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Breast Cancer Survivorship

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Introduction

Breast cancer remains the most common type of cancer among Canadian women, with 28,900 new cases in 2022 alone. Improved detection through screening mammography and advances in multi-modality therapy account for the decline in breast cancer mortality seen in Canada since the 1980s. As 5-year survival rates reach 89%, the number of breast cancer survivors is rising.[1]

The concept of cancer survivorship has existed for decades, as has the appreciation that it is a complex domain of cancer care that begins at the time of diagnosis. Even within the group of patients with breast cancer, survivorship experiences and care needs are diverse, reflecting variability in tumour clinicopathologic characteristics, treatment plans, and prognosis. Evidence-based tools and guidelines suggest the assessment and management of cancer survivor's physical, psychological, social, financial, and employment well-being. There is a need to clinically monitor for breast cancer recurrence and the development of secondary malignancies through screening. Survivorship also warrants attention to health promotion, including weight management, nutrition, physical activity, preventive health, and cessation of alcohol and cigarettes. The provision of survivorship care is the responsibility of all healthcare professionals, which requires close coordination between primary care and specialized cancer centres.[2-4]

In this article, we focus on the physical and psychosocial long-term and late effects faced by survivors of early-stage breast cancer. Many adjuvant therapies for breast cancer are associated with toxicities that negatively impact quality of life (QoL) and adherence. Nonadherence is important to address because it compromises breast cancer outcomes.[4,5]

Long-term and Late Effects Impacting Breast Cancer Survivors

By definition, long-term effects develop during treatment, and late effects develop after completion. Both can persist for years and may include cognitive dysfunction, psychological distress, pulmonary fibrosis, hepatic steatosis, venous thromboembolism, musculoskeletal symptoms, fatigue, osteoporosis, cardiotoxicity, lymphedema, sexual dysfunction, infertility, elevated risk of secondary malignancy, pain, and peripheral neuropathy. Survivors may be left physically and functionally limited after treatment.[3] The risk of physical and psychosocial long-term and late effects in those treated for early-stage breast cancer relates to receptor status, locoregional nodal involvement, genetic predisposition, type of local and systemic treatment strategies employed, duration and dose of therapy, patient age at diagnosis, sex, co-morbidities, and socioeconomic and lifestyle factors.[2-4] In early-stage breast cancer, local therapy is provided with curative intent. Patients typically undergo surgery (breast-conserving or mastectomy with or without axillary lymph node dissection), with or without radiation, and/or reconstruction (immediate or delayed). When patients have an underlying genetic predisposition, specifically in the breast and ovarian susceptibility genes *BRCA1/2*, surgery may involve the contralateral breast, ovaries, and fallopian tubes. Decisions regarding systemic therapy are more nuanced. A combination of endocrine therapy, chemotherapy, biologics, and/or targeted agents may be employed before surgery (neoadjuvant) or after surgery (adjuvant).[2] **Table 1** summarizes systemic therapies available for early-stage breast cancer.[3,6]

Assessment for long-term and late effects should begin at diagnosis but certainly upon treatment initiation as endorsed by national and international evidence-based tools and guidelines, including the College of Family Physicians of Canada (CFPC), European Society of Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO).[2-4] When possible, effects should be anticipated and prevented. Symptoms and signs should be clinically assessed using standardized instruments. Management strategies should incorporate early education, self-management techniques, and pharmacologic and non-pharmacologic interventions. Co-morbidities and polypharmacy, particularly prevalent in older adults (>60 years), who account for most breast cancer cases, should be addressed as they impact long-term and late effects.[1,4]

Below, we discuss the long-term and late effects on neuropsychiatric, bone, reproductive, and sexual health in breast cancer survivors. We focused on these effects due to their high prevalence.

Neuropsychiatric Health

At the time of diagnosis, up to 1 in 4 patients with breast cancer experience some degree of cognitive impairment. This figure rises to 1 in 3 during and for up to 10 years after chemotherapy in breast cancer survivors.[2,7,8] Although chemotherapy has the greatest association with cognitive decline, correlations have also been described for surgery, anaesthesia, radiation, and endocrine therapy.[2] Cognitive decline secondary to treatment is hard to quantify. Studies evaluating this have marked heterogeneity in methodologies, assessment parameters, and time periods of interest. Patient characteristics, including age, menopausal status, education level, and IQ, add further complexity.[2,8]

Cognitive domains impacted by breast cancer and its treatment are broad ranging, including concentration, executive function, memory (particularly short-term), visuospatial awareness, language, and motor functioning.[7] Impact ranges from subtle to severe, causing distress and impaired QoL, which disrupts social, relationship, employment, and financial well-being.[2,3]

Assessments for cognitive impairment include patient self-reporting, short cognitive screening tools, and standardized neuropsychological tests. Patient self-reporting is subjective and results in higher prevalence rates. However, although perceived cognitive problems may not impair performance on objective cognitive assessments, their validity should not be questioned. Unvalidated concerns leave patients disempowered and unsupported with poorer QoL.[8] When cognitive impairment is identified, objectively or subjectively, reversible contributing factors, including fatigue, pain, insomnia, anxiety, depression, and/or menopause-related hormonal changes should be assessed.[2,7,8]

What to do when cognitive impairment is identified in a survivor of breast cancer is less clear. Advice from the ASCO is to refer the patient for formal neurocognitive assessment and rehabilitation, including, where available,

Class of therapy	Treatment indication	Notable long-term and late effects
Chemotherapy	Higher recurrence risk relating to clinicopathologic features and/or gene expression profile testing	**Generic effects:** • Cognitive impairment • Peripheral neuropathy • Osteoporosis • Premature ovarian failure and infertility • Increased risk of second malignancy
Anthracycline-based	Higher-risk breast cancer relating to triple-negative disease, and axillary node positivity in HR+ disease.	• Cardiotoxicity, including heart failure, myocardial infarction, and arrhythmias
Non-anthracycline-based	Where anthracycline-based therapy is not indicated or contraindicated e.g., pre-existing cardiac co-morbidity	• General chemotherapy effects
Endocrine therapy	HR+ disease	**Generic effects:** • Vasomotor symptoms (hot flashes) • Genitourinary changes of menopause (vaginal dryness and atrophy)
Tamoxifen	Pre-menopausal women	• Hepatic steatosis • Venous thromboembolism • Increased risk of secondary malignancy, specifically endometrial cancer
Aromatase inhibitors	Pre-menopausal women undergoing medical (GnRH agonist) or surgical (oophorectomy) OFS Post-menopausal women	• Musculoskeletal symptoms • Osteoporosis
GnRH agonists	Pre-menopausal women requiring OFS due to higher recurrence risk relating to clinicopathologic features and/or gene expression profile testing	• Cardiotoxicity relating to hypertension and dyslipidemia • Osteoporosis
CDK4/6 inhibitors	HR+ disease with higher recurrence risk relating to tumour size, axillary node positivity, grade, and/or Ki67 score	• Gastrointestinal toxicity, specifically chronic diarrhea • Fatigue • Bone marrow suppression • Musculoskeletal symptoms

Class of therapy	Treatment indication	Notable long-term and late effects
PARP inhibitors	Germline BRCA1/2 mutation with higher recurrence risk relating to receptor status, tumour size, axillary node positivity, and/or residual disease post neoadjuvant systemic therapy	• Fatigue • Bone marrow suppression • Increased risk of secondary malignancy, specifically acute myeloid leukemia and myelodysplastic syndrome
HER2-directed therapy	HER2+ disease	
Trastuzumab		• Cardiotoxicity, including heart failure, myocardial infarction, and arrhythmias
Pertuzumab		• Cardiotoxicity, including heart failure, myocardial infarction, and arrhythmias • Gastrointestinal toxicity, specifically chronic diarrhea
Neratinib		• Gastrointestinal toxicity, specifically chronic diarrhea • Fatigue
Bone-modifying agents	Post-menopausal women (including pre-menopausal women receiving OFS), especially if at higher recurrence risk	Generic effects: • Atypical femur fractures • Osteonecrosis of the jaw • Hypocalcaemia
Bisphosphonates		• Nephrotoxicity
Denosumab		• Generic bone-modifying agent effects

Table 1. Systemic therapies available for early-stage breast cancer and their notable long-term and late effects.[3,6]; *courtesy of Nancy Nixon, MD, FRCPC*
Abbreviations: CDK: cyclin-dependent kinase; **GnRH:** gonadotropin releasing hormone; **HER2:** human epidermal growth factor receptor 2; **HR:** hormone receptor; **OFS:** ovarian function suppression; **PARP:** poly (ADP-ribose) polymerase.

group cognitive training. There is inconsistent data to support pharmacologic therapy with modafinil, a non-amphetamine central nervous system stimulant. However, prescribers should be aware that these are associated with several cardiovascular and psychiatric adverse effects.[2]

A diagnosis of breast cancer is distressing, and survivors are at a higher risk of adverse mental health outcomes compared to women without cancer. Adverse mental health outcomes include depression, anxiety, and suicide.[9] Up to 1 in 5 survivors of breast cancer may be affected for years after diagnosis. Reasons for adverse mental health outcomes are complex, including morbidity from other long-term and late effects, difficulties reintegrating into social, intimate, and professional relationships, and uncertainty about the future. Fear of recurrence is a significant cause of distress, depression, and anxiety. This fear may be heightened in those with a higher symptom burden, shorter interval of time since diagnosis, and receipt of chemotherapy.[2] Breast cancer survivorship may also be associated with a higher risk of post-traumatic stress disorder,

Long-term and late effects	Contributing therapies	Assessment	Management
Neuropsychiatric health			
Cognitive impairment	Greatest body of evidence is for chemotherapy, but links are also reported with surgery, radiation, and endocrine therapy	**Subjective:** patient self-reporting **Objective:** short cognitive screening tools and neuropsychological tests When cognitive impairment is subjectively or objectively identified; assess and address reversible contributing factors	**Pharmacologic:** Inconsistent data for modafinil **Non-pharmacologic:** Neurocognitive rehabilitation, including group cognitive training
Distress, depression, and anxiety	N/A	**Distress:** distress thermometer, Depression: Patient Health Questionnaire-9 **Anxiety:** Generalized Anxiety Disorder 7-item scale If depression is identified, screen for suicidal ideation	**Pharmacologic:** Anti-depressants and anxiolytics as per general population but avoid SSRIs in patients on tamoxifen **Non-pharmacologic:** psychotherapy
Bone health			
Osteoporosis & fractures	Endocrine therapy, particularly AIs +/- OFS	• Screen for additional risk factors • Baseline DEXA in pre- and post-menopausal women receiving AI and thereafter every 2 years on therapy	• Lifestyle modification, including daily calcium and vitamin D intake to prevent bone loss • Bone-modifying agents if osteoporosis is diagnosed
Reproductive and sexual health			
Infertility	Chemotherapy, particularly alkylating agents, platinum-based and taxanes Endocrine therapy pauses reproductive plans	Discuss FP and referral to reproductive specialists at outset of breast cancer diagnosis in women of childbearing age Discuss interrupting therapy to try and conceive with primary oncologist	Ovarian and/or embryo cryopreservation is the standard of care Alternative FP techniques include ovarian tissue cryopreservation and ovarian hormone suppression
Genitourinary syndrome of menopause	Endocrine therapy	Screen for symptoms, including vaginal dryness, itching, recurrent UTIs and dyspareunia	Patient education on avoiding irritants, regular use of non-hormonal vaginal moisturizers with non-hormonal lubrication prior to sexual intercourse

Table 2. Assessment and management of key long-term and late effects in breast cancer survivorship; *courtesy of Nancy Nixon, MD, FRCPC*
Abbreviations: AI: aromatase inhibitor; **DEXA:** dual-energy X-ray absorptiometry; **FP:** fertility preservation; **OFS:** ovarian function suppression; **SSRIs:** selective serotonin reuptake inhibitors; **UTIs:** urinary tract infections

somatization, bipolar affective disorder, and obsessive-compulsive disorder. However, these outcomes are studied less frequently, and therefore, the level of evidence for these outcomes is lower.[9]

The distress thermometer, patient health questionnaire-9, and generalized anxiety disorder 7-item scale screen for distress, depression, and anxiety, respectively. A more thorough assessment should be employed for those patients who are known to be at the highest risk, including patients who are young, have psychiatric co-morbidities, are of low socioeconomic status, and/or are unemployed. When elevated scores are identified, further assessment and management is warranted. Patients with depression should always be screened for suicidal ideation.[2]

Breast cancer survivors experiencing adverse mental health outcomes should be referred to mental health professionals and/or psychosocial oncology specialists based on the local resources available. Pharmacologic strategies, including anti-depressants and anxiolytics, as employed in the general population, are appropriate, except for selective serotonin reuptake inhibitors in women on tamoxifen, as efficacy is impaired in this group.[3] Non-pharmacologic strategies also play an important role and include psychotherapy, mindfulness, expression of positive emotions, spiritual interventions, hope therapy, and meaning-making interventions.[2]

Bone Health

Bone loss occurs progressively in women with age. Driven by estrogen deficiency, bone loss is most marked post-menopause. Endocrine therapy expedites the rate and magnitude of bone loss, reducing bone mineral density (BMD) and increasing fracture risk, even upon treatment discontinuation.[10] Concomitant risk factors, including a personal or family history of fractures, low physical activity, excess alcohol use, and smoking, may exacerbate effects.[2] BMD loss is highest (up to 11% per year), in pre-menopausal women receiving aromatase inhibitors (AIs) with ovarian function suppression (OFS). Even women receiving tamoxifen, considered to have anti-resorptive properties, lose up to 2% of their BMD annually.[11] Loss of BMD should also be considered in pre-menopausal women at risk of premature ovarian failure with chemotherapy and where glucocorticoids are used.[2] In post-menopausal women in whom OFS is not required, bone loss and fracture risk are most pronounced with the use of AIs. Extending AI therapy beyond five years increases the fracture risk further and is an important consideration.[10]

Strategies to prevent bone loss should be considered at diagnosis. Although evidence is limited, lifestyle modifications, including physical activity, weight-bearing exercises, and cessation of smoking and alcohol, should be advised. Daily intake of vitamin D (600-1000 IU) and calcium (1200 mg) should be encouraged, and supplementation should be considered.[2] Osteoporosis Canada provides guidance on assessment of bone health in patients with breast cancer who are using endocrine therapy, which they recognize as a high-risk medication. Post-menopausal women should be screened with a baseline DEXA scan upon AI initiation, which should be repeated every two years while on therapy. This is also warranted in premenopausal women receiving AI with OFS.[12]

Select post-menopausal patients with early-stage breast cancer receive adjuvant bone-modifying agents to reduce recurrence risk and improve mortality, as outlined in **Table 2**. Beyond this context, bone-modifying agents, including bisphosphonates and denosumab, are largely reserved for osteoporosis treatment. These are not routinely used for prevention, given their risks of atypical femur fractures, jaw osteonecrosis, and, in the case of denosumab, rebound osteolysis.[2,10]

Reproductive and Sexual Health

Breast cancer is the most common malignancy diagnosed in Canadian women of childbearing age.[1] Many of the systemic therapies employed compromise fertility and reproductive hopes. This detrimentally impacts the well-being of breast cancer survivors. Chemotherapy, particularly alkylating agents, platinum-based chemotherapy, and taxanes, are gonadotoxic, resulting in premature ovarian insufficiency and infertility. Endocrine agents, although not gonadotoxic per se, require women with hormone receptor-positive (HR+) breast cancer to pause reproductive plans for the 5-10 years they are on treatment. Less is known about whether and how HER2-directed therapies, poly (ADP-ribose) polymerase (PARP) inhibitors, and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors impact fertility. While biological parenthood is possible for young breast cancer survivors, it requires pretreatment planning and intervention.

Thus, at the time of breast cancer diagnosis, fertility preservation (FP) should be discussed, and a referral made to reproductive specialists, even in patients who express ambivalence towards reproduction.[10,13] We recognize, however, that the lack of financial resources remains a significant barrier to access because FP is not publicly funded in Canada.

Assisted reproductive technologies (ART) with either oocyte and/or embryo cryopreservation remains the standard of care for FP in patients with breast cancer before starting therapy. Therapeutic advances mean ART can be started at any time during the menstrual cycle, minimizing treatment delays. Simplistically, gonadotropins stimulate the ovaries to produce multiple mature oocytes, which are then retrieved and fertilized to produce embryos, in cases where sperm is available. In HR+ breast cancer, in which high levels of estradiol should be avoided, ovarian stimulation is performed with AIs or tamoxifen. This reduces circulating estradiol without affecting the number of oocytes retrieved, their maturation, or fertilization.[10,13] Ovarian stimulation is safe in breast cancer and does not compromise recurrence or survival, even in HR+ disease.[14]

Alternative FP options are available, including ovarian tissue cryopreservation and ovarian hormone preservation. Ovarian tissue cryopreservation can be performed immediately and does not require stimulation. Once considered experimental, it can achieve live birth rates of ~60%; however, anaesthesia, these data are based on patients with and without cancer.[15] Ovarian hormone preservation involves concurrent administration of chemotherapy with gonadotropin receptor hormone agonists (GnRHa). The ovaries are suppressed by GnRHa, protecting them from the gonadotoxic effects of chemotherapy. Data supporting GnRHa use is largely obtained from women with other causes of premature ovarian failure and aim to reduce long-term risks to bone and cardiovascular health. There is some data that use in breast cancer reduces the risk of premature ovarian failure and improves pregnancy rates, but the evidence is limited. ASCO continues to advise that it should not be used instead of proven FP methods.[13,16]

Although we recognize that pregnancy and trying to conceive are important considerations for young breast cancer survivors, discussing the likelihood of this, reproductive outcomes, and maternal safety is beyond this article's scope. However, we emphasize that young breast cancer survivors can become pregnant, but close consultation with the patient's primary oncologist is needed. Many of our systemic therapies are teratogenic, and washouts are required. There is clear guidance on chemotherapy (12 months), trastuzumab (7 months), and tamoxifen (3 months) use, but less information is available for pertuzumab, CDK4/6 inhibitors, and PARP inhibitors.[17] Regarding endocrine therapy, the POSITIVE landmark study showed that treatment interruptions for up to 2 years, during which young women can try to conceive, did not worsen short-term breast cancer outcomes (breast cancer-free interval and distant relapse-free survival). Given the natural history of HR+ breast cancer, in which delayed recurrences occur, long-term follow-up is needed to safely determine if and how treatment interruptions impact relapse rates and survival.[18]

Genitourinary syndrome of menopause (GSM) also compromises breast cancer survivors' sexual health. Largely related to endocrine therapy, it is also observed in women with premature ovarian insufficiency post-chemotherapy. GSM is caused by estrogen suppression to levels below that naturally expected post-menopause. Vaginal and vulval atrophy secondary to hypoestrogenism results in dryness, which can itch and burn, with increased risks of urinary tract infections and dyspareunia. Left untreated, vaginal stenosis and shortening may develop. The detrimental impact of GSM on survivor well-being cannot be understated and is an important cause of treatment nonadherence.[10]

Patient education is vital for managing GSM, as simple strategies can help. Irritants, including feminine washes, alcohol-based wipes, and topical agents containing artificial fragrances, parabens, petroleum, propylene glycol, and glycerin, should be avoided. Non-hormonal moisturizers and lubricants should be recommended, recognizing that patients often require clarification on their differential use. Non-hormonal moisturizers are for regular use, with application to the vaginal and vulval mucosa at least three times per week. Simple emollients, including coconut oil, may suffice, but hyaluronic acid-containing agents are also helpful. Consistent use is key for beneficial effects. Prior to sexual intercourse, non-hormonal lubricants should be applied. Silicone-based lubricants are preferred, but water-based versions are also acceptable. Should dyspareunia remain problematic, consider vaginal stenosis and shortening. If found on physical examination, pelvic floor physical therapy and use of a vaginal

dilator at least three times a week should be encouraged. Again, consistency is key. The role of hormonal moisturizers, specifically estradiol or dehydroepiandrosterone preparations, remains a source of ongoing debate, given apprehension regarding systemic absorption. Concern was recently renewed based on published data suggesting increased recurrence risk when used in women with HR+ breast cancer.[19] Proposed harmful effects of topical hormonal therapy should be balanced against increased recurrence risk secondary to endocrine therapy nonadherence. Careful counselling is warranted for women in whom non-hormonal strategies have failed, and hormonal moisturizers are being considered.[10]

Although GSM contributes to sexual dysfunction and disrupted sexual intimacy in breast cancer survivors, further complexities exist that relate to decreased libido, arousal concerns, loss of sexual sensitivity of the skin, and orgasmic concerns that do not just affect women on endocrine therapy. Chemotherapy, surgery, and radiation all contribute, and many breast cancer survivors are affected. Referral for interventions, including psychoeducational support, group therapy, intensive psychotherapy, and sexual and/or marital counselling, are advised by ASCO.[2]

Treatment Adherence

Assessment and management of long-term and late effects is crucial because it influences treatment adherence. In early-stage breast cancer, compliance is particularly problematic with adjuvant endocrine therapy, despite its value in recurrence rate reduction (~1/2 in the first 10 years) and survival improvement (1/3 in the first 15 years) in HR+ disease.[20] A third of patients receiving endocrine therapy are nonadherent. Further, adherence decreases over time, on average by ~25% from year 1 to 5. Although these reductions in adherence are observed with all endocrine agents, nonadherence is higher with tamoxifen than AIs. Thus, pre-menopausal breast cancer survivors are impacted most.[21]

Nonadherence is difficult to quantify. Clinicians often rely on patient self-reporting, a measure consistently proven to overestimate adherence. In a prospective study measuring serum detection of tamoxifen in approximately 1,200 pre-menopausal women, biochemical nonadherence at 1 year was 16%. Even at a median follow-up of only two years, this subgroup had comparatively inferior breast cancer-specific outcomes independent of other prognostic factors.[5] Many pre-menopausal women additionally receive OFS, which increases toxicity. The addition to tamoxifen increases vasomotor symptoms, while the addition to AIs increases impairments in musculoskeletal and sexual health. How this increase in toxicity contributes to treatment nonadherence remains unclear. Certainly, within the landmark SOFT/TEXT clinical trials, early treatment discontinuation was ~20% in patients across all three treatment groups, namely: tamoxifen alone, tamoxifen with OFS, and exemestane (AI) with OFS.[22]

The treatment landscape of early-stage breast cancer is evolving. Notably, two to three years of CDK4/6 inhibition is combined with adjuvant endocrine therapy in HR+ disease. Although currently only approved by Health Canada for patients with a pre-defined higher recurrence risk, access may broaden in years to come. In the monarchE trial, the addition of abemaciclib (CDK4/6 inhibitor) to endocrine therapy increased grade ≥3 adverse effects and treatment discontinuation.[23] Despite treatment evolution, benefits in breast cancer-specific outcomes will not be gained in real-world clinical practice if patients remain nonadherent because of long-term and late effects.

Conclusion

As 5-year breast cancer survival rates reach 89%, now more than ever, healthcare providers have an obligation to recognize the experiences and care needs of survivors. Survivorship is a complex domain of cancer care that starts at the time of diagnosis. It encompasses assessment for disease recurrence, screening of secondary malignancies, health promotion, and management of both long-term and late effects of treatments received. Long-term and late effects impair QoL and contribute to treatment nonadherence and are, therefore, crucial to address.

Cognitive impairment predates a breast cancer diagnosis in 1 in 4 patients. This can worsen during treatment and last many years after. Although patients self-report cognitive impairment post-therapy at higher rates than that detected through objective measures, validity should not be questioned as this disempowers the patient and compromises QoL. Breast cancer survivors are at greater risk of adverse mental health outcomes than those without cancer. This

includes distress, depression, anxiety, and suicide. Validated screening tools are available and should be employed to ensure patients will receive the pharmacologic and non-pharmacologic therapies needed.

Bone health is markedly compromised by endocrine therapy, which increases the rate and magnitude of BMD loss, increasing fracture risk. Risk is greatest with AIs, and prescribers should be particularly mindful when co-administering with OFS, and consider treatment extension beyond five years. Evidence for lifestyle modification strategies is limited but should be encouraged to prevent BMD. Bone-modifying agents should only be used to treat (not prevent) osteoporosis, as this therapy can also disrupt bone health.

Chemotherapy is gonadotoxic, and endocrine therapy disrupts reproductive plans for years while on treatment. Breast cancer is the most common malignancy diagnosed in women of childbearing age, and FP should be discussed before treatment initiation. Referral to reproductive specialists should be made, even when patients are ambivalent, recognizing that in Canada, financial limitations are a barrier to pursue FP. It is important not to underestimate the impact of GSM on sexual dysfunction. Ask patients if they are symptomatic, and inform them there are simple strategies that, with consistent use, can prove effective.

Long-term and late effects contribute to treatment nonadherence. This is particularly important with endocrine therapy, because despite solid evidence supporting reductions in recurrence risk and improved survival, many patients do not comply. Nonadherence increases over time. Although there is currently no evidence to suggest nonadherence increases with the addition of OFS, the addition of CKD4/6 inhibition has been shown to increase treatment discontinuation. Therapeutic advances will not lead to improved breast cancer-specific outcomes in real-world practice unless long-term toxicities are assessed and addressed, as is crucial for effective survivorship care.

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