Menopause 4

Managing menopause after cancer

Martha Hickey, Partha Basu, Jenifer Sassarini, Mariken E Stegmann, Elisabete Weiderpass, Karen Nakawala Chilowa, Cheng-Har Yip, Ann H Partridge, Donal J Brennan

Lancet 2024; 403: 984–96

Published Online March 5, 2024 https://doi.org/10.1016/S0140-6736(23)02802-7

See Perspectives pages 893 and 894

This is the fourth in a Series of four papers about menopause. All papers in the Series are available at www.thelancet.com/series/menopause-2024

Department of Obstetrics, Gynaecology and Newborn Health, University of Melbourne and the Royal Women's Hospital, Melbourne, VIC, Australia (Prof M Hickey MBChB MD); **Early Detection, Prevention and Infections Branch, International Agency for Research on Cancer, WHO, Lyon, France** (P Basu MD PhD); **Department of Obstetrics and Gynaecology, School of Gynaecology, University of Glasgow, Glasgow, UK** (J Sassarini MBChB PhD); **Department of Primary and Long-term Care, University Medical Center Groningen, University of Groningen, Groningen, Netherlands** (M E Stegmann MD PhD); **International Agency for Research on Cancer, WHO, Lyon, France** (E Weiderpass MD PhD); **Teal Sisters, Lusaka, Zambia** (K Nakawala Chilowa); **Department of Surgery, University of Malaya, Kuala Lumpur, Malaysia** (Prof C-H Yip MD); **Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA** (Prof A H Partridge MD MPH); **Gynaecological Oncology Group, UCD School of Medicine, Mater Misericordiae University Hospital, Dublin, Ireland** (Prof D J Brennan MB PhD); **Systems Biology Ireland, UCD School of Medicine, Dublin, Ireland** (Prof D J Brennan)

Globally, 9 million women are diagnosed with cancer each year. Breast cancer is the most commonly diagnosed cancer worldwide, followed by colorectal cancer in high-income countries and cervical cancer in low-income countries. Survival from cancer is improving and more women are experiencing long-term effects of cancer treatment, such as premature ovarian insufficiency or early menopause. Managing menopausal symptoms after cancer can be challenging, and more severe than at natural menopause. Menopausal symptoms can extend beyond hot flushes and night sweats (vasomotor symptoms). Treatment-induced symptoms might include sexual dysfunction and impairment of sleep, mood, and quality of life. In the long term, premature ovarian insufficiency might increase the risk of chronic conditions such as osteoporosis and cardiovascular disease. Diagnosing menopause after cancer can be challenging as menopausal symptoms can overlap with other common symptoms in patients with cancer, such as fatigue and sexual dysfunction. Menopausal hormone therapy is an effective treatment for vasomotor symptoms and seems to be safe for many patients with cancer. When hormone therapy is contraindicated or avoided, emerging evidence supports the efficacy of non-pharmacological and non-hormonal treatments, although most evidence is based on women older than 50 years with breast cancer. Vaginal oestrogen seems safe for most patients with genitourinary symptoms, but there are few non-hormonal options. Many patients have inadequate centralised care for managing menopausal symptoms after cancer treatment, and more information is needed about cost-effective and patient-focused models of care for this growing population.

Introduction

The average age at natural menopause is 51 years in high-income countries (HICs).[1] A systematic review and meta-analysis in 2014 showed an earlier age at menopause in low-income and middle-income countries (LMICs) across Asia, India, Latin America, and the Middle East.[2] Menopause is more likely to be premature (ie, occurring before age 40 years) or early (ie, at age 41–44 years) after cancer and burgeoning evidence indicates that young age at menopause can be a risk factor for chronic disease.[3] A 2017 meta-analysis of 45 studies in female patients who had survived cancer found a median age at menopause of 44 years.[4] Guidelines from the UK National Institute for Health and Care Excellence (NICE) recommend menopausal hormone therapy (MHT) for younger postmenopausal women without contraindications,[5] but often the safety and efficacy of MHT after cancer is uncertain. Crucially, most patients who have troublesome menopausal symptoms after cancer do not have access to effective treatments, even in HICs.[6] This Series paper will address the prevention and management of menopausal symptoms after cancer, including evidence about health disparities if available.[7]

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in some instances, we have referred to "people" rather than "women" to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used "women" in some instances, to avoid inappropriate generalisation. More information is needed about the experience of menopause in transgender men and gender-diverse people. Evidence on menopause in gender-diverse people is scarce and this area needs more attention.[8]

Search strategy and selection criteria

The recommendations in this Series paper are based on a review of the published literature and appraisal of professional guidelines. We searched databases on MEDLINE, Embase, BioMed Central, Cochrane, and Google from Dec 7, 2020, to Jan 8, 2024, with keywords tailored to each section of the manuscript including "cancer", "neoplasm*", "cancer survivor*", "menopause", "postmenopause", "perimenopause", "menopausal symptom*", "vasomotor symptom*", "hot flush*", "hot flash*", "night sweat*", "sleep disturbance*", "sleep disorder*", "vaginal dryness", "genitourinary syndrome of menopause", "dyspareunia", "sexual dysfunction", "quality of life", "menopausal hormone therapy", "hormone therapy", "hormone replacement therapy", "cognitive behaviour therapy", "cognitive behavioral therapy", "non-hormonal treatment*" , "nonhormonal treatment*", "low and middle income countr*", "high income countr*", "cancer", "BRCA1", "BRCA2", "risk reducing salpingo-oophorectomy", "RRSO", "osteoporosis", "premature ovarian failure", "premature ovarian insufficiency", "chemotherapy", "radiation", "venous thrombo-embolic disease", "multidisciplinary care". We cross-referenced these terms with "systematic review*", "meta-analysis", "metaanalysis", "randomised/randomized controlled

trial*", "clinical guideline*", "clinical practice guideline*". We also searched websites and guidelines of menopause societies including the British Menopause Society, International Menopause Society, North American Menopause Society, Australasian Menopause Society, and the NICE guidelines. The Turning Research into Practice and PubMed databases were searched for evidence-based guidelines and systematic reviews. We prioritised the most recent evidence from randomised controlled trials and recommendations from international guidelines based on systematic reviews of the evidence (eg, WHO, International Agency for Research on Cancer, NICE, US Preventive Task Force, National Comprehensive Cancer Network, and American Society of Clinical Oncology). Only publications in English were included.

The growing burden of menopausal symptoms after cancer treatment

In premenopausal women, treatment for common cancers such as breast, gynaecological, haematological, and some low colorectal cancers will often cause ovarian damage, potentially inducing permanent menopause.[9] Perimenopausal or postmenopausal women diagnosed with oestrogen-receptor-positive cancers while taking MHT will be advised to stop, which can cause resurgent vasomotor symptoms that are further exacerbated by anti-oestrogen therapy.[10]

The standard of care for premenopausal high-risk oestrogen-receptor-positive breast cancer includes gonadotoxic chemotherapy followed by ovarian suppression plus oral endocrine therapy. This treatment can lead to more severe vasomotor symptoms (ie, hot flushes and night sweats) compared with natural menopause, particularly in younger women.[11,12] Patients with oestrogen-receptor-positive postmenopausal breast cancer are advised to take third-generation aromatase inhibitors (eg, anastrozole, letrozole, and exemestane), which can induce or aggravate menopausal symptoms including hot flushes, night sweats, and vaginal dryness.[13] Menopausal symptoms are a common reason for not starting or prematurely stopping endocrine therapy, which directly increases morbidity and mortality from breast cancer.[11] Newer protocols extending endocrine therapy from 5 years to 10 years in oestrogen-receptor-positive or progesterone-receptor-positive cancer are likely to increase the burden of symptoms. In a 2021 community-based survey (n=385), the prevalence of menopausal symptoms in survivors of breast cancer 6 years after diagnosis was high: 346 (90%) had vasomotor symptoms or sleep disturbance, 289 (75%) had vaginal dryness, 240 (62%) had mood swings, and 229 (59%) had sexual difficulties.[6] Severity of hot flushes and sleep disturbance predicted their inability to resume everyday activities. Less than a third were offered treatment and less than half found this to be effective. These symptoms can cause distress and impair quality of life, and managing these symptoms is a leading priority for patients with cancer.[14] Around a third of patients with breast cancer are dissatisfied with the information provided about the effects of cancer treatment on reproductive outcomes such as menopause.[15]

Around one in 400 women are at elevated risk of ovarian cancer due to pathogenic gene variants such as *BRCA1* or *BRCA2*.[16,17] International guidelines advise risk-reducing bilateral salpingo-oophorectomy by age 35–40 years, which will induce surgical menopause.[18] Patients' concerns about managing menopausal symptoms after bilateral salpingo-oophorectomy are a leading barrier to this potentially life-saving surgery[19] and many clinicians are uncertain how best to manage surgical menopause in this population.[20] The clinical case in panel 1 emphasises the importance of pre-operative counselling about the probable consequences of surgical menopause in these patients and of postoperative symptom management. In 2023, new international consensus guidelines provided recommendations for symptom management and prevention of chronic disease following risk-reducing salpingo-oophorectomy in premenopausal women with the *BRCA1* or *BRCA2* pathogenic variant.[21]

Key messages

- More than 9 million women are diagnosed with cancer each year and treatments commonly induce early menopause and menopausal symptoms
- Many patients do not have access to effective treatments, even in high-income countries, with an even greater impairment of quality of life and psychological distress in low-income settings
- Diagnosing menopause after cancer can be challenging and many women resume menstruation within 2 years of chemotherapy completion; undetectable anti-Müllerian hormone at 30 months predicts menopause after chemotherapy for breast cancer and menopause is almost universal after ovarian radiation
- Women younger than 45 years without contraindications should be offered an individualised treatment plan including menopausal hormone therapy after cancer treatment
- If menopausal hormone therapy is contraindicated, non-pharmacological and non-hormonal treatments are available for vasomotor symptoms; vaginal oestrogen seems to be safe for most patients with cancer and growing evidence supports safety after breast cancer
- Multidisciplinary management of menopause after cancer is essential and should include primary care and, if appropriate, allied health practitioners
- Reaching the population who need treatment is a global problem and online platforms are being developed to better support and empower patients with cancer to make shared, evidenced-based decisions with their local health-care provider

Correspondence to:
Professor Martha Hickey, Department of Obstetrics, Gynaecology, and Newborn Health, The Women's Hospital, Melbourne, VIC 3052, Australia
hickeym@unimelb.edu.au

***Panel 1*: Fictional clinical case study**

- A 37-year-old woman with a male partner and two children aged 5 years and 3 years visited her primary care provider because of sleeping difficulties. The primary care provider knows her well. The patient previously had imaging to investigate right-sided pain, which revealed a complex ovarian mass. This mass was subsequently found to be stage 1C1 high-grade serous ovarian cancer. She had a total abdominal hysterectomy and removal of both ovaries, staging laparotomy, and adjuvant systemic chemotherapy. Genetic testing showed that she carried the *BRCA1* pathogenic variant, so both ovaries were removed. She also decided to undergo risk-reducing bilateral mastectomy with informed consent.
- When the primary care provider asked more about her sleeping problems, the patient started to cry. She was frustrated by this show of emotion and said that she was not herself anymore. She found that minor problems were harder to deal with and she easily became emotional, which had caused arguments with her partner and her parents. Her family members were concerned about her health during her cancer treatment, but now that she was cured, they did not understand why she was always angry or sad. When she tried to make up with her partner, he often wanted to initiate sex. However, sexual intercourse was painful. Also, she was self-conscious about her appearance after mastectomy.
- She was concerned about these changes and the effect they had on her life, especially at night. When she eventually fell asleep, she sometimes suddenly woke up feeling very hot, sweaty, and anxious. Sometimes these sensations also occurred during the day. After telling her story, she felt relieved to have told someone about her problems and was hopeful that the primary care provider could help to solve them.
- The primary care provider discussed with the patient that her symptoms (mood changes, vaginal dryness, hot flushes, and sleep disturbance) are all common after surgical menopause. This information gave great relief to the patient, who did not realise that removing her ovaries might have this effect. Previously she was blaming herself for feeling angry or sad, felt guilty about being unwilling to have penetrative intercourse, and was concerned about her relationship. She was also fearful that night sweats were a sign of brain metastases from her ovarian cancer. The primary care provider gave her information about symptoms after surgical menopause and possible treatments and made another appointment.
- When she returned a week later, the patient felt somewhat better. However, she continued to experience troublesome hot flushes, sleep disturbance, and vaginal dryness. The primary care provider had contacted the gynaecological oncologist to discuss treatment options. They advised that there were no contraindications to menopausal hormone therapy (MHT) in women with a history of high-grade serous ovarian cancer; however, the relevant studies had small sample sizes and short follow-up. Although the patient had a *BRCA1* pathogenic variant, there were no substantial concerns about breast cancer because she had undergone bilateral mastectomy and would be receiving oestrogen-only MHT.
- Together, the patient and the primary care provider discussed the treatment options. Initially, the patient was reluctant to consider pharmacological therapies because she had taken so much medication in the previous year. During an individualised discussion of the risks and benefits, the primary care provider explained that MHT was the most effective treatment for hot flushes and night sweats and would also prevent bone loss. The patient and the primary care provider made a joint decision that she should try MHT.
- A month later, the patient reported that her vasomotor symptoms were greatly improved and her sleep was much better. Her relationship with her family had improved and she had returned to work. She had recommenced sexual activity but continued to experience vaginal dryness, so the primary care provider offered vaginal topical oestrogen. However, the patient continued to experience anxiety, particularly a fear of cancer recurrence. Together, they agreed that help from a psychologist was needed, and the patient was referred for cognitive behavioural therapy.

Around 1·8 million women are diagnosed with gynaecological cancers every year and treatments such as bilateral oophorectomy, pelvic radiation, and gonadotoxic chemotherapy commonly induce premature ovarian insufficiency (POI) or early menopause.[22] In 2020, around 10% of cancers diagnosed in women were colorectal.[23] Colorectal cancer rates are increasing in younger women, particularly rectal and anal cancer, which are commonly treated with pelvic irradiation that will induce menopause.[24]

Leukaemia and lymphomas comprise about 4% of all cancers in women younger than 50 years and are commonly treated with a stem-cell transplant.[24] Gonadotoxic chemotherapy before stem-cell transplantation will induce menopause in around 80% of premenopausal women, depending on their age and nature of the conditioning regimen.[25,26]

Unmet needs of women with cancer in LMICs

Survivors of cancer who are socioeconomically disadvantaged have poor health-related quality of life, in both low-income and high-income settings, due to underdiagnosis of menopausal symptoms and barriers to timely and appropriate care.[27] Multiple studies have shown that general physical health declines during midlife (age 35–65 years) in women from LMICs.[28] Impaired quality of

life and psychological distress after cancer treatment is more severe in survivors from LMICs compared with survivors in HICs. Longitudinal studies reported young age and late cancer stage at diagnosis, low education and health literacy, financial hardships, and inadequate availability of supportive care as the primary reasons for continued distress of the people who survived cancer in LMICs.[29]

Menopause-related symptoms and their consequences often receive little attention, as follow-up care is focused predominantly on surveillance for cancer recurrence. Minimising the health consequences of menopausal symptoms induced or exacerbated by cancer treatment and offering resource-appropriate solutions will substantially improve the quality of life of thousands of women every year.

Preservation of ovarian function before cancer treatment

Cancer treatments, including oophorectomy, gonadotoxic chemotherapy, and pelvic radiation, can induce menopause. Recognising the potential short-term and long-term value of preserving ovarian function, the European Society of Medical Oncology has produced guidelines recommending strategies to preserve fertility and ovarian function after cancer (panel 2).[30] Gonadotoxic chemotherapy, particularly regimens containing alkylating agents, commonly damage ovarian function and can induce permanent menopause.[31] The effect of new targeted therapies and immunotherapy on ovarian function is uncertain, but in mice, immunotherapy is gonadotoxic and reduces ovarian reserve.[32] In 2018, a systematic review found that ovarian suppression with gonadotropin-hormone-releasing hormone analogues before chemotherapy for breast cancer reduced chemotherapy-induced ovarian failure by around 50%.[33] A randomised trial is underway to determine if gonadotropin-releasing hormone agonists provide ovarian protection in young women and adolescents undergoing chemotherapy for cancer (eg, breast, lymphoma, leukaemia, and sarcoma),[34] but evidence to date shows little benefit for patients with haematological cancer.[35] The effect of pre-chemotherapy gonadotropin-hormone-releasing hormone analogues on age at menopause and long-term ovarian function is unknown.

Pelvic radiation for locally advanced colorectal and cervical cancers will induce menopause in around 94·1% of premenopausal women.[36] There are few effective options for preventing ovarian damage due to chemotherapy. Preclinical data suggest that modification of pathways to primordial follicle apoptosis can protect the ovaries during chemoradiation.[37] However, this approach has not yet been trialled in women. Moving the ovaries outside the field of radiation (transposition) can be protective and should be discussed as part of shared decision making. A 2019 systematic review of ovarian transposition before external beam pelvic radiation (n=765) concluded that ovarian function could be preserved in 20–100% of cases,[38] with efficacy primarily dependent on age. In a small series of 22 women with low rectal (n=20) or anal (n=2) cancer, transposition preserved ovarian function in 90% of participants younger than 40 years but only in 38% of those older than 40 years[39] (panel 2).

***Panel 2*: Circumstances in which ovarian function can be preserved in gynaecological cancer**

Consider ovarian preservation in premenopausal women with:

- Cervical cancer—stage 1 or 2A human papillomavirus-associated adenocarcinoma and squamous carcinoma of the cervix undergoing radical hysterectomy
- Endometrial cancer—stage 1 low grade (not associated with Lynch syndrome or *TP53* mutated); future molecular subtyping of endometrial cancer might improve stratification of care
- Ovarian cancer—stage 1 (A) low grade, contralateral ovary could be preserved after explaining the 6–13% risk of recurrence in the preserved ovary; germ cell tumours with early unilateral disease

Consider elective transposition in women younger than 40 years with:

- Cervical cancer—locally advanced, if primary chemoradiation is planned
- Rectal cancer—requiring neo-adjuvant chemoradiation
- Cancer requiring pelvic radiation (eg, anal, vulval, sarcoma)

Consider intra-operative transposition in women with:

- Cervical cancer—if radical hysterectomy is abandoned due to positive node or if adjuvant radiation is likely
- Rectal cancer—if adjuvant radiation is likely to be needed due to close margins or intra-operative complications

Diagnosing and managing menopause after cancer

There are no consensus criteria for diagnosing menopause after cancer. General diagnostic criteria, such as more than 12 months of amenorrhoea and elevated follicle stimulating hormone, cannot reliably be used, as ovarian function can resume many years after treatment. Although circulating anti-Müllerian hormone can indicate reduced ovarian reserve after chemotherapy, it does not reliably predict fertility, duration of reproductive life-span, or ovarian function.[40] A cross-sectional study of 1043 women aged 20–35 years found that 31·6% had amenorrhoea after cancer treatment, with risk factors including chemotherapy, older age at diagnosis, and never having been pregnant. Overall, 70% resumed menstruation, with almost all (90%) resuming menstruation within 2 years of treatment.[41]

Women younger than 45 years with prolonged amenorrhoea after gonadotoxic cancer treatment should be offered MHT, provided they do not have

	Effect of MHT on cancer outcomes	Level of evidence	MHT use
Breast cancer: overall	Systematic review and meta-analysis (n=4050) found increased risk of recurrence with tibolone or MHT (HR 1·46)[46]	Moderate	Avoid MHT
Breast cancer: oestrogen-receptor-negative	Subgroup analysis found no increased risk of recurrence with tibolone or MHT (HR 1·19)[46]	Moderate	Consider MHT in specific patients*
Breast cancer: oestrogen-receptor-positive	Subgroup analysis found increased risk of recurrence (HR 1·80) with tibolone or MHT[46]	Moderate	Avoid MHT
Uterine sarcomas	European guidelines suggest avoiding MHT, might be oestrogen sensitive[48]	Very low	Avoid MHT
Ovarian cancer: low-grade serous and granulosa cell	European guidelines suggest avoiding MHT, might be oestrogen sensistive[48]	Very low	Avoid MHT
Low-grade, early-stage endometrial cancer	Systematic review found no effect on cancer outcomes[49]	Moderate	Consider MHT
Cervical cancer	One small retrospective study (n=120) found no effect on cancer outcomes;[50] European guidelines suggest offering MHT[51]	Very low	Consider MHT
Haematological cancer	One small study (n=130) showed no effect on cancer outcomes[52]	Very low	Consider MHT
Early cutaneous malignant melanoma	One small study (n=206) showed no effect on cancer outcomes[53]	Very low	Consider MHT
Colorectal cancer	One large prospective study (n=834)[54] and one national cohort study[55] reported improved cancer outcomes	Low	Consider MHT
Hepatocellular cancer	One case–control study (n=244) reported improved cancer outcomes[56]	Very low	Consider MHT
Ovarian germ cell tumours	European guidelines suggest offering on an individualised basis[48]	Very low	Consider MHT
Epithelial ovarian cancer	Systematic review found uncertain evidence for efficacy or safety of MHT[57]	Moderate	Consider MHT
Vaginal, vulval, and anal squamous cell carcinoma	Do not express oestrogen receptors, MHT thought to be safe[58]	Very low	Consider MHT
Kidney cancer	Meta-analysis suggests better cancer outcomes with MHT[59]	Low	Consider MHT
Lung cancer	Mixed evidence: prospective cohort study (n=727)[60] and SEER data (n=485)[61] showed improved cancer outcomes; retrospective study (n=498)[62] and RCT[63] showed increased mortality	Moderate	Consider MHT

Figure 1: **Use of systemic MHT (or tibolone) by cancer type**
Red indicates that MHT should be avoided; yellow indicates that MHT should be considered. Grading uses the Grading of Recommendations, Assessment, Development, and Evaluation approach.[64] MHT=menopausal hormone therapy. HR=hazard ratio. RCT=randomised controlled trial. *After oestrogen-receptor-negative breast cancer, consider MHT if menopausal symptoms do not respond to non-hormonal treatments, particularly following bilateral mastectomy. Discuss with the patient that evidence to inform the safety of MHT in these circumstances is limited.[65-69]

contraindications. Management should be tailored to the individual, taking into account the patient's age, cancer type, time since diagnosis (competing risks change over time), quality of life (menopausal symptoms), comorbidities (eg, venous thromboembolism, polypharmacy, and the potential for drug interactions), risk factors for chronic disease (eg, osteoporosis and ischaemic heart disease), and views and preferences. Evidence of moderate-to-low quality from the general population suggests that transdermal MHT does not increase venous thromboembolism rates.[42] Since patients with cancer are at elevated risk of venous thromboembolism, we recommend offering transdermal rather than oral MHT. Testing of ovarian function after 12 months can be considered, depending on the cancer treatment. For example, ovarian function is unlikely to resume after pelvic radiation without ovarian transposition but might resume after chemotherapy for breast cancer, particularly in young women. In patients aged 40–45 years with breast cancer and secondary amenorrhoea after chemotherapy, an undetectable anti-mullerian hormone at 30 months is a reliable predictor of permanent menopause.[43]

In addition to MHT, there is growing evidence supporting the efficacy of non-hormonal and non-pharmacological therapies for menopausal symptoms, which has substantially increased treatment options for the management of vasomotor symptoms and (to a lesser extent) genitourinary symptoms associated with menopause.[44]

MHT

In the general population, MHT reduces vasomotor symptoms by around 85% and treating vasomotor symptoms can also improve sleep and quality of life.[45] Less is known about the efficacy and safety of MHT after cancer, but a systematic review reported an increased risk of recurrence following oestrogen-receptor-positive (but not negative) breast cancer.[46] Much of the evidence informing this systematic review came from a large randomised controlled trial (RCT) of tibolone (LIBERATE), which reported a significantly increased risk of new breast cancers and breast cancer recurrence with tibolone compared with placebo.[47] When the findings from LIBERATE were removed from the systematic review, there was no longer a statistically significant harm for patients with breast cancer. However, given concerns for an increased risk of breast cancer recurrence, especially in patients who might benefit from low circulating oestrogen concentrations, we generally recommend against MHT in survivors of breast cancer, particularly those with oestrogen-receptor-positive disease. However, exceptions can be made if quality of life is substantially affected or disease risks are low after careful discussion and shared decision making (figure 1).

For patients with cancer and POI or early menopause who are eligible to take MHT, the optimal duration of use is uncertain but should be considered until the average age of menopause (≥45 years) depending on symptoms and other health indices such as bone density. Figure 1 summarises available evidence regarding the safety of MHT after cancer. Figure 2 summarises advice about MHT use in female-specific cancer, and figure 3

provides specific advice for MHT after cancers that affect both men and women. Decisions about MHT after cancer should use a shared decision-making approach, including the patient and the treating oncologist.

Non-pharmacological therapies for vasomotor symptoms

Non-pharmacological approaches can also reduce the effects of vasomotor symptoms after cancer. Cognitive behaviour therapy (CBT) has the strongest evidence base. After breast cancer, CBT is effective delivered to groups, individually, online, or by specialist nurses, with a sustained effect at 26 weeks versus usual care, and it improves sleep and depressive symptoms.[70] CBT reduces interference and bother due to vasomotor symptoms, which is a priority area for patients.[71]

Two small RCTs of hypnosis in patients with breast cancer showed improvements in vasomotor symptoms, mood, and sleep.[44] Stellate ganglion block involves injection of local anaesthetic into the neck for the management of conditions such as complex regional pain and peripheral vascular disease. One small, randomised sham-controlled trial (n=40) showed a reduction in moderate-to-severe vasomotor symptoms with stellate ganglion block.[72,73] However, this procedure is invasive and costly, with small but serious health risks. Acupuncture is of uncertain benefit for vasomotor symptoms but can help with fatigue and joint pain after breast cancer.[44] Small RCTs indicate that yoga, relaxation training, and mindfulness-based stress reduction reduce vasomotor symptoms, with benefits for sleep, depressive symptoms, and self-reported stress.[44] Physical exercise, supplements, and homoeopathy are ineffective.[44] Lifestyle changes, such as dressing in layers, can help and a cool pad pillow topper reduces vasomotor symptoms after breast cancer.[74]

Non-hormonal treatments for vasomotor symptoms

In patients in whom MHT is contraindicated or should be avoided after cancer (table), a burgeoning number of non-hormonal therapies are available. However, unlike MHT these therapies will not improve genitourinary symptoms or prevent fracture. Some antidepressants reduce vasomotor symptoms by 40–60%.[75] The anticonvulsants pregabalin and gabapentin have similar efficacy.[75] The antihypertensive clonidine is less effective than venlafaxine.[44] One small RCT showed that oxybutynin was effective for vasomotor symptoms after breast cancer.[76] There are few head-to-head trials of non-hormonal treatments for vasomotor symptoms, which makes knowing what works best difficult. Selecting non-hormonal treatments should follow a shared decision making approach. For example, gabapentin reduces vasomotor symptoms but can cause drowsiness and hence is often more suitable for night-time symptoms. The dose of escitalopram for vasomotor symptoms is equivalent to the antidepressant dose so can be considered for patients who also have depression. Existing medications will also guide choice. Selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors should not be used together. A suggested approach to starting non-hormonal treatments for vasomotor symptoms is oxybutynin 2·5–5 mg twice a day, escitalopram 10–20 mg, or venlafaxine 37·5 mg increasing to 75 mg controlled release. Gabapentin (300–900 mg) reduces night sweats and causes drowsiness, which might improve sleep.[44] A systematic review of the side-effects of these non-hormonal therapies in patients with breast cancer reported that 81% of patients experienced adverse effects, which were graded as mild in 67%.[77] Higher doses of gabapentin and venlafaxine were most likely to induce side-effects.[77] Antidepressants should be stopped gradually.

Targeted therapy with the neurokinin B receptor antagonist fezolinetant is available in the USA and some European countries. Two large RCTs have compared the efficacy of fezolinetant versus placebo for vasomotor symptoms over 12 weeks, with a 40-week open label extension.[78,79] With 45 mg per day (the dose now marketed), there was a statistically significant reduction in hot flush frequency and severity up to 1 year and serious adverse events were infrequent. Fezolinetant also improved menopause-related quality of life.[80] Although clinical trials of neurokinin B receptor antagonists in patients with cancer have not yet been

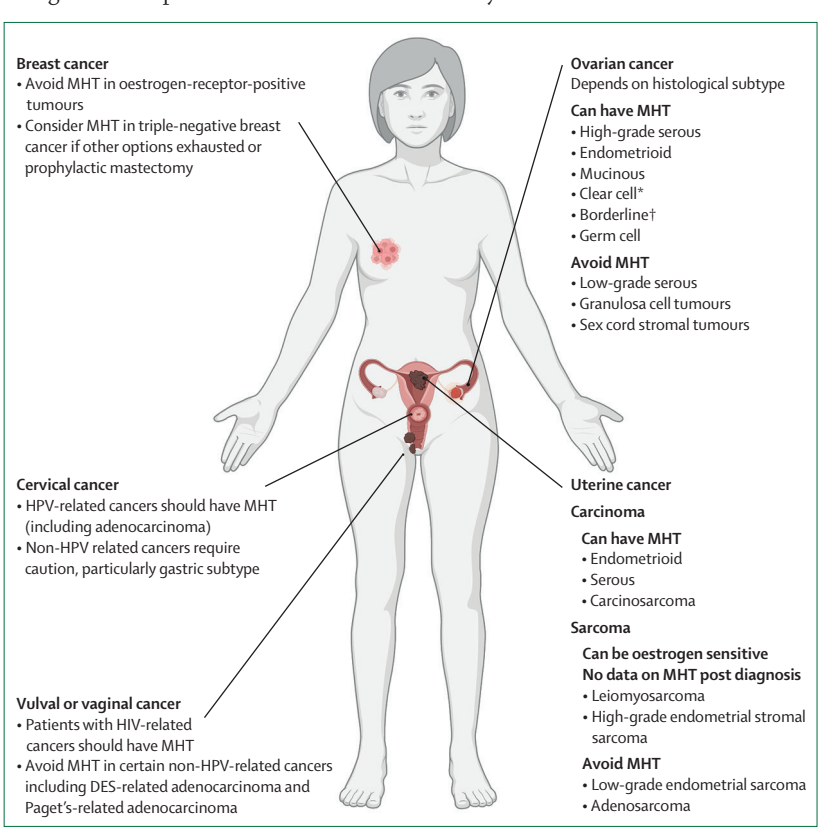

Figure 2: **Use of MHT after female-specific cancers**
MHT=menopausal hormone therapy. HPV=human papillomavirus. *Consider transdermal due to increased venous thromboembolism risk. †Fully resected, no invasive implants.

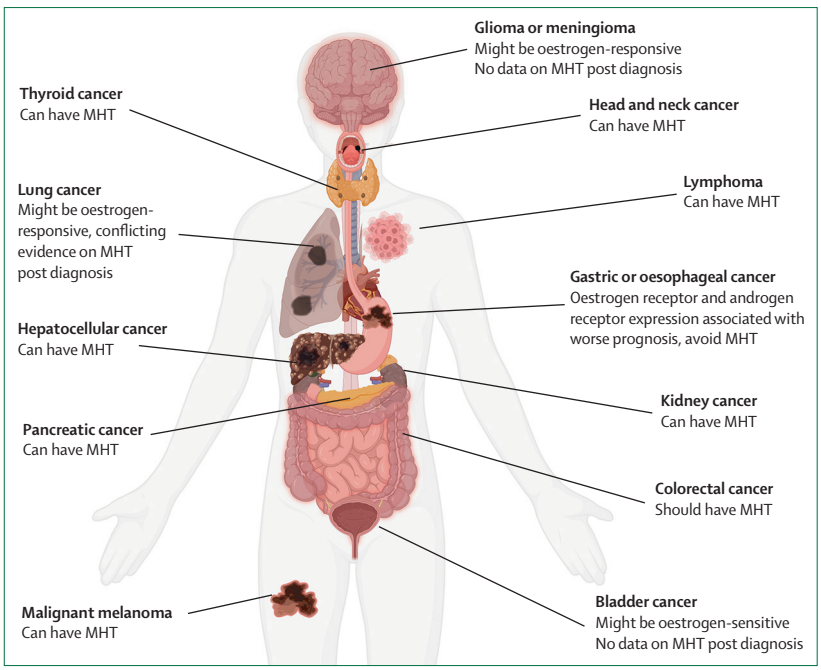

Figure 3: **Use of MHT after non-female specific cancers**
MHT=menopausal hormone therapy.

	Vasomotor symptoms	Sexual dysfunction	Vaginal dryness
Selected SSRIs and SNRIs	Likely	Unlikely*	Unlikely
Specific anticonvulsants	Likely	Unlikely	Unlikely
Oxybutynin	Likely	Unlikely	Unlikely
Clonidine	Likely	Unlikely	Unlikely
Vaginal lubricants or moisturisers	Unlikely	Possible	Possible
Vaginal carbon dioxide laser	Unlikely	Unlikely	Unlikely
Stellate ganglion block	Possible	Unlikely	Unlikely
Cognitive behavioural therapy	Likely	Likely	Unlikely
Physical exercise	Unlikely	Unlikely	Unlikely
Acupuncture	Possible	Unlikely	Unlikely
Hypnosis	Likely	Unlikely	Unlikely
Yoga and mindfulness-based stress reduction	Possible	Unlikely	Unlikely

Effectiveness is defined as likely (evidence from randomised controlled trials), possible (evidence from single-arm studies), or unlikely (no evidence of effectiveness). SNRIs=serotonin norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors. All trials are in patients with breast cancer. Adapted from Franzoi and colleagues with permission.[44] *Does not worsen sexual function when used for vasomotor symptoms.

Table: **Effectiveness of non-hormonal treatments for vasomotor symptoms, sexual difficulties, and vaginal dryness**

published, breast cancer is not a contraindication to fezolinetant use in the USA. However, improvements in vasomotor symptoms with fezolinetant are modest and do not meet the minimally important clinical difference[81] for hot flush frequency or menopause-related quality of life. A meta-analysis published in 2024,[82] which included 2168 patients from five RCTs, reported a 22·5% mean improvement in frequency of vasomotor symptoms, with small improvements in menopause-related quality of life. In 2023, the independent US Institute for Clinical and Economic Review concluded that fezolinetant was less effective than MHT for vasomotor symptoms, and that MHT might provide additional benefits for sleep, vaginal dryness, and fracture prevention.[83]

Managing sexual difficulties and dysfunction

In 2016, a systematic review reported that sexual dysfunction affected 78% of patients with gynaecological cancer and 65% of patients with breast or colorectal cancer, particularly premenopausal women.[84] Sexual dysfunction can arise from factors that are biological (eg, menopause or surgery), psychological (eg, depression, anxiety, or body image), interpersonal (eg, relationship and communication issues), and sociocultural (eg, religion or cultural). A holistic approach including partners might be best suited to address these issues. The American Society of Clinical Oncology advises that health-care professionals should initiate a discussion about sexual problems with all patients with cancer and offer psychosocial or psychosexual counselling to improve sexual response, body image, intimacy and relationship issues, and overall sexual functioning and satisfaction.[85] However, less than 25% of patients with cancer seek professional help.[86] Less is known about the psychosexual effects of cancer in LMICs, where there might be substantial cultural differences in beliefs and understanding about sex and approaches to managing sexual dysfunction compared with HICs.[87]

Management of genitourinary symptoms and sexual dysfunction after breast cancer

A 2018 consensus guideline from the American College of Obstetrics and Gynecology advised non-hormonal agents as first-line therapy, with vaginal oestrogens reserved for persistent symptoms after discussion with the treating oncologist.[88,89] In the general population, vaginal oestrogens improve dryness with no differences between products.[90] Although often recommended for long-term use, a 2020 systematic review reported that safety data are limited to 1 year.[91] Less is known about the efficacy and safety of vaginal oestrogen after breast cancer. In 2022, a Danish data linkage study reported a small increase in breast cancer recurrence in patients taking adjuvant aromatase inhibitors and using vaginal oestrogen, although their survival was no worse.[92] In 2024, a UK registry-based study of 49 237 patients aged 40–79 years with breast cancer showed no evidence of increased breast cancer mortality in those who used versus those who did not use vaginal oestrogen, although only 5% used vaginal oestrogen.[93] Vaginal oestrogens are systemically absorbed in small but measurable amounts, which are dose dependent, with low and ultra-low doses leading to low or no measurable absorption.[94] In the general population, an RCT of daily vaginal prasterone for 12 weeks showed a reduction in pain during sexual activity and an improvement in vaginal dryness.[95] However, one RCT (n=464) of vaginal prasterone after

breast cancer showed no benefit compared with vaginal moisturiser at 8 weeks.[96]

Ospemifene is an oral treatment for vaginal dryness that is approved for use after breast cancer in the UK and the USA. In the general population, ospemifene is superior to placebo for vaginal dryness and improves sexual function at 12 weeks.[97] However, there are no direct comparator trials with vaginal oestrogen, and efficacy and safety of ospemifene after cancer are unknown.[96] There is little evidence to support the efficacy of lubricants and moisturisers. One small RCT comparing silicone with water-based lubricants in patients with breast cancer taking aromatase inhibitors found that silicone lubricants were more effective for sexual pain but more than 80% of patients still had sexual pain despite lubricant use.[98] One RCT of vulval anaesthetic (lignocaine) after breast cancer showed reduced pain with intercourse.[99]

Cancer and its treatment might also reduce libido and sexual satisfaction. One RCT showed that intravaginal testosterone reduced pain and dryness and increased satisfaction in patients with breast cancer taking aromatase inhibitors.[100] However, the safety of testosterone after breast cancer is uncertain. Psychosexual interventions including CBT, education, and counselling might be helpful.[101] An RCT showed that CBT improved overall sexual function and desire, arousal and vaginal lubrication, and sexual pleasure and reduced discomfort and distress after breast cancer.[102] Brief sexual counselling by telephone or in person might also be effective.[103]

Management of genitourinary symptoms and sexual dysfunction after pelvic radiotherapy

The vaginal effects of external beam radiotherapy or brachytherapy, particularly vaginal dryness, fibrosis, and shortening, which can present as pain with sexual activity and impaired sexual function, can be more severe than those of chemotherapy.[101] Vaginal dilators are recommended to maintain vaginal capacity after pelvic radiation, but uptake is low at less than 25% of patients and the evidence base is scant.[101] In 2014, a systematic review found no reliable evidence that routine regular vaginal dilation during radiotherapy prevents stenosis or improves quality of life.[104] Vaginal oestrogen is commonly offered with little evidence to support efficacy. Pelvic floor dysfunction, including urinary and faecal incontinence, dyspareunia, and vaginismus, are common after gynaecological cancer treatment. A small RCT (n=34) showed that pelvic floor physiotherapy improved sexual function after gynaecological cancer.[105]

Integrative oncology

Integrative oncology describes the use of complementary treatments alongside conventional cancer therapies. This approach takes a patient-centred, evidence-informed perspective and uses mind–body practices, natural products, and lifestyle modifications alongside conventional treatments. Integrative oncology might include therapies such as CBT, mindfulness, and hypnosis for vasomotor symptoms, mood, and sleep.[106] Patients with cancer in many settings rely on traditional, complementary, and integrative treatments that are culturally appropriate and more accessible than conventional therapies.[107] Although there is very little evidence to support the use of traditional and complementary therapies in cancer treatment, several randomised controlled trials have shown benefits for reducing symptoms such as fatigue, depression, anxiety, and insomnia, which could improve quality of life.[108]

Multidisciplinary care

Managing menopause after cancer requires a multidisciplinary clinical team and the use of an evidence base to inform practice, optimal models for service delivery, and investment in sectors such as primary care and allied health. Tertiary-based care cannot meet the needs of the growing number of people who survive cancer. Since menopausal symptoms affect a wide range of these patients, siloed care within tumour streams could lead to duplication of precious services.

In Australia, the multidisciplinary Menopausal Service after Cancer (MSAC) provided by gynaecologists, endocrinologists, and primary care and allied health providers manages vasomotor and genitourinary symptoms, sleep and mood disturbance, and sexual difficulties across cancer types and in one place.[109] A 2021 study showed statistically significant improvements in the four most troublesome symptoms (ie, hot flushes, fatigue, sleep difficulties, and loss of interest in sex) in patients whose care was managed through MSAC.[110] To minimise cost and reduce waste, clear guidelines are needed to support the management of menopausal symptoms after cancer. This approach should include high-quality information for patients about hormonal, non-hormonal, and psychological treatment options that stratify risk according to cancer type. Involving patients in decisions about their care and enabling them to make informed choices is key and is likely to lead to better outcomes.

COVID-19 changed how medical care is delivered. Telemedicine can extend the reach of care and increase convenience for patients. In 2021, a systematic review reported that digital health interventions were helpful and effective for supportive care in patients with cancer. Most studies reported positive outcomes for symptoms such as fatigue and pain, health-related quality of life, functional capacity, and mood compared with usual care, although most studies were in breast cancer.[111] Telehealth is also accessible and effective for managing menopausal symptoms after cancer and could reduce the burden of hospital appointments. Patients with cancer often prefer video telehealth when physical examination is not needed.[112] Telehealth can also be delivered directly to the primary care provider who has reviewed and examined the patient, which can reduce the need for tertiary referral.[113]

Tertiary care should be multidisciplinary, inclusive of all symptomatic patients, and should aim to manage all

common symptoms.[114] In-person visits are needed for vulval and vaginal examination to manage chronic genital graft versus host disease, which affects around 30% of allograft patients in whom effective management can prevent severe complications such as vaginal stenosis.[115]

In breast cancer, RCT evidence supports the role of nurse practitioners in patient counselling and education and to assess symptoms.[116] Allied health professionals such as primary care providers are well placed to provide ongoing psychological support, monitor for short-term and long-term complications of cancer treatment, modify risk factors, and make timely onward referral as needed. Care delivered by allied health-care professionals and their peers in discussion with cancer specialists might be more sustainable than ongoing tertiary care.

Health disparities in LMICs

Rates of treatment-induced menopause are elevated in LMICs, where the average age at cancer diagnosis is 40–50 years compared with 66 years in HICs.[24] In these settings, more women are diagnosed with cancer when they are still premenopausal and are exposed to treatments that are likely to induce POI or early menopause. Prevention and management of treatment-induced menopause is an unmet need in LMICs. Supportive care should be integrated into the comprehensive cancer care model through the training of primary and tertiary health-care providers and the provision of essential and affordable medication to manage symptoms. Education for patients and their carers should include identification of symptoms, self-management approaches, and pathways for seeking care. Scarcity of evidence from high-quality research is commonly cited as the key reason for not integrating traditional and complementary medicine into cancer survivorship care.[117]

For more on the **resource for LGBTQI+ people with cancer** see https://www.cancercouncil.com.au/cancer-information/lgbtqi/

Evidence gaps

Almost all published studies of menopause and cancer are in early breast cancer, and less is known about advanced breast cancer or other cancers in women. There are no reliable ways of predicting who will experience severe or prolonged menopausal symptoms following cancer treatment. In breast cancer, vaginal dryness is more common with aromatase inhibitors than tamoxifen, and some evidence suggests that switching between tamoxifen and aromatase inhibitors can improve vasomotor symptoms in postmenopausal women.[13,118] Among premenopausal women, switching to tamoxifen plus ovarian function suppression or tamoxifen alone might improve vaginal dryness, and this treatment can be considered by the treating oncologist when weighing the advantages and disadvantages of disease risks and tolerance of therapy.[119] Decisions regarding the necessity and type of hormonal therapy used for breast cancer treatment depend on menopausal status, evolving literature, disease risk, and patients' comorbidities, tolerance over time, and preferences.

For more on the **personalised online resources** see https://thisisgo.ie/

Although aromatase inhibitors have become the standard of care for many patients with oestrogen-positive breast cancer (with ovarian suppression in premenopausal women), there are commonly issues with access and cost for women in LMICs. Tamoxifen is widely used for premenopausal and postmenopausal women in these settings, and it is included in WHO's list of essential cancer medicines. More information is needed about the effect of long-term tamoxifen use on menopausal symptoms and quality of life for patients from LMICs, especially when they transition from premenopausal to postmenopausal. Most clinical trials of treatments for menopausal symptoms were done in older women but younger patients with cancer can experience severe symptoms and worse quality of life.[120] Little is known about the effects of cancer treatment in lesbian, gay, bisexual, transgender, queer or questioning, and intersex (LGBTQI+) individuals, but some people report hostility and prejudice from health-care providers and anxiety about disclosing their sexual orientation and gender identity.[121] In Australia, these data have informed a new information resource for LGBTQI+ people with cancer.

Although new non-hormonal and non-pharmacological treatments are needed for patients with contraindications to MHT, young patients with cancer who are eligible to take MHT might not be offered it. New MHT preparations are emerging, including selective oestrogen receptor modulators and non-hormonal therapies targeting the neurokinin B receptor. One targeted therapy (Q-122) has shown moderate efficacy for vasomotor symptoms in patients with breast cancer taking endocrine therapy.[122] Fezolinetant is available in some countries for vasomotor symptoms, with efficacy, safety, and tolerability shown up to 1 year in the general population.[78,123] However, efficacy and safety of this agent after cancer are not clear.

Safe and effective non-hormonal treatments for managing genitourinary symptoms after cancer are needed. The efficacy of vaginal laser is uncertain. A 2021 randomised sham-controlled trial of vaginal laser for genitourinary symptoms in postmenopausal women, of whom around half had previous breast cancer, found no difference between the sham and laser groups.[124] In 2023, a randomised trial of carbon dioxide laser on sexual function in survivors of breast cancer showed no benefit over sham laser.[125]

Reaching the population who need treatment is a global problem. Novel online information and treatment resources based on stepped care aim to increase knowledge and improve access to treatment. In gynaecological cancer, new personalised online resources co-developed with patients provide much-needed information and symptomatic support.

Contributors

MH conceived and designed the paper, wrote the initial draft, and was responsible for revising this draft based on comments from the other authors. PB, JS, MES, EW, KNC, C-HY, AHP, and DJB made substantial

contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MH is responsible for the final approval of this manuscript and agrees to be accountable. PB and EW are personnel of the International Agency for Research on Cancer or WHO. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer or WHO.

Declaration of interests

MH declares salary funding from the Australian National Health and Medical Research Council, support for meeting attendance from the UK National Institute for Health and Care Excellence, and the following roles: principal investigator for a clinical trial of salpingectomy vs salpingo-oophorectomy for prevention of ovarian cancer (TUBA-WISP II); board member for Breastscreen Victoria; editor for the Cochrane Collaboration; recipient of a fellowship from the Lundbeck Foundation (2022-23); site investigator for a clinical trial of a non-hormonal agent (Q-122) for vasomotor symptoms in patients with breast cancer (QUE Oncology, 2020-22); and site investigator for a clinical trial of a medical device for treating vaginal dryness (Madorra). JS is a site investigator for neurokinin B antagonist for vasomotor symptoms and has received travel grants for conference attendance from Mylan and Besins. AHP has received royalties for coauthorship of the breast cancer survivorship section of UpToDate. DJB acknowledges financial support from Precision Oncology Ireland, which is part-funded by the Science Foundation Ireland Strategic Partnership Programme (grant number 18/SPP/3522), and has received co-funding from AstraZeneca. DJB is the principal investigator of an investigator-initiated clinical trial of digital cognitive behavioural therapy and gabapentin for treatment of menopause symptoms after cancer, supported by the Irish Cancer Society (WHIBREN2020). DJB has received speaker fees or honoraria from Bayer, GSK, MSD, Olympus, and AstraZeneca and has participated on a data safety monitoring board or advisory board for Astellas, Bayer, and GSK. All other authors declare no competing interests.

References

1 Zhu D, Chung H-F, Pandeya N, et al. Body mass index and age at natural menopause: an international pooled analysis of 11 prospective studies. *Eur J Epidemiol* 2018; **33:** 699–710.

2 Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *Int J Epidemiol* 2014; **43:** 1542–62.

3 Xu X, Jones M, Mishra GD. Age at natural menopause and development of chronic conditions and multimorbidity: results from an Australian prospective cohort. *Hum Reprod* 2020; **35:** 203–11.

4 Overbeek A, van den Berg MH, van Leeuwen FE, Kaspers GJ, Lambalk CB, van Dulmen-den Broeder E. Chemotherapy-related late adverse effects on ovarian function in female survivors of childhood and young adult cancer: a systematic review. *Cancer Treat Rev* 2017; **53:** 10–24.

5 Lumsden MA, Davies M, Sarri G. Diagnosis and management of menopause: the National Institute for Health and Care Excellence (NICE) guideline. *JAMA Intern Med* 2016; **176:** 1205–06.

6 Peate M, Saunders C, Cohen P, Hickey M. Who is managing menopausal symptoms, sexual problems, mood and sleep disturbance after breast cancer and is it working? Findings from a large community-based survey of breast cancer survivors. *Breast Cancer Res Treat* 2021; **187:** 427–35.

7 Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand challenge in global health. *Lancet* 2017; **389:** 847–60.

8 Glyde T. LGBTQIA+ menopause: room for improvement. *Lancet* 2022; **400:** 1578–79.

9 Szabo RA, Marino JL, Hickey M. Managing menopausal symptoms after cancer. *Climacteric* 2019; **22:** 572–78.

10 Perrone G, Capri O, Galoppi P, et al. Menopausal symptoms after the discontinuation of long-term hormone replacement therapy in women under 60: a 3-year follow-up. *Gynecol Obstet Invest* 2013; **76:** 38–43.

11 Bernhard J, Luo W, Ribi K, et al. Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials. *Lancet Oncol* 2015; **16:** 848–58.

12 Marino JL, Saunders CM, Emery LI, Green H, Doherty DA, Hickey M. Nature and severity of menopausal symptoms and their impact on quality of life and sexual function in cancer survivors compared with women without a cancer history. *Menopause* 2014; **21:** 267–74.

13 Ganz PA, Cecchini RS, Julian TB, et al. Patient-reported outcomes with anastrozole versus tamoxifen for postmenopausal patients with ductal carcinoma in situ treated with lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet* 2016; **387:** 857–65.

14 Boundouki G, Wilson R, Duxbury P, et al. Patient and public priorities for breast cancer research: a qualitative study in the UK. *BMJ Open* 2021; **11:** e036072.

15 Scanlon M, Blaes A, Geller M, Majhail NS, Lindgren B, Haddad T. Patient satisfaction with physician discussions of treatment impact on fertility, menopause and sexual health among pre-menopausal women with cancer. *J Cancer* 2012; **3:** 217–25.

16 National Cancer Institute. BRCA gene mutations: cancer risk and genetic testing. Nov 19, 2020. https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet (accessed Feb 8, 2024).

17 Liu YL, Breen K, Catchings A, et al. Risk-reducing bilateral salpingo-oophorectomy for ovarian cancer: a review and clinical guide for hereditary predisposition genes. *JCO Oncol Pract* 2022; **18:** 201–09.

18 Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19:** 77–102.

19 Hickey M, Rio I, Trainer A, Marino JL, Wrede CD, Peate M. Exploring factors that impact uptake of risk-reducing bilateral salpingo-oophorectomy (RRBSO) in high-risk women. *Menopause* 2020; **27:** 26–32.

20 Hickey M, Rio I, Trainer A, Marino JL, Wrede CD, Peate M. What information do healthcare professionals need to inform premenopausal women about risk-reducing salpingo-oophorectomy? *Menopause* 2020; **27:** 20–25.

21 Nebgen DR, Domchek SM, Kotsopoulos J, et al. Care after premenopausal risk-reducing salpingo-oophorectomy in high-risk women: scoping review and international consensus recommendations. *BJOG* 2023; **130:** 1437–50.

22 Brennan A, Brennan D, Rees M, Hickey M. Management of menopausal symptoms and ovarian function preservation in women with gynecological cancer. *Int J Gynecol Cancer* 2021; **31:** 352–59.

23 International Agency for Research on Cancer. Colorectal cancer. https://www.iarc.who.int/cancer-type/colorectal-cancer/ (accessed Feb 15, 2024).

24 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–49.

25 Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol* 2018; **36:** 1994–2001.

26 Lee YJ, Kim JS, Jo JC, et al. Risk factors of menopause after allogeneic hematopoietic cell transplantation in premenopausal adult women. *Eur J Haematol* 2023; **111:** 449–57.

27 Niksic M, Rachet B, Warburton FG, Wardle J, Ramirez AJ, Forbes LJ. Cancer symptom awareness and barriers to symptomatic presentation in England--are we clear on cancer? *Br J Cancer* 2015; **113:** 533–42.

28 Leone T. Women's mid-life health in low and middle income countries: a comparative analysis of the timing and speed of health deterioration in six countries. *SSM Popul Health* 2018; **7:** 100341.

29 Kimman ML, Jan S, Peters SAE, et al. Health-related quality of life and psychological distress among cancer survivors in Southeast Asia: results from a longitudinal study in eight low- and middle-income countries. *BMC Med* 2017; **15:** 10.

30 Lambertini M, Peccatori FA, Demeestere I, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO clinical practice guidelines. *Ann Oncol* 2020; **31:** 1664–78.

31 Poorvu PD, Frazier AL, Feraco AM, et al. Cancer treatment-related infertility: a critical review of the evidence. *JNCI Cancer Spectr* 2019; **3:** pkz008.

32 Winship AL, Alesi LR, Sant S, et al. Checkpoint inhibitor immunotherapy diminishes oocyte number and quality in mice. *Nat Cancer* 2022; **3:** 1–13.

33 Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. *J Clin Oncol* 2018; **36:** 1981–90.

34 Rodriguez-Wallberg KA, Nilsson HP, Bergh J, et al. ProFertil study protocol for the investigation of gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy aiming at fertility protection of young women and teenagers with cancer in Sweden-a phase III randomised double-blinded placebo-controlled study. *BMJ Open* 2023; **13:** e078023.

35 Demeestere I, Brice P, Peccatori FA, et al. No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. *J Clin Oncol* 2016; **34:** 2568–74.

36 Wan J, Gai Y, Li G, Tao Z, Zhang Z. Incidence of chemotherapy- and chemoradiotherapy-induced amenorrhea in premenopausal women with stage 2/3 colorectal cancer. *Clin Colorectal Cancer* 2015; **14:** 31–34.

37 Kim S, Kim SW, Han SJ, et al. Molecular mechanism and prevention strategy of chemotherapy- and radiotherapy-induced ovarian damage. *Int J Mol Sci* 2021; **22:** 7484.

38 Hoekman EJ, Broeders EABJ, Louwe LA, Nout RA, Jansen FW, de Kroon CD. Ovarian function after ovarian transposition and additional pelvic radiotherapy: a systematic review. *Eur J Surg Oncol* 2019; **45:** 1328–40.

39 Sioulas VD, Jorge S, Chern JY, et al. Robotically assisted laparoscopic ovarian transposition in women with lower gastrointestinal cancer undergoing pelvic radiotherapy. *Ann Surg Oncol* 2017; **24:** 251–56.

40 Anderson RA, Cameron D, Clatot F, et al. Anti-Müllerian hormone as a marker of ovarian reserve and premature ovarian insufficiency in children and women with cancer: a systematic review. *Hum Reprod Update* 2022; **28:** 417–34.

41 Jacobson MH, Mertens AC, Spencer JB, Manatunga AK, Howards PP. Menses resumption after cancer treatment-induced amenorrhea occurs early or not at all. *Fertil Steril* 2016; **105:** 765–72.

42 Goldštajn MŠ, Mikuš M, Ferrari FA, et al. Effects of transdermal versus oral hormone replacement therapy in postmenopause: a systematic review. *Arch Gynecol Obstet* 2023; **307:** 1727–45.

43 Anderson RA, Kelsey TW, Perdrix A, et al. Diagnostic and predictive accuracy of anti-mullerian hormone for ovarian function after chemotherapy in premenopausal women with early breast cancer. *Breast Cancer Res Treat* 2022; **192:** 273–82.

44 Franzoi MA, Agostinetto E, Perachino M, et al. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. *Lancet Oncol* 2021; **22:** e303–13.

45 Sarri G, Pedder H, Dias S, Guo Y, Lumsden MA. Vasomotor symptoms resulting from natural menopause: a systematic review and network meta-analysis of treatment effects from the National Institute for Health and Care Excellence guideline on menopause. *BJOG* 2017; **124:** 1514–23.

46 Poggio F, Del Mastro L, Bruzzone M, et al. Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2021; **191:** 269–75.

47 Kenemans P, Bundred NJ, Foidart JM, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol* 2009; **10:** 135–46.

48 Rees M, Angioli R, Coleman RL, et al. European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis. *Maturitas* 2020; **134:** 56–61.

49 Edey KA, Rundle S, Hickey M. Hormone replacement therapy for women previously treated for endometrial cancer. *Cochrane Database Syst Rev* 2018; **5:** CD008830.

50 Ploch E. Hormonal replacement therapy in patients after cervical cancer treatment. *Gynecol Oncol* 1987; **26:** 169–77.

51 Cibula D, Pötter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Int J Gynecol Cancer* 2018; **28:** 641–55.

52 Yang X, Wang C, He X, et al. Hormone therapy for premature ovarian insufficiency patients with malignant hematologic diseases. *Climacteric* 2017; **20:** 268–73.

53 MacKie RM, Bray CA. Hormone replacement therapy after surgery for stage 1 or 2 cutaneous melanoma. *Br J Cancer* 2004; **90:** 770–72.

54 Chan JA, Meyerhardt JA, Chan AT, Giovannucci EL, Colditz GA, Fuchs CS. Hormone replacement therapy and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006; **24:** 5680–86.

55 Ji J, Sundquist J, Sundquist K. Use of hormone replacement therapy improves the prognosis in patients with colorectal cancer: a population-based study in Sweden. *Int J Cancer* 2018; **142:** 2003–10.

56 Hassan MM, Botrus G, Abdel-Wahab R, et al. Estrogen replacement reduces risk and increases survival times of women with hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2017; **15:** 1791–99.

57 Saeaib N, Peeyananjarassri K, Liabsuetrakul T, Buhachat R, Myriokefalitaki E. Hormone replacement therapy after surgery for epithelial ovarian cancer. *Cochrane Database Syst Rev* 2020; **1:** CD012559.

58 Brennan A, Rees M. Menopausal hormone therapy in women with benign gynaecological conditions and cancer. *Best Pract Res Clin Endocrinol Metab* 2021; **35:** 101575.

59 Zhang X, Du Y, Tan X, et al. The relationship between hormone replacement therapy and risk of kidney cancer in women: a meta-analysis. *Cancer Control* 2020; **27:** 1073274820930194.

60 Clague J, Reynolds P, Henderson KD, et al. Menopausal hormone therapy and lung cancer-specific mortality following diagnosis: the California Teachers Study. *PLoS One* 2014; **9:** e103735.

61 Katcoff H, Wenzlaff AS, Schwartz AG. Survival in women with NSCLC: the role of reproductive history and hormone use. *J Thorac Oncol* 2014; **9:** 355–61.

62 Ganti AK, Sahmoun AE, Panwalkar AW, Tendulkar KK, Potti A. Hormone replacement therapy is associated with decreased survival in women with lung cancer. *J Clin Oncol* 2006; **24:** 59–63.

63 Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet* 2009; **374:** 1243–51.

64 Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook. October, 2013. https://gdt.gradepro.org/app/handbook/handbook.html (accessed Feb 15, 2024).

65 Gordhandas S, Norquist BM, Pennington KP, Yung RL, Laya MB, Swisher EM. Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations; a systematic review of risks and benefits. *Gynecol Oncol* 2019; **153:** 192–200.

66 Steenbeek MP, Harmsen MG, Hoogerbrugge N, et al. Association of salpingectomy with delayed oophorectomy versus salpingo-oophorectomy with quality of life in BRCA1/2 pathogenic variant carriers: a nonrandomized controlled trial. *JAMA Oncol* 2021; **7:** 1203–12.

67 Hickey M, Moss KM, Krejany EO, et al. What happens after menopause? (WHAM): a prospective controlled study of vasomotor symptoms and menopause-related quality of life 12 months after premenopausal risk-reducing salpingo-oophorectomy. *Gynecol Oncol* 2021; **163:** 148–54.

68 Hickey M, Moss KM, Krejany EO, et al. What happens after menopause? (WHAM): a prospective controlled study of sleep quality up to 12 months after premenopausal risk-reducing salpingo-oophorectomy. *Gynecol Oncol* 2021; **162:** 447–53.

69 Hickey M, Moss KM, Brand A, et al. What happens after menopause? (WHAM): a prospective controlled study of depression and anxiety up to 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy. *Gynecol Oncol* 2021; **161:** 527–34.

70 Hunter MS. Cognitive behavioral therapy for menopausal symptoms. *Climacteric* 2021; **24:** 51–56.

71 Lensen S, Archer D, Bell RJ, et al. A core outcome set for vasomotor symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) global initiative. *Menopause* 2021; **28:** 852–58.

72 Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM. Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women. *Menopause* 2014; **21:** 807–14.

73 Rahimzadeh P, Imani F, Nafissi N, Ebrahimi B, Faiz SHR. Comparison of the effects of stellate ganglion block and paroxetine on hot flashes and sleep disturbance in breast cancer survivors. *Cancer Manag Res* 2018; **10:** 4831–37.

74 Marshall-McKenna R, Morrison A, Stirling L, et al. A randomised trial of the cool pad pillow topper versus standard care for sleep disturbance and hot flushes in women on endocrine therapy for breast cancer. *Support Care Cancer* 2016; **24:** 1821–29.

75 Hickey M, Szabo RA, Hunter MS. Non-hormonal treatments for menopausal symptoms. *BMJ* 2017; **359:** j5101.

76 Leon-Ferre RA, Novotny PJ, Wolfe EG, et al. Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603). *JNCI Cancer Spectr* 2019; **4:** pkz088.

77 Hervik JB, Stub T. Adverse effects of non-hormonal pharmacological interventions in breast cancer survivors, suffering from hot flashes: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2016; **160:** 223–36.

78 Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet* 2023; **401:** 1091–102.

79 Johnson KA, Martin N, Nappi RE, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. *J Clin Endocrinol Metab* 2023; **108:** 1981–97.

80 Santoro N, Waldbaum A, Lederman S, et al. Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). *Menopause* 2020; **27:** 1350–56.

81 Constantine GD, Graham S, Clerinx C, et al. Behaviours and attitudes influencing treatment decisions for menopausal symptoms in five European countries. *Post Reprod Health* 2016; **22:** 112–22.

82 Bonga KN, Mishra A, Maiti R, Padhy BM, Meher BR, Srinivasan A. Efficacy and safety of fezolinetant for the treatment of menopause-associated vasomotor symptoms: a meta-analysis. *Obstet Gynecol* 2024, published online Jan 16. https://doi.org/10.1097/aog.0000000000005508.

83 Beaudoin FL, McQueen RB, Wright A, et al. Fezolinetant for moderate to severe vasomotor symptoms associated with menopause: effectiveness and value; final evidence report. Jan 23, 2023. https://icer.org/wp-content/uploads/2022/06/ICER_Menopause_FinalReport_01232023.pdf (accessed Feb 9, 2024).

84 Maiorino MI, Chiodini P, Bellastella G, Giugliano D, Esposito K. Sexual dysfunction in women with cancer: a systematic review with meta-analysis of studies using the Female Sexual Function Index. *Endocrine* 2016; **54:** 329–41.

85 Carter J, Lacchetti C, Andersen BL, et al. Interventions to address sexual problems in people with cancer: American Society of Clinical Oncology Clinical Practice Guideline adaptation of Cancer Care Ontario Guideline. *J Clin Oncol* 2018; **36:** 492–511.

86 Schover LR. Sexual quality of life in men and women after cancer. *Climacteric* 2019; **22:** 553–57.

87 Sopfe J, Pettigrew J, Afghahi A, Appiah LC, Coons HL. Interventions to improve sexual health in women living with and surviving cancer: review and recommendations. *Cancers (Basel)* 2021; **13:** 3153.

88 Faubion SS, Larkin LC, Stuenkel CA, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from the North American Menopause Society and the International Society for the Study of Women's Sexual Health. *Menopause* 2018; **25:** 596–608.

89 Farrell R. ACOG committee opinion no 659: the use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. *Obstet Gynecol* 2016; **127:** e93–96.

90 Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2016; **2016:** CD001500.

91 Crandall CJ, Diamant A, Santoro N. Safety of vaginal estrogens: a systematic review. *Menopause* 2020; **27:** 339–60.

92 Cold S, Cold F, Jensen MB, Cronin-Fenton D, Christiansen P, Ejlertsen B. Systemic or vaginal hormone therapy after early breast cancer: a Danish observational cohort study. *J Natl Cancer Inst* 2022; **114:** 1347–54.

93 McVicker L, Labeit AM, Coupland CAC, et al. Vaginal estrogen therapy use and survival in females with breast cancer. *JAMA Oncol* 2024; **10:** 103–08.

94 Santen RJ, Mirkin S, Bernick B, Constantine GD. Systemic estradiol levels with low-dose vaginal estrogens. *Menopause* 2020; **27:** 361–70.

95 Labrie F, Archer DF, Koltun W, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause* 2018; **25:** 1339–53.

96 Barton DL, Sloan JA, Shuster LT, et al. Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). *Support Care Cancer* 2018; **26:** 643–50.

97 Archer DF, Goldstein SR, Simon JA, et al. Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: a phase 3, randomized, double-blind, placebo-controlled, multicenter trial. *Menopause* 2019; **26:** 611–21.

98 Hickey M, Marino JL, Braat S, Wong S. A randomized, double-blind, crossover trial comparing a silicone- versus water-based lubricant for sexual discomfort after breast cancer. *Breast Cancer Res Treat* 2016; **158:** 79–90.

99 Goetsch MF, Lim JY, Caughey AB. A practical solution for dyspareunia in breast cancer survivors: a randomized controlled trial. *J Clin Oncol* 2015; **33:** 3394–400.

100 Davis SR, Robinson PJ, Jane F, White S, White M, Bell RJ. Intravaginal testosterone improves sexual satisfaction and vaginal symptoms associated with aromatase inhibitors. *J Clin Endocrinol Metab* 2018; **103:** 4146–54.

101 Suvaal I, Hummel SB, Mens JM, et al. A sexual rehabilitation intervention for women with gynaecological cancer receiving radiotherapy (SPARC study): design of a multicentre randomized controlled trial. *BMC Cancer* 2021; **21:** 1295.

102 Hummel SB, van Lankveld JJDM, Oldenburg HSA, et al. Efficacy of internet-based cognitive behavioral therapy in improving sexual functioning of breast cancer survivors: results of a randomized controlled trial. *J Clin Oncol* 2017; **35:** 1328–40.

103 Marcus AC, Garrett KM, Cella D, et al. Can telephone counseling post-treatment improve psychosocial outcomes among early stage breast cancer survivors? *Psychooncology* 2010; **19:** 923–32.

104 Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. *Cochrane Database Syst Rev* 2014; **2014:** CD007291.

105 Yang EJ, Lim JY, Rah UW, Kim YB. Effect of a pelvic floor muscle training program on gynecologic cancer survivors with pelvic floor dysfunction: a randomized controlled trial. *Gynecol Oncol* 2012; **125:** 705–11.

106 Hoffman CJ, Ersser SJ, Hopkinson JB, Nicholls PG, Harrington JE, Thomas PW. Effectiveness of mindfulness-based stress reduction in mood, breast- and endocrine-related quality of life, and well-being in stage 0 to 3 breast cancer: a randomized, controlled trial. *J Clin Oncol* 2012; **30:** 1335–42.

107 Mao JJ, Pillai GG, Andrade CJ, et al. Integrative oncology: addressing the global challenges of cancer prevention and treatment. *CA Cancer J Clin* 2022; **72:** 144–64.

108 Calcagni N, Gana K, Quintard B. A systematic review of complementary and alternative medicine in oncology: psychological and physical effects of manipulative and body-based practices. *PLoS One* 2019; **14:** e0223564.

109 Hickey M, Emery LI, Gregson J, Doherty DA, Saunders CM. The multidisciplinary management of menopausal symptoms after breast cancer: a unique model of care. *Menopause* 2010; **17:** 727–33.

110 Hollingworth J, Walsh L, Tran S, et al. Does a multidisciplinary menopausal symptoms after cancer clinic reduce symptoms? *Support Care Cancer* 2022; **30:** 2245–52.

111 Marthick M, McGregor D, Alison J, Cheema B, Dhillon H, Shaw T. Supportive care interventions for people with cancer assisted by digital technology: systematic review. *J Med Internet Res* 2021; **23:** e24722.

112 Rachagan N, Szabo RA, Rio I, Rees F, Hiscock HM, Hickey M. Video telehealth to manage menopausal symptoms after cancer: a prospective study of clinicians and patient satisfaction. *Menopause* 2023; **30:** 143–48.

113 Kwok J, Olayiwola JN, Knox M, Murphy EJ, Tuot DS. Electronic consultation system demonstrates educational benefit for primary care providers. *J Telemed Telecare* 2018; **24:** 465–72.

114 Cohen PA, Brennan A, Marino JL, Saunders CM, Hickey M. Managing menopausal symptoms after breast cancer—a multidisciplinary approach. *Maturitas* 2017; **105:** 4–7.

115 Lev-Sagie A, Adar-Walling E, Gumer A, Grisariu S, Avni B. Management and long-term consequences of genital graft versus host disease following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2020; **55:** 2234–43.

116 Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst* 2000; **92:** 1054–64.

117 WHO. WHO Traditional Medicine Strategy 2014–23. Geneva: World Health Organization, 2013.

118 Kadakia KC, Kidwell KM, Seewald NJ, et al. Prospective assessment of patient-reported outcomes and estradiol and drug concentrations in patients experiencing toxicity from adjuvant aromatase inhibitors. *Breast Cancer Res Treat* 2017; **164:** 411–19.

119 Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018; **379:** 122–37.

120 Di Meglio A, Havas J, Gbenou AS, et al. Dynamics of long-term patient-reported quality of life and health behaviors after adjuvant breast cancer chemotherapy. *J Clin Oncol* 2022; **40:** 3190–204.

121 Ussher JM, Perz J, Allison K, et al. Attitudes, knowledge and practice behaviours of oncology health care professionals towards lesbian, gay, bisexual, transgender, queer and intersex (LGBTQI) patients and their carers: a mixed-methods study. *Patient Educ Couns* 2022; **105:** 2512–23.

122 Vrselja A, Latifi A, Baber RJ, et al. Q-122 as a novel, non-hormonal, oral treatment for vasomotor symptoms in women taking tamoxifen or an aromatase inhibitor after breast cancer: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2022; **400:** 1704–11.

123 Neal-Perry G, Cano A, Lederman S, et al. Safety of fezolinetant for vasomotor symptoms associated with menopause: a randomized controlled trial. *Obstet Gynecol* 2023; **141:** 737–47.

124 Li F, Picard-Fortin V, Maheux-Lacroix S, et al. The efficacy of vaginal laser and other energy-based treatments on genital symptoms in postmenopausal women: a systematic review and meta-analysis. *J Minim Invasive Gynecol* 2021; **28:** 668–83.

125 Mension E, Alonso I, Anglès-Acedo S, et al. Effect of fractional carbon dioxide vs sham laser on sexual function in survivors of breast cancer receiving aromatase inhibitors for genitourinary syndrome of menopause: the LIGHT randomized clinical trial. *JAMA Netw Open* 2023; **6:** e2255697.