequences of pain and stress through peripheral and central nervous system mechanisms.[101–103]

Myofascial and Musculoskeletal Injury

Structural and functional adverse effects of surgery and radiation in the pelvic floor myofascia, pelvic girdle, and nongenital musculoskeletal areas may be benefited by physical therapy. For vulvar and pelvic pain, physical therapists may utilize external and internal (intravaginal or intrarectal) manual therapies, including soft tissue mobilization, myofascial release, biofeedback, electrical stimulation, and therapeutic exercises.[63,104] In difficult cases, low-dose diazepam, 5-mg tablets or compounded in suppositories, inserted vaginally or rectally before physical therapy, helps relax pelvic floor muscles to facilitate manual maneuvers; it can also be used nightly during the treatment course and before intercourse.[105] Dry needling or lidocaine injections of myofascial trigger points may improve associated sexual pain. Botulinum toxin injections, into specific hypertense, shortened, or overactive muscles that do not respond to manual therapy, reduce muscle tension, a frequent component of dyspareunia.[106–108] Like epithelium, pelvic floor muscles and connective tissues are supported by estrogen through their own receptors; low-dose vulvovaginal estrogen can improve vascularity and stiffness in iatrogenic menopause. Mind–body therapies counter pain- and stress-induced sympathetic nervous system overactivity that further tightens muscles, decreases blood flow, and impairs healing. Broader musculoskeletal adverse effects, from chemotherapy, endocrine therapies, and targeted and immune agents, also benefit from integrative modalities including yoga, qigong, acupuncture, and nutritional supplements.[55,96]

Other Mechanisms

Extremity or vulvar lymphedema after cancer surgery requires referral to expert physical or occupational therapists or other lymphedema specialists for manual lymphatic drainage, compression wraps and garments, and a home exercise program.[34,56] Physical exercise is now recognized to benefit lymphedema and pain in the breast, chest wall, axilla, and extremities. Historically, women treated for breast cancer were advised against vigorous arm activity, especially with lymphedema; many are still unaware of recent research, systematically reviewed by Bicego, showing improvement in pain and range of movement, and lack of harm, from moderate exercise.[95,109] Yoga in particular is a valuable therapy in this setting with benefits beyond physical pain relief.[35,67] Acupuncture is emerging as a treatment for lymphedema.[110]

A newly appreciated adverse effect of chemotherapy, targeted agents, pelvic radiotherapy, and hypoestrogenism is the unfavorable alteration of vaginal and gut microbiomes.[111] Ensuing vaginitis, diarrhea, and perianal skin irritation may compound sexual pain and improve with oral and vaginal probiotic supplements.

Intestinal, anal, and rectal adverse effects are common after cancer treatments; persistent life-altering bowel disturbances occur in up to 30% after pelvic radiation.[68,112] The lower urinary tract is also sensitive to radiation exposure and at risk for acute and late adverse effects causing bladder pain with intercourse.[53] These include irritative voiding symptoms, radiation cystitis, recurrent infections, and hematuria as well as chronic toxicities such as bladder stones, loss of bladder capacity or compliance, and urethral stricture.

Treatment Considerations

Management of sexual pain and dysfunction in women affected by cancer is a team project, and many large cancer centers now have specialists in gynecology, psychosexual counseling, physical therapy, and mind–body medicine integrated into their survivorship programs. Most patients do not have easy access to these centers for regular ongoing care and count on ob-gyns to treat their sexual pain. Obstetrician–gynecologists can optimize care by

collaborating with oncologic colleagues to support universal screening and treatment of sexual pain. Developing a team of community experts is crucial to this mission. This team needs a sex therapist knowledgeable about sexual pain; those certified by the American Association of Sexuality Educators, Counselors, and Therapists are advised, because sexual pain and dysfunction is now a required "core knowledge area."[113] The team also needs a physical therapist with expertise in pelvic floor dysfunction to add key preventive and treatment approaches; locate one through the websites of the International Pelvic Pain Society or the American Physical Therapy Association (See Appendix 5, available online at http://links.lww.com/AOG/A857, for patient and professional resources.). Including community mind–body professionals such as meditation and yoga instructors in the team is optimal, because these practices reduce stress that exacerbates persistent pain and dysfunction. Open communication with the team, the patient, and her partner (if one exists) is necessary. Nurses are underutilized in the sexual health care of women affected by cancer; involving them with team communication, coordination, and patient education can enhance low-resource settings, help clinicians with time issues, and provide patient support. Volunteer peer advocates are also a valuable resource for all practice settings.

Prevention

Preventing treatment-induced sexual pain from developing in the first place is an important goal. Preexisting sexual pain can be recognized and treated to avoid exacerbation by cancer therapies. Anticipatory guidance about potential sexual effects of therapies, at the time of cancer diagnosis, may improve patient understanding and involvement in future treatments such as vaginal dilators. Early use of topical hormones during cancer treatment, to prevent the common adverse effects of hypoestrogenism on genital tissues, is advised for patients at risk.

Contemporary advances in surgical techniques have led, increasingly, to fewer radical procedures in an effort to maximize benefit while reducing morbidity. Developments that result in less risk for sexual pain include reductions in the extent of vulvar cancer resection; the use of selective lymphadenectomy, radiotherapy, and oophorectomy in endometrial cancer based on risk stratification; sentinel lymph node techniques; and nerve-sparing radical hysterectomy for cervical cancer.[114–124] Obstetrician–gynecologists can assist medical, surgical, and radiation oncologists by managing anatomic alterations and adverse effects on the vaginal canal, pelvic floor, and pelvic organs. During long-term survivorship, ob-gyns can monitor and intervene expeditiously to treat late sexual sequelae.

Survivors of childhood cancer are a unique and growing population with many unmet needs.[125] As more reach adulthood, ob-gyns can address gynecologic adverse effects influencing sexual function, including treatment-induced ovarian damage. Combined hormonal contraception is commonly used as hormone replacement, but may not sufficiently support genital tissues for comfortable sexual activity; topical vulvovaginal hormone use should be encouraged if needed.

Obstetrician–gynecologists can also assist women at high risk for cancer make informed decisions about risk-reducing surgery and chemoprevention.

DISCUSSION

As survivorship continues to improve, women affected by cancer will be in the consult and examination rooms of ob-gyns in growing numbers in years to come for well-woman visits, obstetric and gynecologic conditions, or sexual problems. Obstetrician–gynecologists are the most qualified specialists to evaluate and treat sexual pain, dyspareunia, and other vulvovaginal and pelvic pain conditions in these patients. Effective mechanism-based treatments are available, and by utilizing them, knowledgeable and compassionate ob-gyns can close the gaps in care, and advance the quality of life, for millions of women living with or after cancer.

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