Title

Survivorship, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology.

Journal

Journal of the National Comprehensive Cancer Network : JNCCN, 15(9)

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Publication Date

2017-09-01

DOI

10.6004/jnccn.2017.0146

Peer reviewed

Published in final edited form as:

J Natl Compr Canc Netw. 2017 September ; 15(9): 1140–1163. doi:10.6004/jnccn.2017.0146.

Survivorship, Version 2.2017:

Clinical Practice Guidelines in Oncology

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Abstract

Many cancer survivors experience menopausal symptoms, including female survivors taking aromatase inhibitors or with a history of oophorectomy or chemotherapy, and male survivors who received or are receiving androgen-ablative therapies. Sexual dysfunction is also common in cancer survivors. Sexual dysfunction and menopause-related symptoms can increase distress and have a significant negative impact on quality of life. This portion of the NCCN Guidelines for Survivorship provide recommendations for screening, evaluation, and treatment of sexual dysfunction and menopausal symptoms to help healthcare professionals who work with survivors of adult-onset cancer in the posttreatment period.

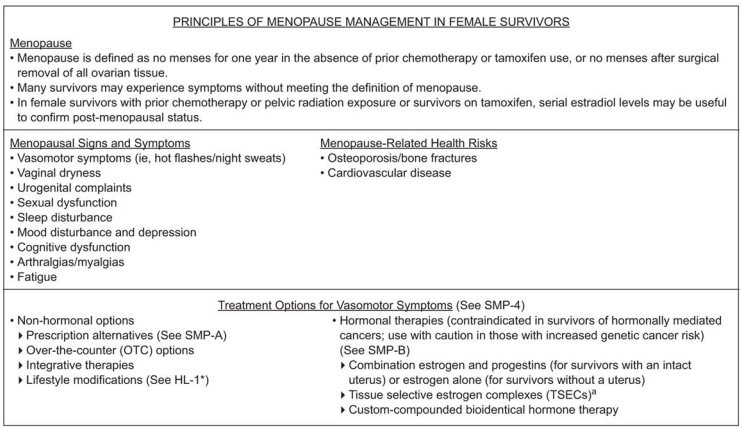
Menopause

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Survivorship define menopause as no menses for 1 year in the absence of prior chemotherapy or tamoxifen use, or no menses after surgical removal of all ovarian tissue. Healthy women reach menopause at a mean age of 51 years, with 95% reaching menopause between 45 and

55 years.[1] Many cancer survivors experience menopausal symptoms without meeting the definition of menopause, including female survivors on aromatase inhibitors or with a history of oophorectomy or chemotherapy and male survivors who received or are receiving androgen ablative therapies (ie, androgen deprivation therapy [ADT]). These symptoms can include hot flashes/night sweats, vaginal dryness, urinary complaints, sexual dysfunction, sleep disturbance, mood disturbance, depression, cognitive dysfunction, arthralgias/myalgias, and fatigue; these menopausal symptoms can occur in both men and women. Males may also experience gynecomastia, decreased testicle size, and thinning of body hair. Menopausal symptoms can have a profound impact on quality of life (QoL).[2,3]

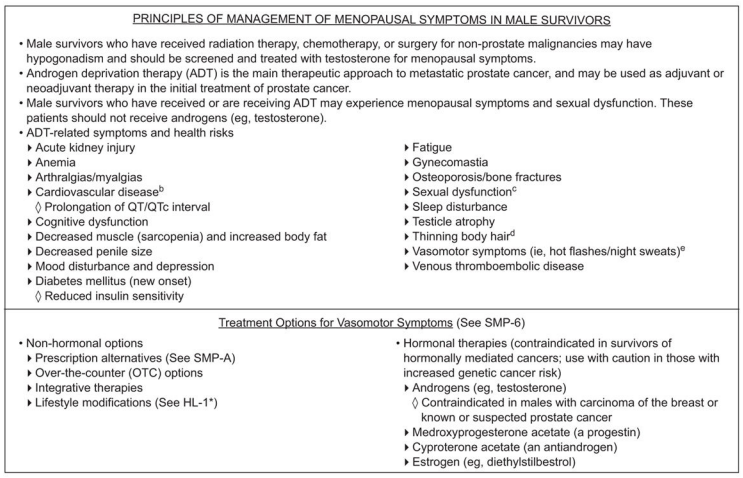
Menopausal symptoms in cancer survivors have been most extensively studied in female survivors after breast cancer treatment, with hot flashes reported occurring in approximately 46% to 73% of survivors.[2,4–6] In one study of breast cancer survivors diagnosed at age ≤40 years, 46% reported hot flashes, 51% reported vaginal dryness, and 39% reported dyspareunia. [6] Similarly, approximately 50% to 80% of men on ADT experience hot flashes, which can persist after treatment.[7–12] The incidence of gynecomastia in men on ADT varies with the method of ADT used and can be as high as 80% in those on estrogen therapy.[9,13]

Premenopausal cancer survivors who have received chemotherapy may experience transient or permanent menopause.[14–16] If appropriate and desired, referral for fertility preservation should be considered before chemotherapy, because studies report that 33% to 73% of premenopausal women treated for breast cancer become perimenopausal or postmenopausal after treatment.[2] Younger survivors with irregular menses may have primary ovarian insufficiency and may develop menopausal symptoms. [17] These women may or may not be fertile and should be counseled about the possibility of pregnancy despite amenorrhea.



SMP-1

MENOPAUSE-RELATED SYMPTOMS (Females)



PRINCIPLES OF MANAGEMENT OF MENOPAUSAL SYMPTOMS IN MALE SURVIVORS

- Male survivors who have received radiation therapy, chemotherapy, or surgery for non-prostate malignancies may have hypogonadism and should be screened and treated with testosterone for menopausal symptoms.
- Androgen deprivation therapy (ADT) is the main therapeutic approach to metastatic prostate cancer, and may be used as adjuvant or neoadjuvant therapy in the initial treatment of prostate cancer.
- Male survivors who have received or are receiving ADT may experience menopausal symptoms and sexual dysfunction. These patients should not receive androgens (eg, testosterone).
- ADT-related symptoms and health risks
  - Acute kidney injury
  - Anemia
  - Arthralgias/myalgias
  - Cardiovascular disease[b]
    - ◊ Prolongation of QT/QTc interval
  - Cognitive dysfunction
  - Decreased muscle (sarcopenia) and increased body fat
  - Decreased penile size
  - Mood disturbance and depression
  - Diabetes mellitus (new onset)
    - ◊ Reduced insulin sensitivity
  - Fatigue
  - Gynecomastia
  - Osteoporosis/bone fractures
  - Sexual dysfunction[c]
  - Sleep disturbance
  - Testicle atrophy
  - Thinning body hair[d]
  - Vasomotor symptoms (ie, hot flashes/night sweats)[e]
  - Venous thromboembolic disease

Treatment Options for Vasomotor Symptoms (See SMP-6)

- Non-hormonal options
  - Prescription alternatives (See SMP-A)
  - Over-the-counter (OTC) options
  - Integrative therapies
  - Lifestyle modifications (See HL-1*)
- Hormonal therapies (contraindicated in survivors of hormonally mediated cancers; use with caution in those with increased genetic cancer risk)
  - Androgens (eg, testosterone)
    - ◊ Contraindicated in males with carcinoma of the breast or known or suspected prostate cancer
  - Medroxyprogesterone acetate (a progestin)
  - Cyproterone acetate (an antiandrogen)
  - Estrogen (eg, diethylstilbestrol)

*Available online, in these guidelines, at NCCN.org.

[b]In males, androgen deprivation therapy (ADT) may increase cardiovascular morbidity and mortality, notably in the first 6 months of therapy and in men with two or more prior cardiovascular events. An increase in serum LDL-cholesterol, HDL-cholesterol and triglycerides may also be seen.

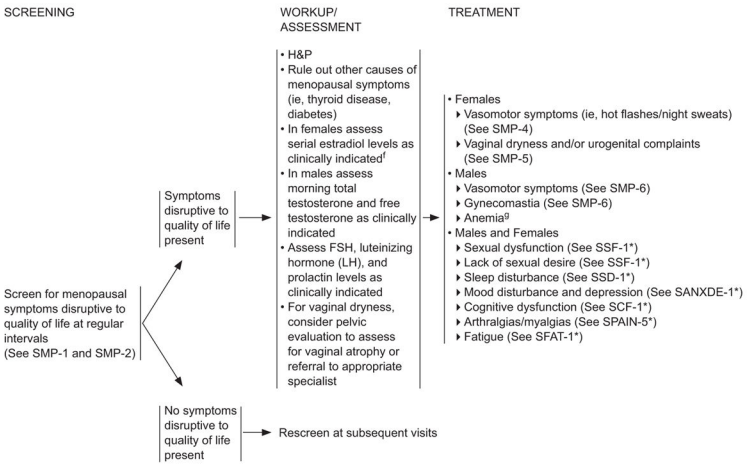
[c]ADT-related sexual dysfunction includes loss of libido, loss of nocturnal and morning erections and varying degrees of erectile dysfunction.

[d]Although facial and body hair decrease, some bald men may have some regrowth of scalp hair.

[e]Hot flashes may be associated with nausea, sweating and may occur during sleep.

SMP-2

MENOPAUSE-RELATED SYMPTOMS (Males)



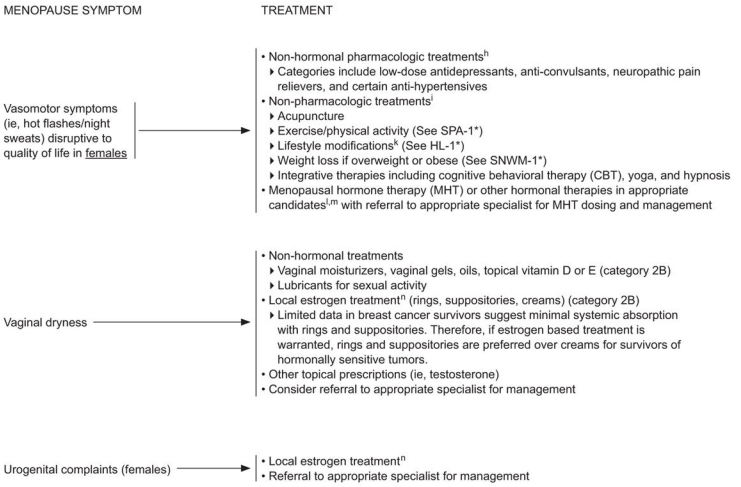
*Available online, in these guidelines, at NCCN.org.

[f]For peri- or pre-menopausal female survivors who have become amenorrheic and later develop bleeding, serial estradiol levels can be useful to determine return of ovarian function. Other markers including follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), and inhibin may provide additional information on ovarian status in female cancer survivors with prior chemotherapy or those on tamoxifen, but alone are not reliable to ensure menopausal status.

[g]ADT-associated anemia is generally responsive to blood transfusions and erythropoietin and should be treated as per the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia (to view the most recent version of these guidelines, visit NCCN.org).

SMP-3

MENOPAUSE-RELATED SYMPTOMS (Females and Males)



*Available online, in these guidelines, at NCCN.org.

[i]Compounds with limited evidence of safety and efficacy (all category 2B)[j]
- Phytoestrogens
- Botanicals
- Dietary supplements
  - Limited data show a possible benefit of black cohosh for vasomotor symptoms in the general population; however, randomized data in breast cancer survivors show no benefit. www.ncbi.nlm.nih.gov/pubmed/16782922

[h]See Non-Hormonal Pharmacologic Treatments and Dosing (SMP-A).

[j]Data are mixed or limited on the effectiveness and safety of these nonpharmacologic treatments in survivors of some cancers.

[k]Drinking alcohol may cause hot flashes in males/females. Individual responses to alcohol may vary. If alcohol is a trigger, consider limiting intake.

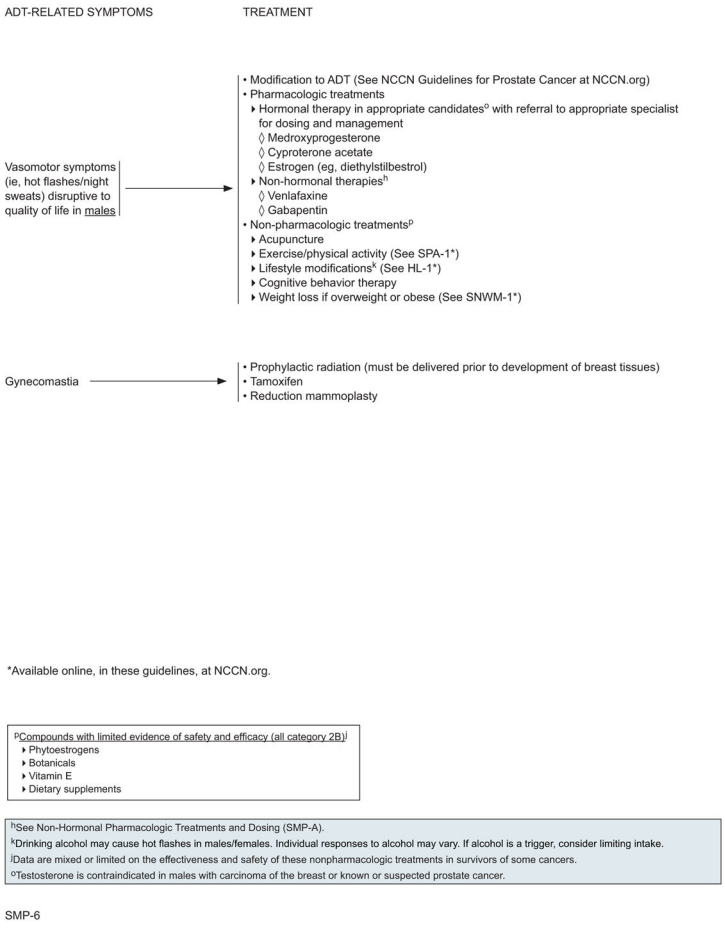
[l]See Principles of Menopausal Hormone Therapy (MHT) Use In Survivors (Females) (SMP-B).

[m]MHT is contraindicated in survivors of hormonally-mediated cancers.

[n]Vaginal estrogen preparations can be used in managing vaginal atrophy, but safety has not been established for use in patients with or survivors of breast cancer.

SMP-4
SMP-5

MENOPAUSE-RELATED SYMPTOMS (Females)



MENOPAUSE-RELATED SYMPTOMS (Males)

NON-HORMONAL PHARMACOLOGIC TREATMENTS AND DOSING[1]

Class	Drug	Commonly used daily dose for managment of vasomotor symptoms	Comments
Antidepressants[2]	Venlafaxine[3] (SNRI)	75 mg	Start at lowest dose possible (25 mg or 37.5 mg) and increase as tolerated
	Desvenlaxafine (SNRI)	100 mg	Start at lowest dose possible (25 mg or 50 mg) and increase as tolerated
	Paroxetine (SSRI)[4]	Low-dose 7.5 mg or Standard paroxetine short acting up to 20 mg, controlled release up to 25 mg	• Low-dose (7.5 mg) paroxetine is the only FDA-approved alternative to hormones for hot flashes • Use with caution for women on tamoxifen
	Escitalopram (SSRI)	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated • Use with caution for women on tamoxifen
	Citalopram (SSRI)	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated • Use with caution for women on tamoxifen
	Fluoxetine (SSRI)[4]	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated • Limited data on effectiveness • Use with caution for women on tamoxifen
	Sertraline (SSRI)[4]	50 mg	• Start at lowest dose possible (25 mg) and increase as tolerated • Limited data on effectiveness • Use with caution for women on tamoxifen
Anti-convulsant	Gabapentin[3]	900 mg (typically 300 mg 3 times a day)	• Start at lowest dose possible (100 mg or 300 mg) and increase as tolerated • Consider starting at night time as this drug tends to cause sedation
	Pregabalin	150–300 mg	Start at lowest dose possible (25 mg) and increase as tolerated
Alpha-agonist hypertensive	Clonidine	0.1 mg (oral or transdermal)	Transdermal preparations may have fewer side effects

[1]For long-term care or maintenance and/or if lack of response, consider referral to appropriate health care specialist. A gradual tapering of dose rather than an abrupt discontinuation of drug is recommended when discontinuing these treatments.

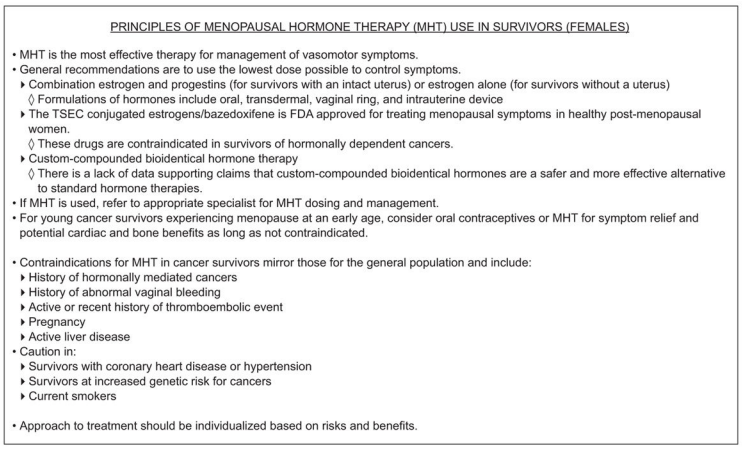
[2]Anticipated clinical response of SSRIs/SNRIs for menopausal symptoms tends to be more rapid than the typical response for depression.

[3]Venlafaxine and gabapentin have been studied for the treatment of menopause symptoms in males, but data are limited. The other therapies have been used but not tested in males.

[4]Pure SSRIs and in particular paroxetine block conversion of tamoxifen to active metabolites through CYP2D6 and should be used with caution for women on tamoxifen.

SMP-A

MENOPAUSE-RELATED SYMPTOMS (Females and Males)



SMP-B

MENOPAUSE-RELATED SYMPTOMS (Females)

Assessment and Evaluation for Menopausal Symptoms

Survivors with menopausal symptoms disruptive to their QoL should be assessed and treated for medical causes of their symptoms such as thyroid disease and diabetes. Laboratory evaluation includes estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin, as clinically indicated. FSH is not a reliable marker of menopausal status in female survivors with prior chemotherapy or pelvic radiation exposure or in female survivors on tamoxifen. In male survivors, morning total testosterone and free testosterone may also be checked if hypogonadism is suspected.[18] For women with complaints of vaginal dryness, a pelvic evaluation should be performed to assess for vaginal atrophy and can be accomplished by referral to an appropriate specialist.

For perimenopausal or premenopausal female survivors who have become amenorrheic and later develop bleeding, serial estradiol levels can be useful to determine return of ovarian function. Other markers, including FSH, anti-Mullerian hormone (AMH), and inhibin, may provide additional information on ovarian status in female cancer survivors with prior chemotherapy or those on tamoxifen, but alone are not reliable to ensure menopausal status.[19,20]

Management of Menopausal Symptoms in Female Survivors

Management of sexual dysfunction, lack of sexual desire, sleep disturbance, mood disturbance, depression, cognitive dysfunction, fatigue, and arthralgias/myalgias is described in other sections of these NCCN Guidelines (visit NCCN.org for the complete version of these guidelines). Management of hot flashes, vaginal dryness, and urogenital complaints associated with menopause are described in the following sections. The panel prefers the use of nonhormonal options as first-line therapy for survivors with menopausal symptoms disruptive to QoL, but hormonal therapies can also be used after consideration of the risks and benefits to an individual survivor.

Nonhormonal Pharmacologic Treatment of Hot Flashes—For the management of hot flashes, nonhormonal pharmacologic options include low-dose antidepressants, anticonvulsants, neuropathic pain relievers, and certain antihypertensives.[21–24]

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to improve vasomotor symptoms in the general population, although the degree of symptom reduction may be smaller than with hormonal treatments.[25–27] A randomized clinical trial in healthy postmenopausal women showed that low-dose paroxetine reduces the frequency and severity of hot flashes.[27] Small studies have shown that SSRIs and SNRIs also reduce the severity and frequency of hot flashes in female cancer and survivor populations.[28–37] One study was a randomized, double-blind, placebo-controlled study of 80 survivors with gynecologic cancers.[29] Results showed that 7.5 mg daily of paroxetine reduced the frequency and severity of vasomotor symptoms and the number of resultant nighttime awakenings.

However, pure SSRIs, and in particular paroxetine, should be used with caution in women taking tamoxifen, because these drugs block the conversion of tamoxifen to active metabolites through inhibition of cytochrome P450 2D6 (CYP2D6).[38] However, analysis of a large database that included almost 17,000 breast cancer survivors found no evidence of an increase in cancer recurrence in women on concurrent tamoxifen and antidepressants, including paroxetine.[39] In contrast, a study of 2,430 breast cancer survivors found an increased risk of cancer death in those taking tamoxifen and an SSRI.[40] The NCCN Panel recommends alternative therapy if available, although no definitive conclusion can be drawn regarding the impact of the interaction between pure SSRIs and tamoxifen. Doses of antidepressants required for improvements in vasomotor symptoms are typically much lower than those needed for depression, and the response is typically faster; side effects include dry mouth, decreased appetite, fatigue, nausea, constipation, and possible sexual dysfunction. On discontinuation, SNRIs and SSRIs should be gradually tapered to minimize withdrawal symptoms.

The anticonvulsants gabapentin and pregabalin have also been shown to improve menopause-related vasomotor symptoms in the general population and in female cancer survivors.[41–46] For example, one trial of 420 breast cancer survivors who experienced ≥2 hot flashes per day found that 900 mg/d of gabapentin decreased the hot flash severity score by 46% at 8 weeks compared with a 15% reduction in the placebo group.[45] As with antidepressants, doses of anticonvulsants used in this setting are lower than in other settings.

Side effects of anticonvulsants include somnolence, so they may be particularly useful when given at bedtime in patients who experience hot flash–disturbing sleep.

Small studies provide evidence that the alphaagonist antihypertensive clonidine can reduce hot flashes in some healthy postmenopausal women.[47,48] Randomized controlled trials (RCTs) in breast cancer survivors also show that clonidine can reduce hot flash frequency and severity in postmenopausal women taking tamoxifen[49,50]; side effects include sleep difficulties, dry mouth, fatigue, dizziness, and nausea.

Several studies have compared nonhormonal pharmacologic treatments. For example, venlafaxine has been compared with clonidine in breast cancer survivors.[51–53] Results of these studies have varied, but it appears that venlafaxine may have a faster effect, but is less well tolerated, than clonidine. A randomized crossover study compared venlafaxine with gabapentin in breast cancer survivors[46] and found that both treatments resulted in similar reductions in hot flash severity. However, 68% of participants indicated a preference for venlafaxine compared with gabapentin (32%).

Nonpharmacologic Treatment of Hot Flashes—Nonpharmacologic treatments, including acupuncture, exercise/physical activity, yoga, lifestyle modifications, weight loss if overweight or obese, hypnosis, and cognitive behavioral therapy (CBT) may help survivors manage hot flashes.[21,23,24,54–59] Phytoestrogens, botanicals, and dietary supplements can also be used (category 2B for all); however, data are mixed or limited on the effectiveness and safety of these particular treatments in the general menopausal population and in cancer survivors.[22,60–67] Vitamin E has been thought to have marginal improvement in vasomotor symptoms in both general menopause and patients with breast cancer, but data are limited and have shown mixed results.[68] Limited data show a possible benefit of black cohosh for vasomotor symptoms in the general population.[69–71] However, randomized data in breast cancer survivors show no benefit.[72]

Acupuncture is used as a treatment for hot flashes in the general population, although evidence supporting its benefit is limited in the noncancer setting. [73,74] Several studies in women with cancer or female survivors have shown acupuncture to be a safe and effective option for managing vasomotor symptoms,[75–78] 3 of which compared acupuncture with either venlafaxine or gabapentin and found acupuncture to be equivalent to or better than drug treatment.[75,77,78]

Yoga may also help survivors manage hot flashes. A randomized trial in 355 healthy perimenopausal and postmenopausal women found that yoga improved QoL associated with menopause, including an improvement in the vasomotor symptom domain. [79] Another RCT showed that yoga improved sleep but did not affect the frequency of symptomatic burden of vasomotor symptoms.[80]

Evidence that exercise/physical activity helps manage hot flashes in postmenopausal women is inconclusive. [21,79,81–87] An RCT of 261 perimenopausal and postmenopausal women found no difference in the frequency of hot flashes between those randomized to an exercise intervention and to the control group.[82] A similar trial involving 248 women also found that

physical activity did not improve vasomotor symptoms.[85] Studies in the survivorship and cancer populations are limited and do not support a role for the use of physical activity specifically to improve hot flash symptoms.[88] Despite the lack of data suggesting a benefit for vasomotor symptoms, the NCCN Panel believes that physical activity should be recommended in menopausal cancer survivors given the many beneficial effects on overall health.

Other lifestyle modifications may also help minimize vasomotor symptoms. In the Women's Health Initiative (WHI) Dietary Modification trial of 17,473 postmenopausal women not taking menopausal hormone therapy (MHT), those who lost ≥10% of their body weight were more likely to eliminate hot flash symptoms than those who maintained their body weight.[56] Data in breast cancer survivors also suggest that weight loss may help alleviate hot flashes in this population.[57,59] A longitudinal study in 761 women showed that those who quit smoking saw improvements in the frequency and severity of hot flashes compared with those who continued to smoke.[89] Although studies of this sort have not been performed in survivor populations, data suggest that survivors who are current smokers are more likely to experience hot flashes.[90] Individual vasomotor responses to alcohol vary.[91] If alcohol triggers hot flashes in an individual survivor, limiting intake should be recommended.

Evidence suggests that CBT may reduce vasomotor symptoms in the general population[92,93] and has been studied for the management of vasomotor symptoms in cancer and survivor populations. In one trial, patients with breast cancer were randomized to either receive CBT, CBT plus an exercise intervention, or a control group.[88] Results suggested that CBT lessened the perceived burden of hot flashes. Another study randomized 96 women with menopausal symptoms after breast cancer treatment to a group CBT intervention or usual care group,[94] and found that the hot flashes and night sweats problem rating was significantly reduced in the CBT arm.

Hormonal Treatment of Hot Flashes—MHT is the most effective treatment for the management of vasomotor symptoms in postmenopausal women.[1,95–99] However, use of long-term MHT is controversial because the associated health risks are thought to outweigh potential benefits. In the past, MHT was typically given to postmenopausal women not only to treat vasomotor symptoms, but with the thought that MHT was effective at preventing heart disease. The best data examining health benefits and risks came from the large WHI study which showed that estrogen alone in postmenopausal women with prior hysterectomy was associated with an increased risk of stroke, a decreased risk of hip fracture, and had no effect on coronary heart disease or breast cancer incidence.[100] In the WHI, estrogen plus progestin in postmenopausal women with a uterus was associated with a decreased risk of colorectal cancer (CRC) and hip fracture and an increased risk of stroke, pulmonary embolism, and invasive breast cancer.[101] The study participants also had a higher rate of death from lung cancer during the intervention and were diagnosed with more advanced stages of CRC during the intervention and follow-up than those who received placebo.[102–104] MHT was also associated with an increase in breast cancer incidence, and the cancers were more likely to be lymph node–positive.[105,106] However, the absolute number of trial participants diagnosed with breast cancer was small, and the absolute risk was low. A systematic review of randomized double-blinded studies of MHT versus placebo found no

evidence that MHT affects the incidence of CRC, but found that MHT increases the risk of breast cancer and death from lung cancer in postmenopausal women taking estrogen and progestins combined.[107]

Data from retrospective studies and an incomplete RCT suggest that MHT is safe to use in survivors of early-stage endometrial cancer.[108–112] In breast cancer survivors, the data are inconclusive because the only 2 RCTs of MHT in this population had conflicting results. The HABITS trial found an increased risk of breast cancer recurrence with the use of MHT, with a cumulative incidence at 5 years of 22.2% in the MHT arm and 8.0% in the control arm.[113] In the Stockholm trial, no difference was seen in breast cancer recurrence after 10.8 years of follow-up.[114]

Overall, based on these data, the panel believes that MHT can be used in appropriate female cancer survivors. Alternatives to MHT should typically be tried first, and patients should be referred to an appropriate specialist for dosing and management of MHT. MHT is contraindicated in survivors with a history of hormonally mediated cancers. Other contraindications for survivors mirror those for the general population and include a history of abnormal vaginal bleeding, active or recent history of thromboembolic event, pregnancy, and active liver disease. In addition, MHT should be used with caution in survivors with coronary heart disease or hypertension, in current smokers, and in those with an increased genetic cancer risk. In general, the lowest dose possible to control symptoms should be used, and treatment should be individualized based on risks.

Hormonal treatments for the relief of hot flashes in women include combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for those without a uterus). Different local and systemic formulations of hormones exist including oral, transdermal, vaginal ring, and an intrauterine device. Estrogen transdermal formulations may be preferred over other formulations due to lower rates of venous thromboembolism (VTE) and stroke.[115] Micronized progestin may be preferred over medroxyprogesterone acetate (MPA) due to lower rates of VTE and breast cancer risk. Other hormonal options for treating hot flashes include novel therapies that combine a selective estrogen receptor modulator (SERM) with estrogen, creating a tissue selective estrogen complex, one of which contains a conjugated estrogen and the SERM bazedoxifene[116] and is FDA-approved for treating menopausal symptoms in healthy postmenopausal women. Custom compounded bioidentical hormones are not recommended because data supporting claims that they are safer and more effective than standard hormones are lacking.[117,118] Young cancer survivors experiencing menopause at an early age can consider oral contraceptives or MHT for symptom relief and potential cardiac and bone benefits as long as not contraindicated.

Treatment of Vaginal Dryness—Vaginal dryness can be treated with over-the-counter vaginal moisturizers, gels, oils, and topicals for comfort and topical vitamin D or E.[119,120] Lubricants can be used for sexual activity.[121,122] Local hormonal treatments can also be used,[101,123–127] although some controversy exists regarding their safety in survivors of hormone-dependent cancers.[128] However, evidence suggests that local estrogen does not increase the risk of breast cancer recurrence.[129] Vaginal estrogen preparations include rings, suppositories, and creams, and they have been shown to be effective for managing symptoms

of vaginal dryness in menopausal women.[127,130] Limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories and are therefore preferred for survivors with hormone-sensitive tumors if estrogen-based treatment is warranted.[128,131] Other topical hormone prescriptions (ie, testosterone) can also be considered, but data regarding safety or effectiveness are limited. One RCT of 441 survivors of breast or gynecologic cancer showed that vaginal dehydroepiandrosterone (DHEA) led to significant improvements in sexual desire, arousal, pain, and overall sexual function.[132] In this trial, clinically important systemic estrogenic activity was not evident, and the treatment was safe and well tolerated.

Overall, the decision to use local hormones should be individualized with a discussion of the possible risks and benefits. Referral to an appropriate specialist for management can also be considered.

Treatment of Urogenital Complaints—Women sometimes present with urogenital complaints associated with menopause, such as urogenital atrophy and urinary incontinence. The NCCN Panel recommends treatment with local vaginal estrogen and referral to an appropriate specialist.[130,133] See “Treatment of Vaginal Dryness,” (previous section) for a discussion on the safety of vaginal estrogen.

Management of ADT-Related Symptoms in Male Survivors

Prostate cancer survivors may be on ADT for 2 to 3 years without evidence of disease (see the NCCN Guidelines for Prostate Cancer, available at NCCN. org), and may experience many symptoms, including hot flashes, gynecomastia, and anemia.

Vasomotor Symptoms—For vasomotor symptoms disruptive to QoL in men, alternative ADT options, such as intermittent ADT or antiandrogen monotherapy, can be tried if deemed appropriate by the treating oncologist (see NCCN Guidelines for Prostate Cancer).

Androgens (eg, testosterone) are used as MHT for the relief of hot flashes in men who have hypogonadism and are cured of prostate cancer or who have hypogonadism from chemotherapy or radiation for other malignancies. However, androgens are contraindicated in men with advanced prostate malignancy on ADT. Hormonal options for the relief of hot flashes in survivors on ADT include MPA, estrogen, and cyproterone acetate.[134–137]

Nonhormonal options include the SSRI venlafaxine and the anticonvulsant gabapentin. Gabapentin has been shown to be safe and moderately effective at controlling hot flashes in men with prostate cancer in 2 RCTs.[138–140] Case reports and small pilot studies have shown that venlafaxine may improve hot flash symptoms in men with prostate cancer undergoing ADT.[141]

As in female cancer survivors, men with ADT-related symptoms can try nonpharmacologic treatments, including acupuncture, exercise/physical activity, yoga, lifestyle modifications, weight loss if overweight or obese, hypnosis, and CBT. Small studies in prostate cancer survivors with a history of ADT have also found that acupuncture is effective at controlling hot flashes in this population.[142,143] A study of 68 patients with prostate cancer on ADT

also found that CBT reduced the perceived burden of hot flashes compared with usual care.[144]

Also as in women with vasomotor symptoms, phytoestrogens, botanicals, and dietary supplements are often used in men (category 2B for all). However, data are very limited on the effectiveness and safety of these nonpharmacologic treatments in survivors on ADT.[145] Furthermore, there are concerns that supplemental vitamin E may increase the risk for prostate cancer.[146,147]

Gynecomastia—Gynecomastia and breast pain can be treated in men on ADT by prophylactic radiation (must be delivered before development of breast tissue), tamoxifen, or reduction mammoplasty.[13,148,149]

Anemia—Anemia in men on ADT is generally responsive to erythropoietin (EPO) and blood transfusions. These men can be treated as per the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia (available at NCCN.org).

Sexual Dysfunction

Cancer treatment, especially hormonal therapy and therapy directed towards the pelvis, can often impair sexual function. In addition, depression and anxiety, which are common in survivors, can contribute to sexual problems. Thus, sexual dysfunction is common in survivors and can cause increased distress and have a significant negative impact on QoL.[150–155] Nonetheless, sexual function is often not discussed with cancer survivors[156–160]; reasons for this include a lack of training of healthcare professionals, discomfort of providers and/or survivors with the topic, survivors' perception of discomfort from the provider, and insufficient time during visits for discussion.[150] However, effective strategies for treating both female and male sexual dysfunction exist, making these discussions a critical part of survivorship care.

Female Sexual Dysfunction

Female sexual problems relate to issues of sexual desire, arousal, orgasm, and pain.[161–163] Sexual dysfunction after cancer treatment is common in female survivors.[154,164–170] A survey of 221 survivors of vaginal and cervical cancers found that the prevalence of sexual problems was significantly higher among survivors than among age- and race-matched controls from the National Health and Social Life Survey (mean number of problems, 2.6 vs 1.1; $P<.001$).[168] A survey of survivors of ovarian germ cell tumors and age-, race-, and education-matched controls found that survivors reported a significant decrease in sexual pleasure.[171]

Female sexual dysfunction varies with cancer site and treatment modalities.[165,166] For example, survivors of cervical cancer treated with radiotherapy had worse sexual functioning scores (for arousal, lubrication, orgasm, pain, and satisfaction) than those treated with surgery, whose sexual functioning was similar to that of age- and race-matched noncancer controls.[165] A systematic review of sexual functioning in cervical cancer survivors found similar results, except that no differences in orgasm/satisfaction were observed.[172]

Chemotherapy seems to be linked to female sexual dysfunction in breast cancer survivors,[166] possibly related to the prevalence of chemotherapy-induced menopause in this population.[162] Furthermore, body-image changes related to breast cancer surgery and reconstruction can affect women's sexual health and well-being.[173] In addition, survivors with a history of hematopoietic stem cell transplant (HSCT) may have multiple types of sexual dysfunction, even 5 to 10 years after diagnosis.[174–176] Some of the sexual dysfunction associated with HSCT is related to graft-versus-host disease (GVHD), which can result in vaginal fibrosis, stenosis, mucosal changes, vaginal irritation, bleeding, and increased sensitivity of genital tissues.[175,177] In addition, high-dose corticosteroids used for chronic GVHD can increase emotional lability and depression, affecting feelings of attractiveness, sexual activity, and sexual QoL.

Male Sexual Dysfunction

The NIH Consensus Conference on Impotence defined impotence as "male erectile dysfunction, that is, the inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[178] In fact, impotence and erectile dysfunction (ED) are not synonymous. Impotence can involve problems of sexual desire, orgasm, or ejaculation, which are not necessarily linked with achieving or maintaining an erection.[179]

ED occurs frequently in the general population and increases with age.[180] In one community-based study, 33% of men aged ≥75 years reported moderate ED or worse.[181] ED is also very common in male cancer survivors. Anticancer treatment modalities used in a variety of cancers have the potential to damage blood vessels, leading to a reduction in blood circulation to the penis and/or damage to the autonomic nervous system. Thus, higher rates of ED are seen in cancer survivors than in the general population. The prevalence of ED in survivors of CRC has been reported to range from 45% to 75%,[151,182,183] and has been reported in up to 90% of survivors of prostate cancer.[184–188]

Male cancer survivors exposed to radiation or chemotherapy often experience hypogonadism, usually primary hypogonadism. Hypogonadism in men refers to a decrease in the production of sperm and/or testosterone. Primary hypogonadism is the result of testicular failure. In these men, testosterone levels and sperm counts are below normal, and serum LH and FSH are above normal. Secondary hypogonadism is a disease of the pituitary or hypothalamus. In men with secondary hypogonadism, serum testosterone levels and sperm counts are subnormal and serum LH and FSH levels are normal or reduced. Adult-onset hypogonadism is characterized by a deficiency of testosterone and a failure of the body to produce an adequate compensatory response. In these men, low testosterone levels are associated with normal or low levels of gonadotropins, suggesting physiologic failure of both the testicles and hypothalamic-pituitary system.

Evaluation and Assessment of Sexual Function

All adult cancer survivors, regardless of gender identity and sexual orientation, should be asked about their sexual function at regular intervals by inquiring about any concerns or distress regarding sexual function, sexual activity, sexual relationships, or sex life. Cancer survivors who report distress should be evaluated further. Inquiries into treatment-related

infertility should be made if indicated, with referrals as appropriate. ASCO's recently updated clinical practice guidelines on fertility preservation for patients with cancer have more information on the topic.[189] It is important for providers to be aware that fertility issues can be addressed in the survivorship phase, whether or not they were addressed before treatment.[190–192] A discussion regarding the need for contraception may also be helpful in some cases, because the incidence of unplanned pregnancies is approximately 3 times higher in cancer survivors than in the general population.[193]

Survivors for whom screening does not indicate an issue with sexual function should be rescreened at subsequent visits. For survivors with sexual function concerns who do not wish to discuss them at the current visit, referral can be made to a sexual health specialist if the patient is interested. These survivors should also be reevaluated and engaged in discussions about the potential impact of treatment on sexual function at future visits.

For survivors who want to discuss their sexual function further, screening tools can be considered, several of which are available for both men and women. For women, options include the Brief Sexual Symptom Checklist for Women, the Arizona Sexual Experiences Scale (ASEX), the Female Sexual Function Index (FSFI), and a breast cancer-specific adaptation of the FSFI (FSFI-BC).[194–197] For men, the Sexual Health Inventory for Men, the Sexual Quality of Life Questionnaire–Men, and the PROMIS Sexual Function and Satisfaction Measures–Male are examples. [180,198,199] The FSFI has been validated in patients with cancer and cancer survivors.[200,201] The FSFI and ASEX were also identified in a systematic review as tools that have acceptable psychometric properties in patients with breast cancer.[202] The other tools have not been validated in cancer or survivor populations.

Survivors with concerns about their sexual function should undergo a more thorough evaluation, including screening for possible psychosocial problems or mental health issues (ie, anxiety, depression, relationship issues, body image concerns, drug or alcohol use) that can contribute to sexual dysfunction. It is also important to identify prescription and over-the-counter medications (especially hormone therapy, narcotics, beta blockers, and SSRIs) that could be a contributing factor. Traditional risk factors for sexual dysfunction, such as cardiovascular disease, diabetes, obesity, smoking, and alcohol abuse, should also be assessed, as well as the patients' oncologic and treatment history. In addition, the impact of cancer and its treatment on sexual function should be explored further. Finally, for men, total morning testosterone should be measured, if indicated by concerns regarding hypogonadism.[18]

Interventions for Female Sexual Dysfunction

Female sexual dysfunction is often multifactorial in nature. Therefore, treatment of sexual dysfunction often requires a multidimensional treatment plan that addresses the underlying issues, which can be physiologic (eg, menopause, illness), disease-induced, medication-induced, psychologic (eg, anxiety, depression), and interpersonal. Informed patient and physician decision-making is the standard for guiding treatment decisions for treatment. Referrals to specialists (ie, psychotherapy, sexual/couples counseling, gynecologic care, sexual health specialist) should be made if appropriate and available.

Overall, the evidence base for interventions to treat female sexual dysfunction in survivors is weak and high-quality studies are needed.[203,204] Based on evidence from other populations, evidence from survivors when available, recommendations from the American Congress of Obstetricians and Gynecologists (ACOG),[161] and consensus among the NCCN Survivorship Panel, the panel made recommendations for treatment of female sexual dysfunction in survivors. The panel recommends that treatment be guided by the specific type of problem. Treatments depend on the type of sexual dysfunction and may include both over-the-counter and prescription options, as well as pelvic physical therapy and integrative therapies. When prescription medications are being considered, the risks and benefits should be discussed or the survivor should be referred to an appropriate healthcare provider (eg, sexual health specialist) for prescription and/or treatment. The evidence base for each recommendation is described herein.

Integrative therapies, including yoga and meditation, may be helpful for female survivors with sexual dysfunction.[79,205] In addition, CBT has been shown to be effective at improving sexual functioning in breast cancer survivors.[206]

Vaginal moisturizers and gels, oils, and topical vitamin D or E can help alleviate symptoms such as vaginal dryness and sexual pain,[120,207] although data on these over-the-counter products are limited in the general population. In one study of breast cancer survivors, the control group used a nonhormonal moisturizer and saw a transient improvement in vaginal symptoms.[118] Topical anesthetics may help with vaginal pain as demonstrated in a study of 46 breast cancer survivors that found that application of lidocaine to the vulvar vestibule before vaginal penetration improved dyspareunia.[208]

Pelvic physical therapy (ie, pelvic floor muscle training) may improve sexual pain, arousal, lubrication, orgasm, and satisfaction. A small study of 34 survivors of gynecologic cancers found that pelvic floor training significantly improved sexual function.[209]

Vaginal dilators are an option for survivors with pain during sexual activity. In addition, they are used for survivors with vaginal stenosis from pelvic radiation. However, evidence for the effectiveness of dilators is limited.[210]

Several topical prescription medications can also be considered for female survivors with sexual dysfunction. For example, vaginal estrogen (pills, rings, or creams) has been shown to be effective in treating vaginal dryness, itching, discomfort, and painful intercourse in postmenopausal women.[101,123–127] A study of 76 postmenopausal breast cancer survivors on aromatase inhibitor therapy found that intravaginal testosterone cream or an estradiol-releasing vaginal ring were safe and improved vaginal atrophy and sexual function.[211]

Vaginal androgens (ie, DHEA; also known as prasterone) can be considered for vaginal dryness or pain with sexual activity. Prasterone received FDA approval in 2016. Several studies have shown prasterone to be effective at reducing dyspareunia in postmenopausal women.[212–216] However, a systematic review and meta-analysis published in 2015 concluded it is uncertain whether prasterone improves menopausal symptoms.[217] An RCT of 441 survivors of breast or gynecologic cancer showed that vaginal DHEA led to significant improvements in sexual desire, arousal, pain, and overall sexual function.[132] In

this trial, clinically important systemic estrogenic activity was not evident, and the treatment was safe and well tolerated. Overall, safety data for the use of androgen-based therapy in survivors of hormonally mediated cancers are limited. The FDA label for prasterone warns that exogenous estrogens are contraindicated in women with a history of breast cancer.[218]

In 2013, the FDA approved the SERM ospemifene for treating moderate to severe dyspareunia in postmenopausal women without known or suspected breast cancer and without a history of breast cancer. [219] Ospemifene has been studied in several large trials of women with postmenopausal vulvar and vaginal atrophy and was found to effectively treat vaginal dryness and dyspareunia.[220–222] No data in the survivor population are available. The NCCN Panel recommends consideration of ospemifene for dyspareunia in survivors of cancers that are not hormonally sensitive.

In August 2015, the FDA approved flibanserin to treat acquired, generalized hypoactive sexual desire disorder in premenopausal women.[223] Meta-analyses have shown that flibanserin resulted in approximately 1 additional satisfying sexual event every 2 months in premenopausal women.[224,225] This drug has not been studied in patients with cancer or survivors, but it is a reasonable option to discuss with premenopausal survivors with low or lack of desire, libido, or intimacy; other options for these survivors include bupropion and buspirone.[226] These drugs have been studied in a few trials involving noncancer populations. [227–229] Despite limited safety and efficacy data, these drugs may be considered as options for hypoactive sexual desire disorder.

Currently, the panel does not recommend the use of oral phosphodiesterase type 5 inhibitors (PDE5i) for female sexual dysfunction due to the lack of data regarding their effectiveness in women. Although thought to increase pelvic blood flow to the clitoris and vagina,[230,231] PDE5i showed contradictory results in RCTs of various noncancer populations of women being treated for sexual arousal disorder.[232–237] More research is needed before a recommendation can be made regarding the use of sildenafil for the treatment of female sexual dysfunction.

Interventions for Male Sexual Dysfunction

Using a consensus-based approach, the NCCN Survivorship Panel concluded that: 1) informed patient and physician decision-making is the standard for guiding treatment decisions for treatment of male sexual dysfunction; and 2) a psychological overlay frequently exists in patients with sexual dysfunction and may be even more pronounced in the face of cancer survivorship. Thus, treatment of male sexual dysfunction may require a multidimensional treatment plan that addresses the underlying issues. Referrals to specialists (ie, psychotherapy, sexual/couples counseling, urology, sexual health specialist) should be made if appropriate and available. Treatment of sexual dysfunction in male survivors should be guided by the specific type of problem.

Treatment for male sexual dysfunction should include modification of risk factors, such as smoking cessation, weight loss, increasing physical activity, and avoiding excess alcohol consumption. Several trials have shown that such lifestyle modifications can improve sexual function in men.[238–241] In fact, one study found that PDE5i treatment with an aerobic

activity program was more effective than PDE5i treatment alone in 60 men with ED.[242] Evidence for these effects in patients with cancer and survivors is lacking.

In addition, treatment of psychosocial problems, with referral to sex and couples therapy as appropriate, can often alleviate symptoms of male sexual dysfunction.[243–247] Small studies in survivors of prostate cancer suggest that these approaches can also be helpful in the survivorship population.[248,249] Therapy is often offered in conjunction with medical therapy.

PDE5i treatment has been shown to improve the symptoms of ED and to be well tolerated.[250,251] These drugs can also be used for problems with male orgasms (eg, less intensity, difficulty achieving). Many studies have also shown the efficacy and tolerability of PDE5i for treating ED in patients with cancer and survivors.[252,253] Importantly, PDE5i is contraindicated in patients taking oral nitrates because together they can lead to a dangerous decrease in blood pressure. [254,255] The timing and dose of on-demand PDE5i should be started conservatively, and it should be titrated to maximum dose if needed.[179] Patients should be monitored periodically for efficacy, side effects, and any significant change in health status. In addition to on-demand PDE5i treatment, studies have shown that daily, low-dose treatment with these drugs can be effective.[256–259]

If total morning testosterone is <300 ng/dL, then hypogonadism is diagnosed and testosterone therapy may relieve symptoms of ED, problems with ejaculation, or problems with orgasm.[260] An RCT in 470 men aged >65 years with testosterone levels <275 ng/dL found that testosterone gel led to improvements in sexual function, desire, and activity.[261,262] Other studies have shown that the addition of testosterone to PDE5i therapy in men with low serum testosterone levels helps improve ED.[263–268] Testosterone therapy should not be used if contraindicated by the primary oncologic diagnosis (eg, prostate cancer on active surveillance, prostate cancer on ADT).

Other treatments may help with ED and ejaculation and orgasm issues. Although evidence in the general population is lacking,[269] studies in prostate cancer survivors suggest that pelvic physical therapy (ie, pelvic floor muscle training) may improve sexual function in this population.[270,271] Vibratory therapy may reduce problems with orgasm.[272] Finally, SSRIs (paroxetine, sertraline, citalopram, fluoxetine) dosed daily or clomipramine dosed on-demand may relieve problems with ejaculation (dry, retrograde, delayed, or climacturia).[273–276]

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(Please note: Underlining denotes the lead of the subcommittee)

Specialties: ξBone Marrow Transplantation; λCardiology; ɛEpidemiology; ΠExercise/Physiology; ΩGynecology/Gynecologic Oncology; ‡Hematology/Hematology Oncology; ΦInfectious Diseases; ÞInternal Medicine; †Medical Oncology; ΨNeurology/Neuro-Oncology; #Nursing;; ≅Nutrition Science/Dietician; ¥Patient Advocacy; €Pediatric Oncology; θPsychiatry, Psychology, Including Health Behavior; £Supportive Care Including Palliative, Pain Management, Pastoral Care, and Oncology Social Work; ¶Surgery/Surgical Oncology; ωUrology

Individual Disclosures for Survivorship Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
K. Scott Baker, MD, MS	Cincinnati Childrens Medical Center	None	None	5/1/17
Shrujal Baxi, MD, MPH	AstraZeneca Pharmaceuticals LP; and Bristol-Myers Squibb Company	AstraZeneca Pharmaceuticals LP; and Flatiron Health	None	7/14/17
Gregory Broderick, MD	None	Repros	AbbVie	7/17/17
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Crystal S. Denlinger, MD	Advaxis; Astex Pharmaceuticals; Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; Incyte; MedImmune Inc.; Merrimack Pharmaceuticals; OncoMed Pharmaceuticals; and Pfizer Inc.	Eli Lilly and Company; EMD Serono; and Merrimack Pharmaceuticals	None	2/9/17
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Terry S. Langbaum, MAS	None	None	None	8/8/17
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Jose G. Montoya, MD	None	None	None	9/15/16
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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty conflict:

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[b]The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:

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NCCN Categories of Evidence and Consensus

Category 1

Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A

Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B

Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3

Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.