Menaging Menopause After Gynecologic Cancers

Dr Kerstin Gustafson

Faculty/Presenter Disclosure

Faculty

Dr. Kerstin Gustafson, MD, FRCSC, MSCP

Relationships with Financial Sponsors

Advisory boards and/or speaker fees have been received in the last year from Astellas, Pfizer, Bayer, Novo-Nordisk, Knight and Searchlight Pharma. Dr Gustafson has received speaking fees from not-for-profit organizations including UBC, and SOGC, and CMS

Patents for drugs and devices

None

Potential for conflict(s) of interest:

I may speak about some products made by companies from whom I have received consulting fees and honoraria

Mitigating Potential Bias

I will be speaking generally about treatment options based on clinical guidelines and practice standards, rather than focussing on specific medications. I will use generic names of medications when named and follow recommended guideline standards.

Language use:

I will use the word “women” in this presentation in discussing adults assigned female at birth and acknowledge that gender and sexuality are complex and that some may not identify with this term. Recommendations apply to all individuals who are experiencing menopause even if they do not identify as women

Objectives

- Review cancer-specific risks related to MHT
- Summarize SOGC, Cancer Canada, NCCN, ASCO, ESMO guidance
- Provide practical prescribing recommendations
- Outline safe non-hormonal alternatives
- Support shared decision-making

Scope of the Issue

- Every women who lives to midlife will experience menopause
- The average age of menopause is around 51, right at the time that risk of breast and endometrial cancer start to rise
- Hormonal factors in perimenopause may contribute to those risks
- Symptoms of menopause can impact QOL, and may be worsened by cancer therapies

Table 3. Age-specific incidence per 100,000 person-years in non-Hispanic white women from the NHS cohort, excluding only women with prevalent cancer of interest and no positive follow-up time.

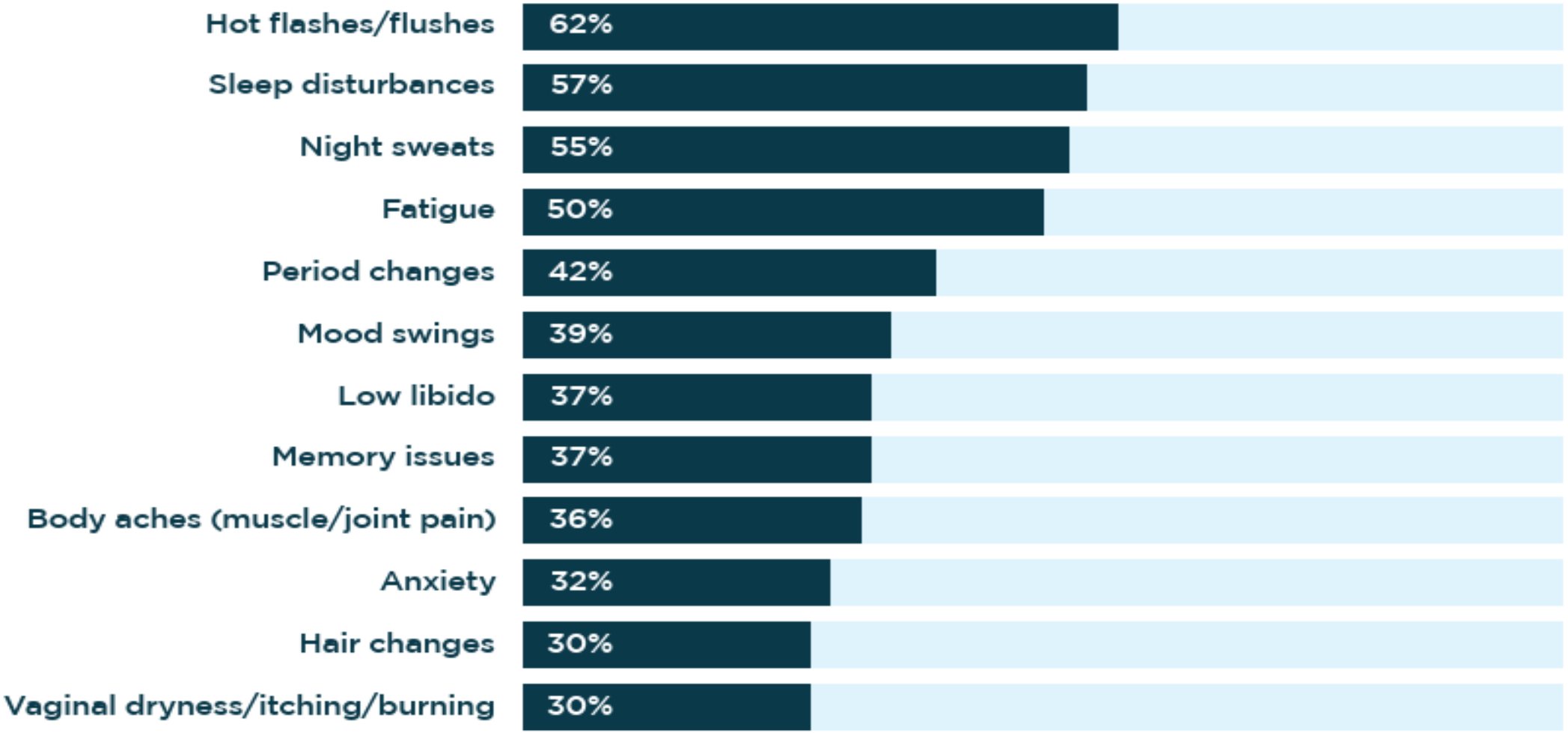
Age Group	Breast Cancer	Endometrial Cancer[a]	Ovarian Cancer
50–54 y	293.2	40.7	25.1
55–59 y	312.5	42.8	34.1
60–64 y	352.0	40.2	36.3
65–69 y	347.1	45.0	40.8
All	325.5	49.7	34.0

[a]Cancer of the corpus uteri or uterus, not otherwise specified.

doi:10.1371/journal.pmed.1001492.t003

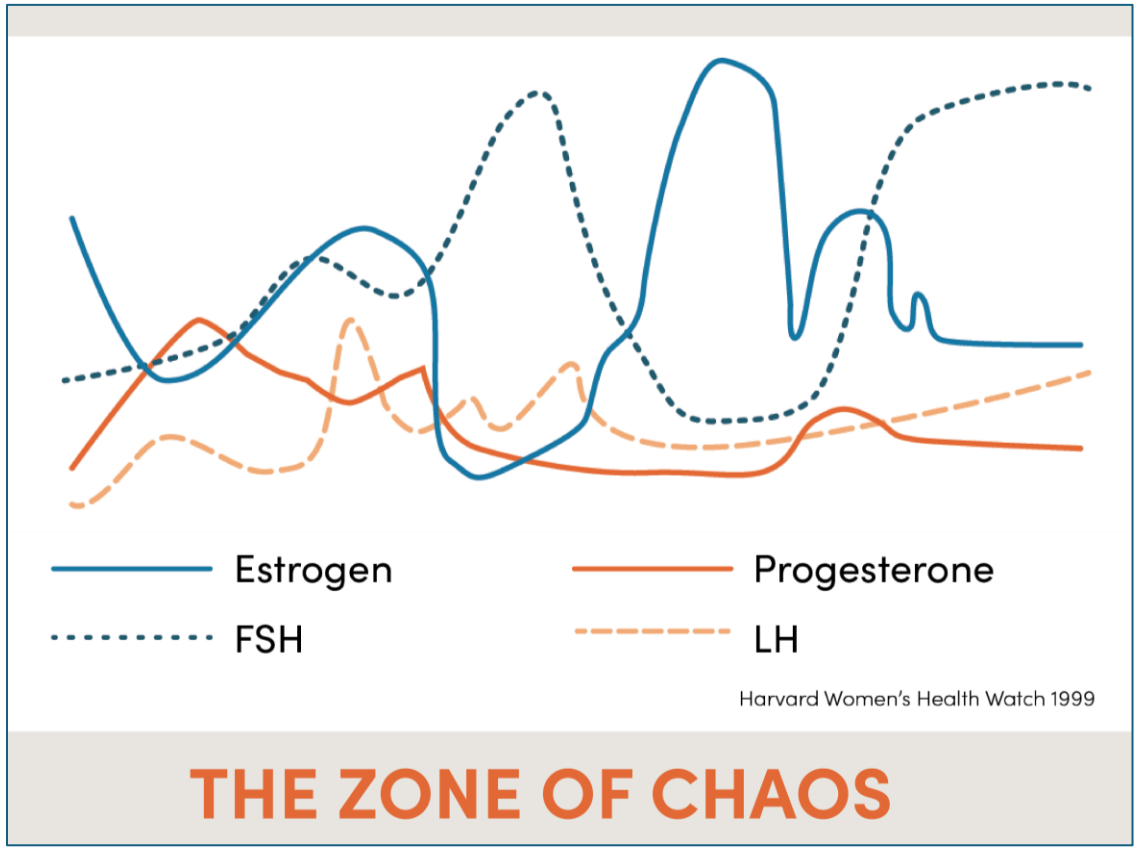
Experience of Symptoms

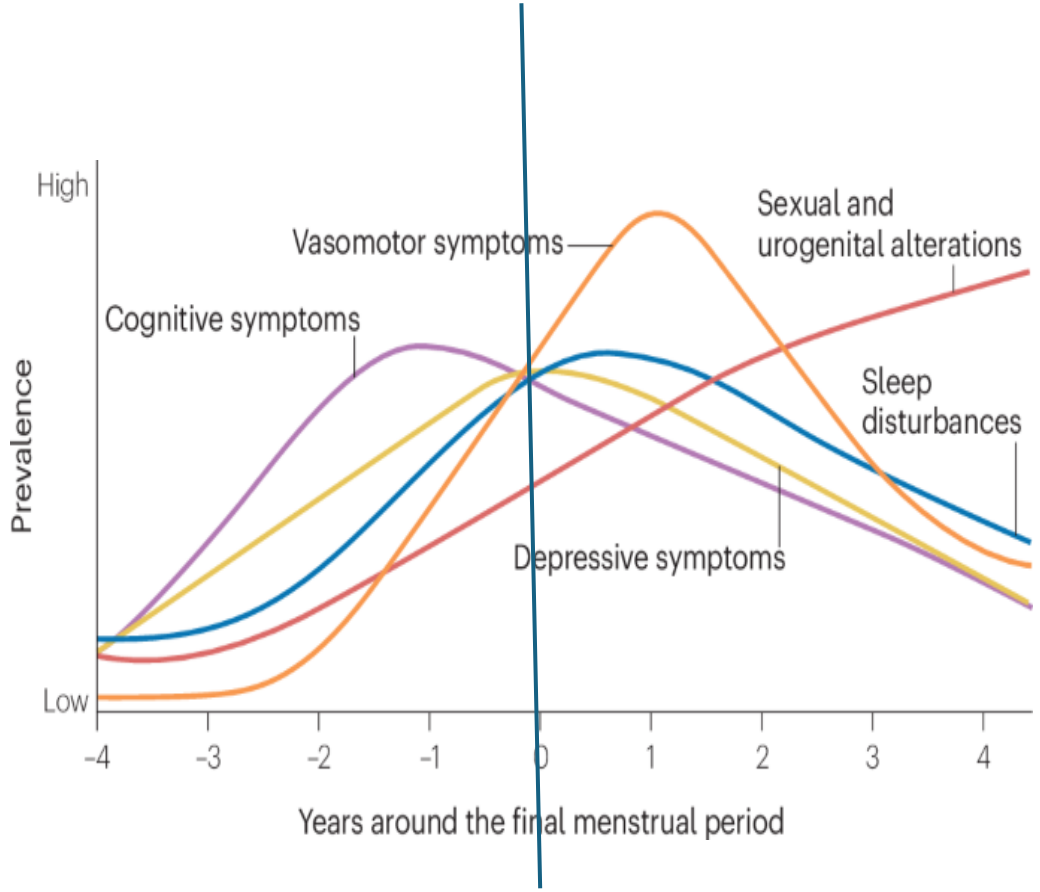
95% said they experienced menopausal symptoms with an average of seven symptoms reported.



https://menopausefoundationcanada.ca/wp-content/uploads/2022/10/MFC-Report_The-Silence-and-the-Stigma_Menopause-in-Canada_October-2022.pdf

When do symptoms occur?





Thurston, R.C., Thomas, H.N., Castle, A.J. *et al.* Menopause as a biological and psychological transition. *Nat Rev Psychol* **4**, 530–543 (2025). https://doi.org/10.1038/s44159-025-00463-9

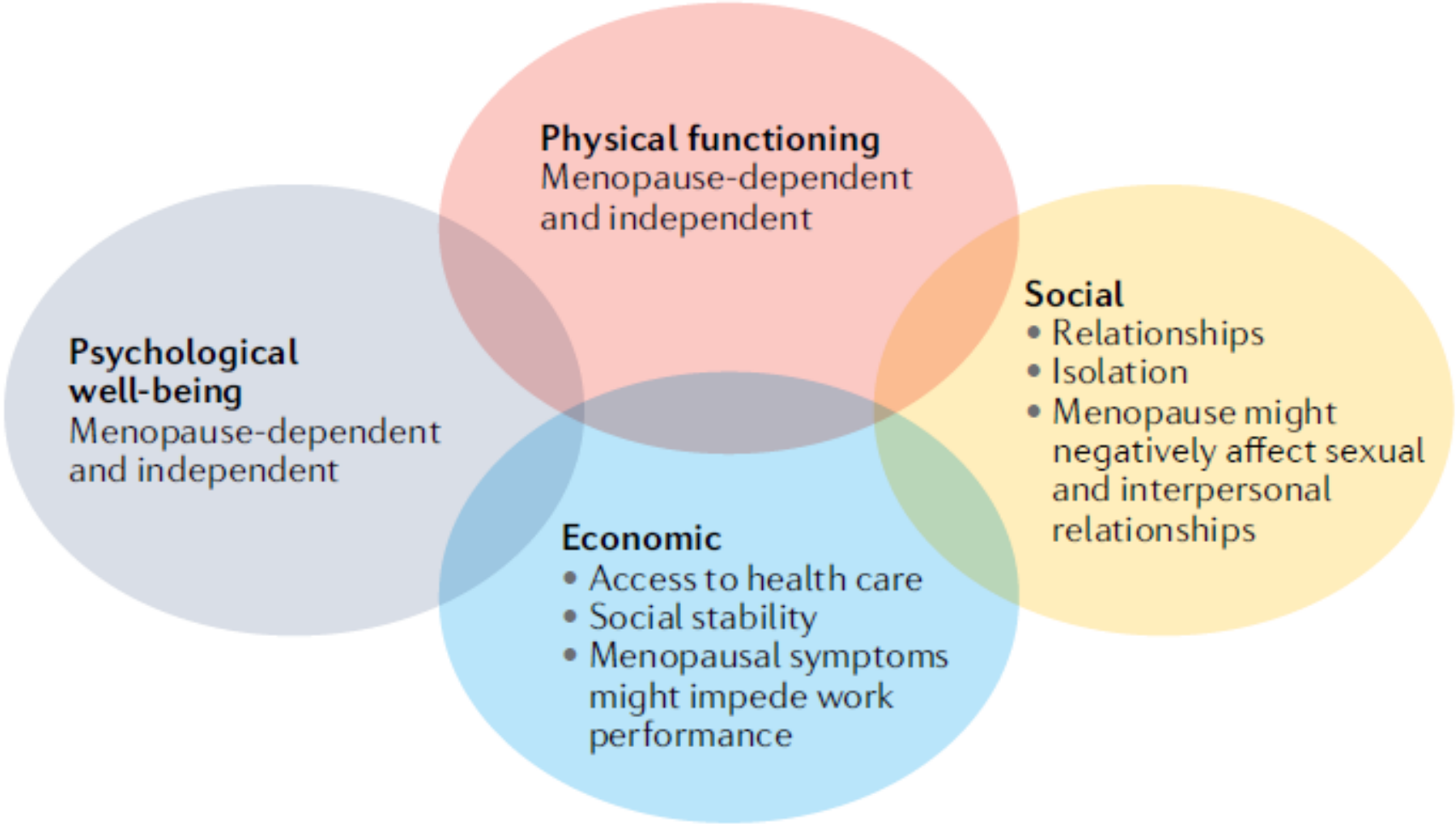
How does cancer treatment impact menopausal symptoms?

- Treatment often causes sudden declines in estrogen levels
- AI's further decrease estrogen to undetectable
- In conjunction with the stress of cancer treatments, symptoms are often more severe than general population

Treatment	How it may affect menopause	Usually temporary or permanent?
Chemotherapy	Can affect the ovaries, causing estrogen levels to decline and periods to become irregular or stop. Menopause symptoms may include hot flushes, night sweats, joint pain and vaginal dryness.	Temporarily or permanently
Tamoxifen	Does not cause menopause, but blocks the effects of oestrogen in some parts of the body. This can cause menopause-like symptoms such as hot flushes, night sweats and vaginal dryness	Symptoms are temporary and occur during treatment.
Aromatase inhibitors	Do not cause menopause, but lowers oestrogen levels and can cause menopause-related symptoms such as hot flushes, vaginal dryness, joint pain and changes to bone density.	Temporarily during treatment.
Ovarian suppression	Temporarily stops the ovaries from producing oestrogen, which can cause menopause symptoms such as hot flushes, night sweats, joint pain and vaginal dryness.	Temporarily during treatment.
Ovary removal	Causes immediate and permanent menopause because the ovaries are surgically removed.	Permanent.
Stopping HRT	Can cause menopause symptoms to return or worsen, particularly if HRT is stopped suddenly.	Symptoms may improve over time, but this varies.

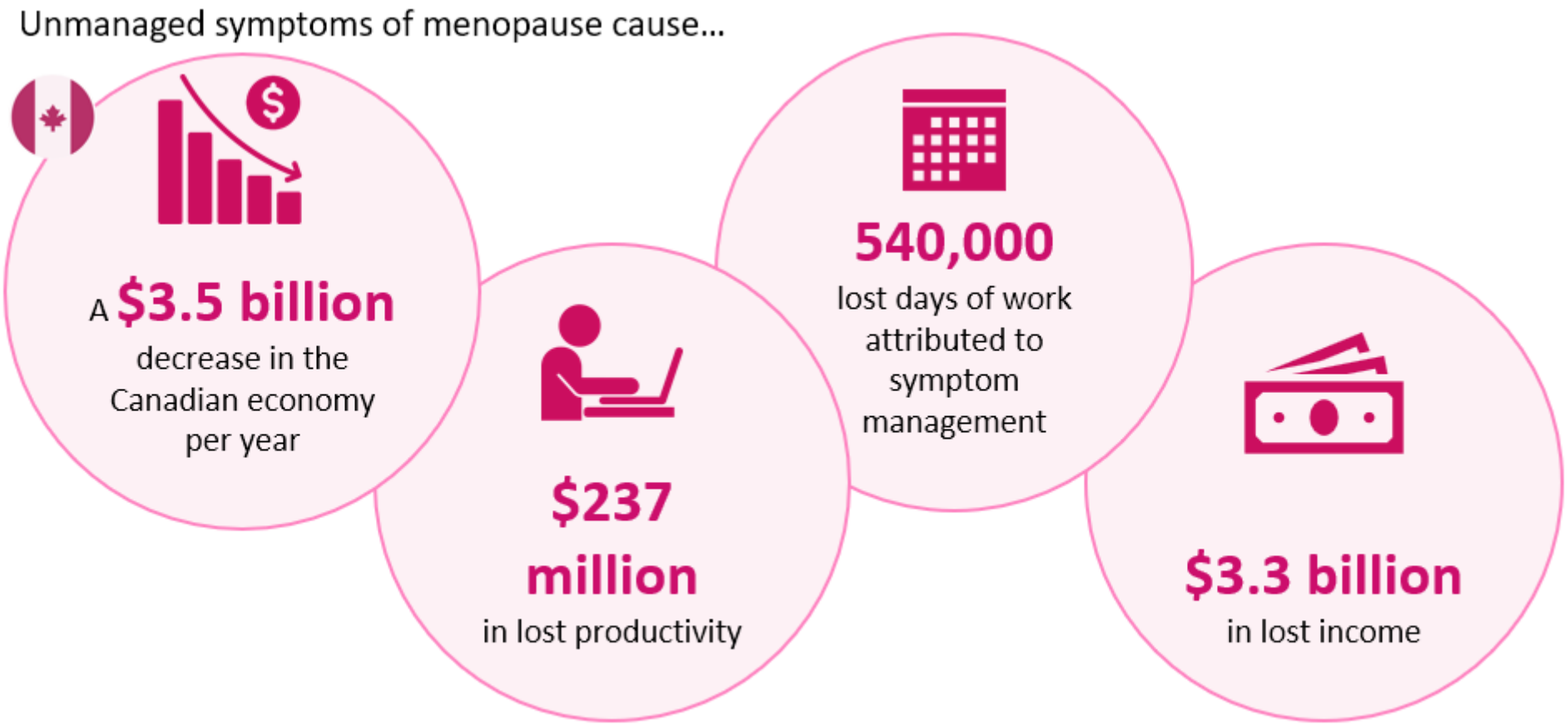
https://www.breastcancertrials.org.au/menopause-and-breast-cancer/?srsltid=AYCX9vL6MYxGYulPh3KIUfmNoDefdmMWIMx2vllpQ8u9ONEdn5jnUGJU

Symptoms are always multifactorial



Davis, S.R., Baber, R.J. Treating menopause — MHT and beyond. *Nat Rev Endocrinol* 18, 490–502 (2022). https://doi.org/10.1038/s41574-022-00685-4

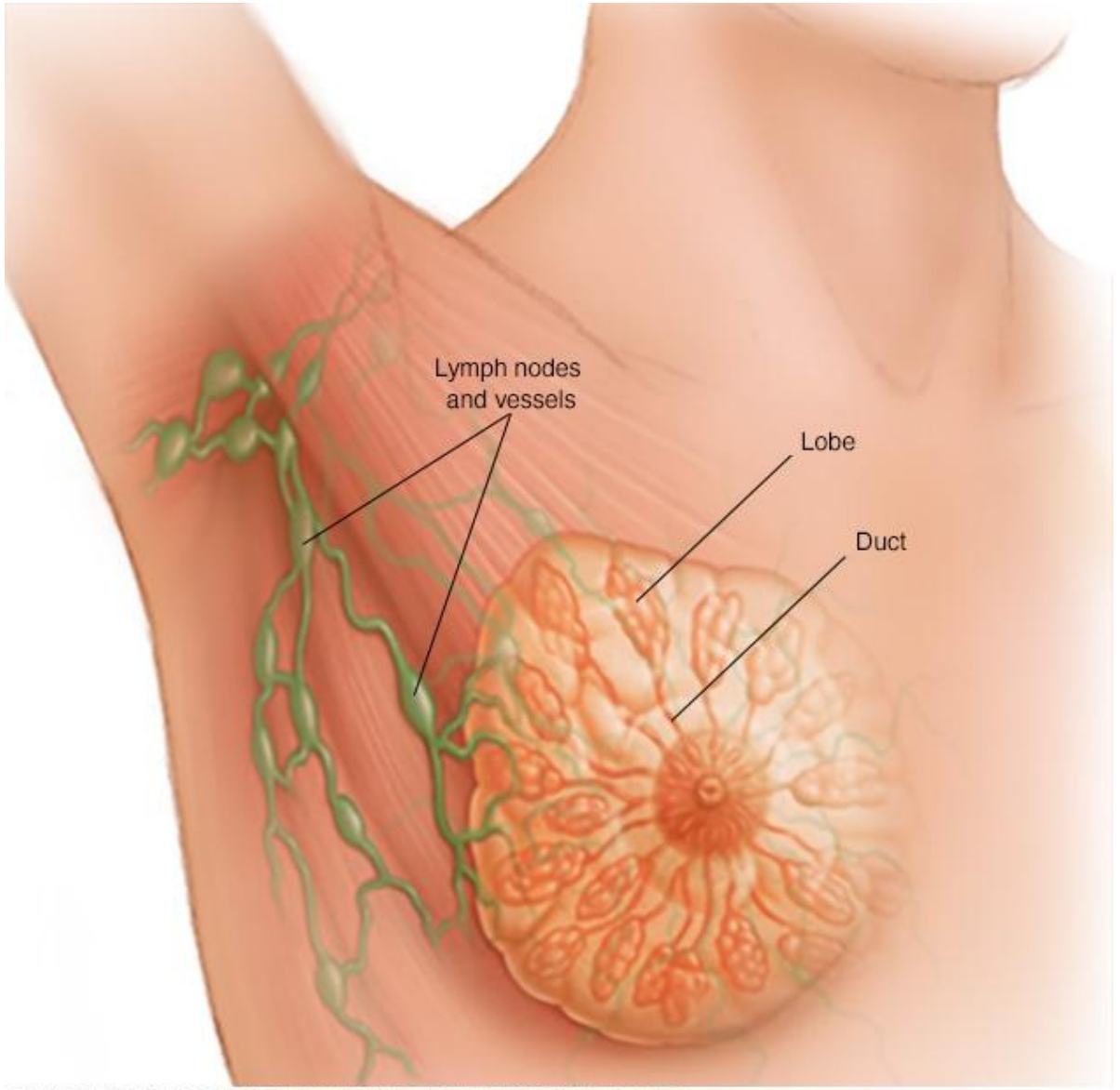
What are the costs of NOT treating menopausal symptoms?



VMS, vasomotor symptoms.

1. Menopause Foundation of Canada. Menopause and Work in Canada. 2023. Available at: https://menopausefoundationcanada.ca/pdf_files/Menopause_Work_Canada_2023EN.pdf Accessed Jan 2024.

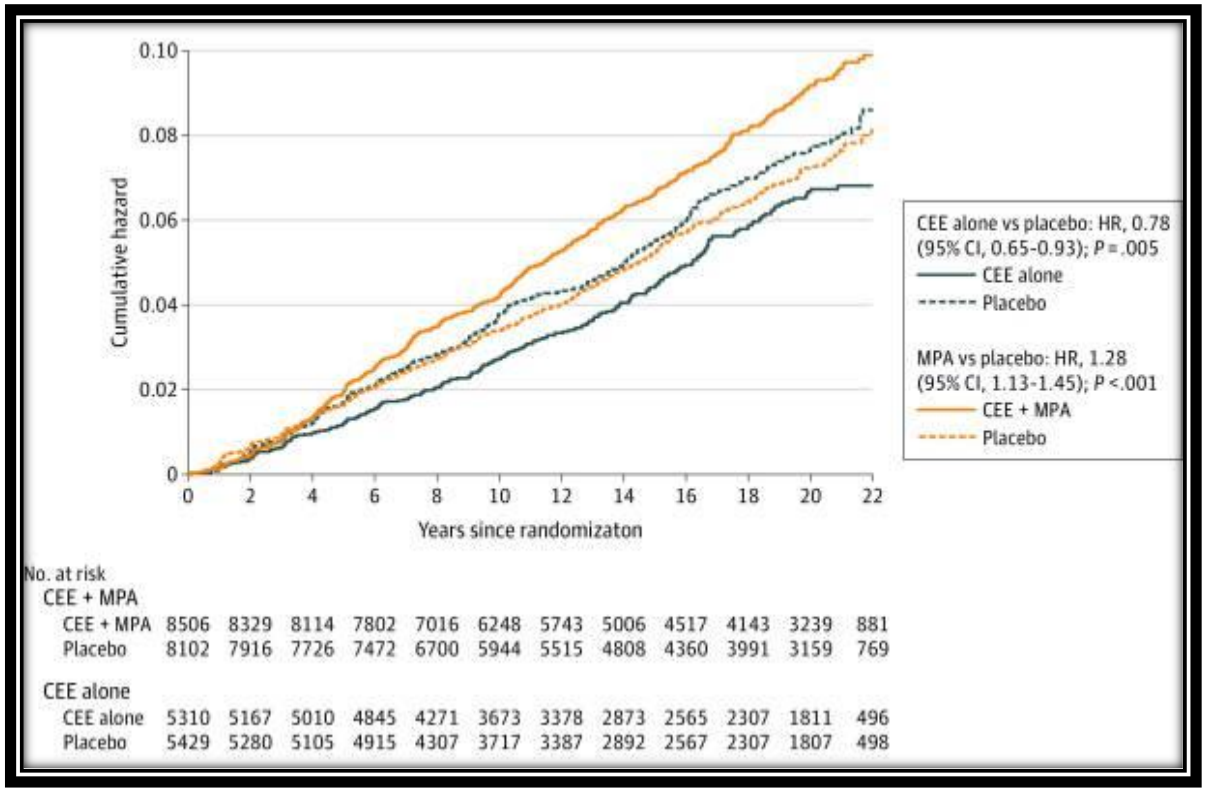
Breast Cancer



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Does Hormone therapy CAUSE breast cancer?

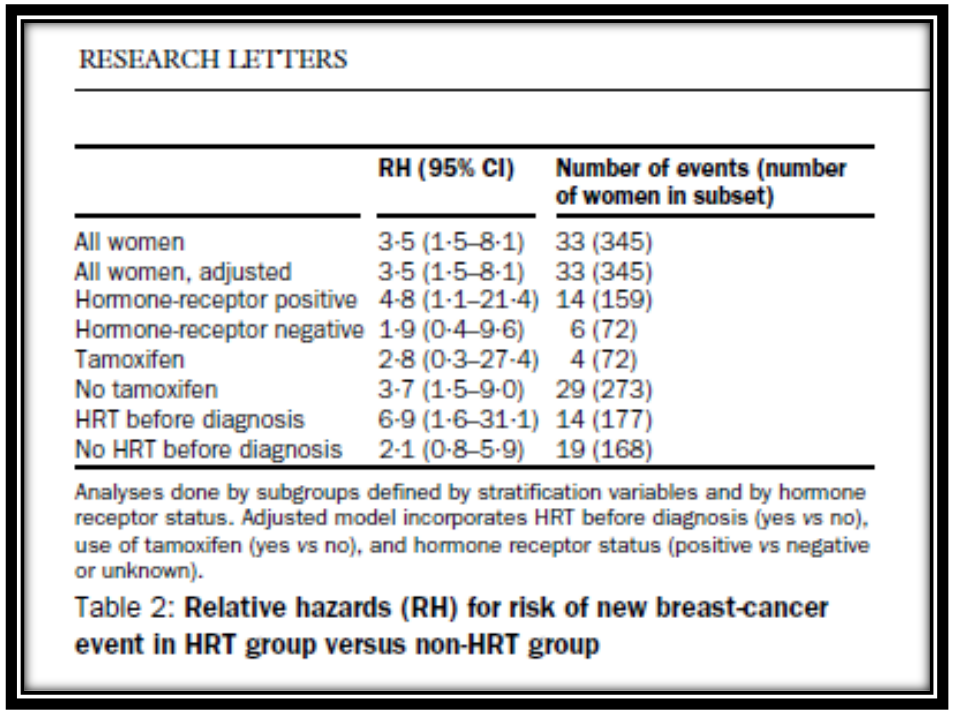
- Many known RF for breast cancer
- Standard E+P regimens increase breast density
- Higher dose E+P is associated with an increased risk over time
- Absolute risk increase with MHT remains low (~1/1000 extra cases after 5 years of use)
- Background risk assessment must be individualized
- No increased risk with CES alone and E2 probably no risk up to 10 years



Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, Barrington W, Kuller LH, Simon MS, Lane D, Johnson KC, Rohan TE, Gass MLS, Cauley JA, Paskett ED, Sattari M, Prentice RL. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 2020 Jul 28;324(4):369-380. doi: 10.1001/jama.2020.9482. PMID: 32721007; PMCID: PMC7388026.

Does MHT increase recurrence risk? HABITS

- Scandinavian RCT of 434 early-stage breast cancer survivors to either receive menopausal hormone therapy
- Prematurely stopped on December 17, 2003,
- Median follow-up of 2.1 years
- Interim analysis showed significantly more new breast cancer events in the MHT group (26 cases) compared to the non-hormone group (7 cases), yielding a relative HR of roughly 3.3
- Extended analysis (median 4 years) confirmed a higher cumulative incidence and a HR of 2.4 (95% CI: 1.3 to 4.2), showing a 5-year cumulative incidence of 22.2% for the hormone group versus 8.0% for the control group. [1]
- The specific type of HRT was directed by local practice



RESEARCH LETTERS

	RH (95% CI)	Number of events (number of women in subset)
All women	3·5 (1·5–8·1)	33 (345)
All women, adjusted	3·5 (1·5–8·1)	33 (345)
Hormone-receptor positive	4·8 (1·1–21·4)	14 (159)
Hormone-receptor negative	1·9 (0·4–9·6)	6 (72)
Tamoxifen	2·8 (0·3–27·4)	4 (72)
No tamoxifen	3·7 (1·5–9·0)	29 (273)
HRT before diagnosis	6·9 (1·6–31·1)	14 (177)
No HRT before diagnosis	2·1 (0·8–5·9)	19 (168)

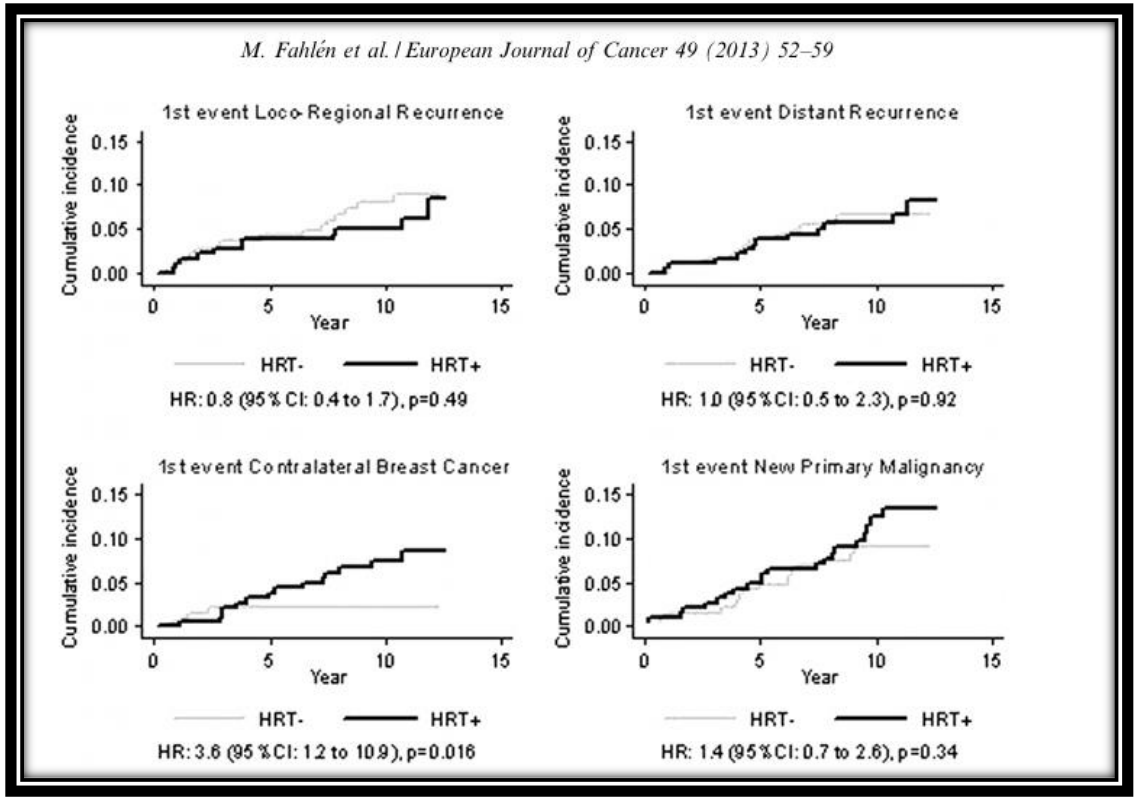
Analyses done by subgroups defined by stratification variables and by hormone receptor status. Adjusted model incorporates HRT before diagnosis (yes *vs* no), use of tamoxifen (yes *vs* no), and hormone receptor status (positive *vs* negative or unknown).

Table 2: **Relative hazards (RH) for risk of new breast-cancer event in HRT group versus non-HRT group**

Holmberg L, Anderson H; HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer--is it safe?), a randomised comparison: trial stopped. Lancet. 2004 Feb 7;363(9407):453-5. doi: 10.1016/S0140-6736(04)15493-7. PMID: 14962527.

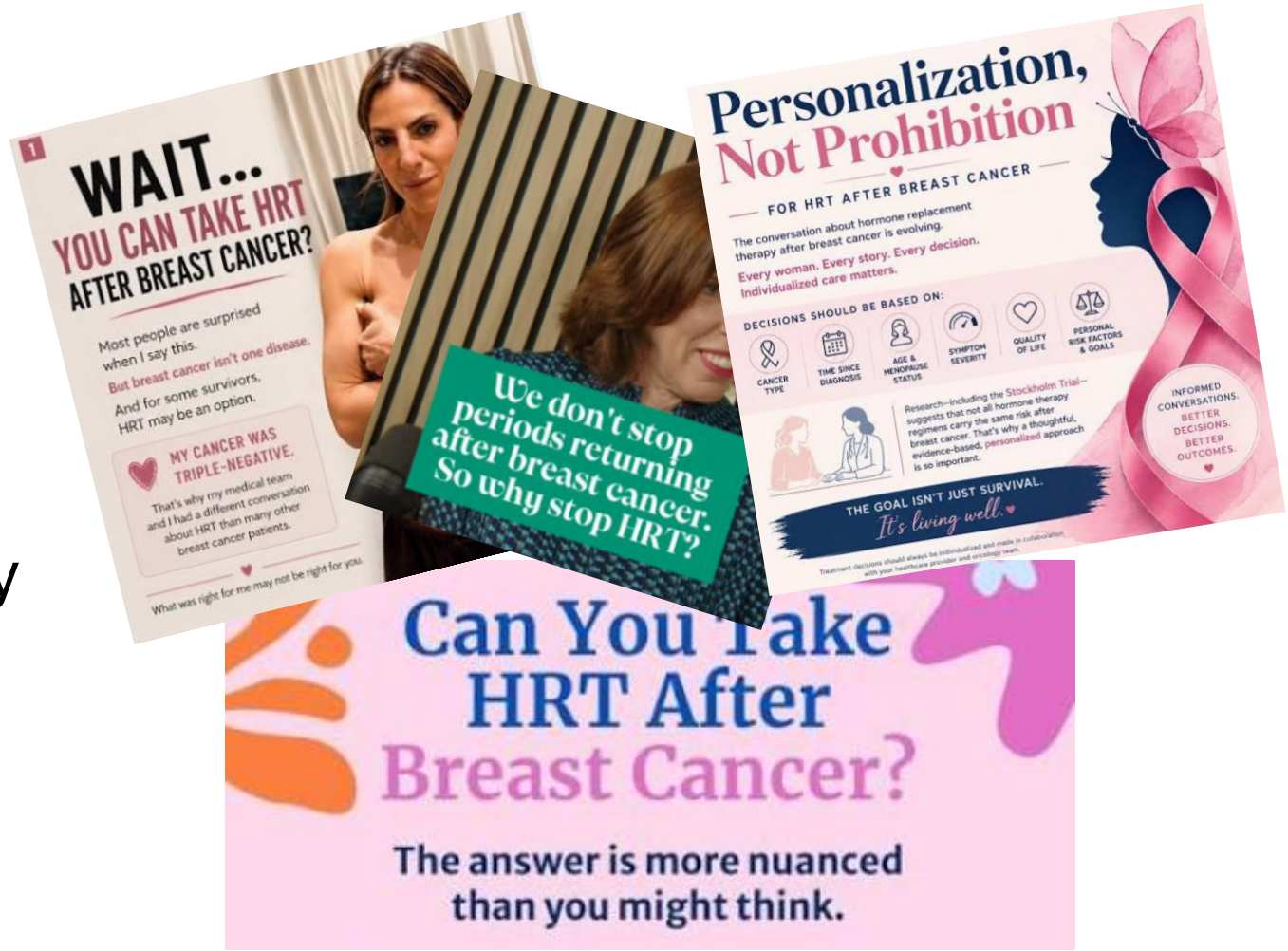
Uncertainty over the HABITS doctrine

- Stockholm: The number of new events did not differ significantly between groups
- The increased recurrence in HABITS has been attributed to higher progestogen exposure.
- As both trials were prematurely closed, data do not allow firm conclusions.
- Both studies found no increased mortality from breast cancer or other causes from HRT.
- Findings suggest that, in some women symptom relief may outweigh the potential risks of HRT…



This has led to a change in social narrative…

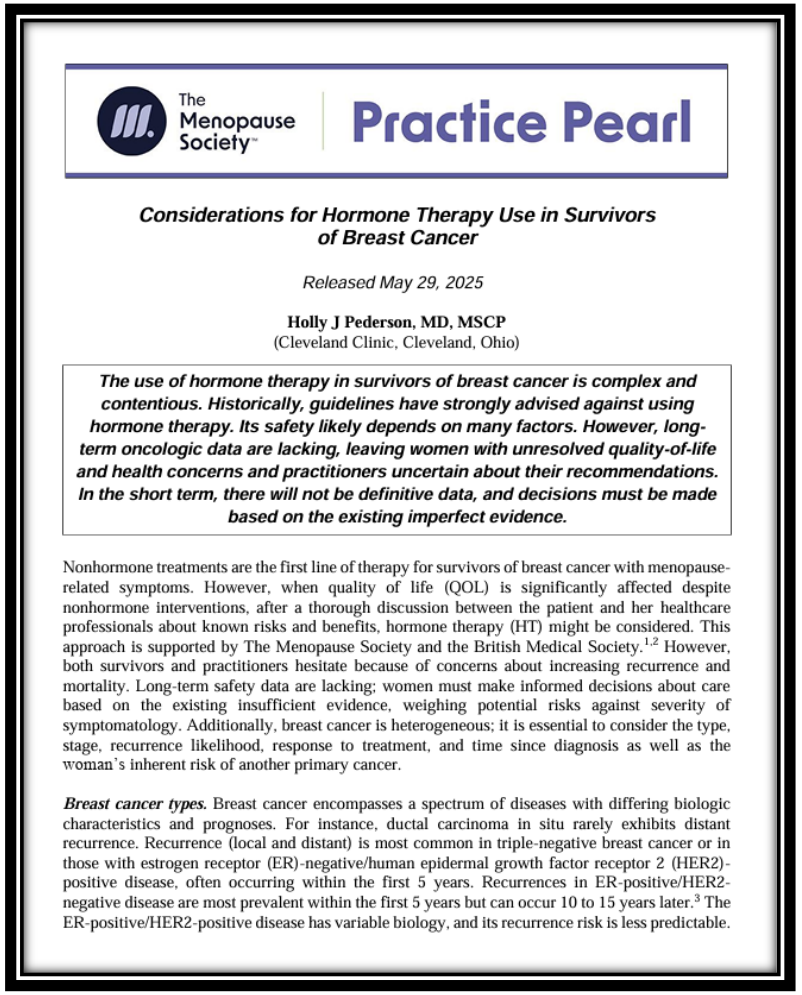
- Patients will not accept a flat “no” as an answer, as they are aware of the gaps in the data
- The best conversations address this nuance
- The most challenging are likely to be:
  - Triple Negative
  - Very young
  - Very symptomatic



This has also led to a change in guidance

The panel agreed that some women may choose to take MHT, (off-label use) and accept an increased risk of relapse in exchange for relief from menopausal symptoms and an improved quality of life, and that preferences may vary according to individual circumstances and the absolute risk of relapse. All respondents agreed or strongly agreed with statements supporting shared decision making and individualized menopause care

Glynne S, Simon J, Branson A, Payne S, Newson L, Manyonda I, Cleator S, Douek M, Usiskin S, Tobias JS, Vaidya JS. Menopausal hormone therapy for breast cancer patients: what is the current evidence? Menopause. 2026 Jan 1;33(1):88-117. doi: 10.1097/GME.0000000000002627. PMID: 41025376; PMCID: PMC12727074.



The Menopause Society™ | Practice Pearl

Considerations for Hormone Therapy Use in Survivors of Breast Cancer

Released May 29, 2025

Holly J Pederson, MD, MSCP
(Cleveland Clinic, Cleveland, Ohio)

The use of hormone therapy in survivors of breast cancer is complex and contentious. Historically, guidelines have strongly advised against using hormone therapy. Its safety likely depends on many factors. However, long-term oncologic data are lacking, leaving women with unresolved quality-of-life and health concerns and practitioners uncertain about their recommendations. In the short term, there will not be definitive data, and decisions must be made based on the existing imperfect evidence.

Nonhormone treatments are the first line of therapy for survivors of breast cancer with menopause-related symptoms. However, when quality of life (QOL) is significantly affected despite nonhormone interventions, after a thorough discussion between the patient and her healthcare professionals about known risks and benefits, hormone therapy (HT) might be considered. This approach is supported by The Menopause Society and the British Medical Society.[1,2] However, both survivors and practitioners hesitate because of concerns about increasing recurrence and mortality. Long-term safety data are lacking; women must make informed decisions about care based on the existing insufficient evidence, weighing potential risks against severity of symptomatology. Additionally, breast cancer is heterogeneous; it is essential to consider the type, stage, recurrence likelihood, response to treatment, and time since diagnosis as well as the woman's inherent risk of another primary cancer.

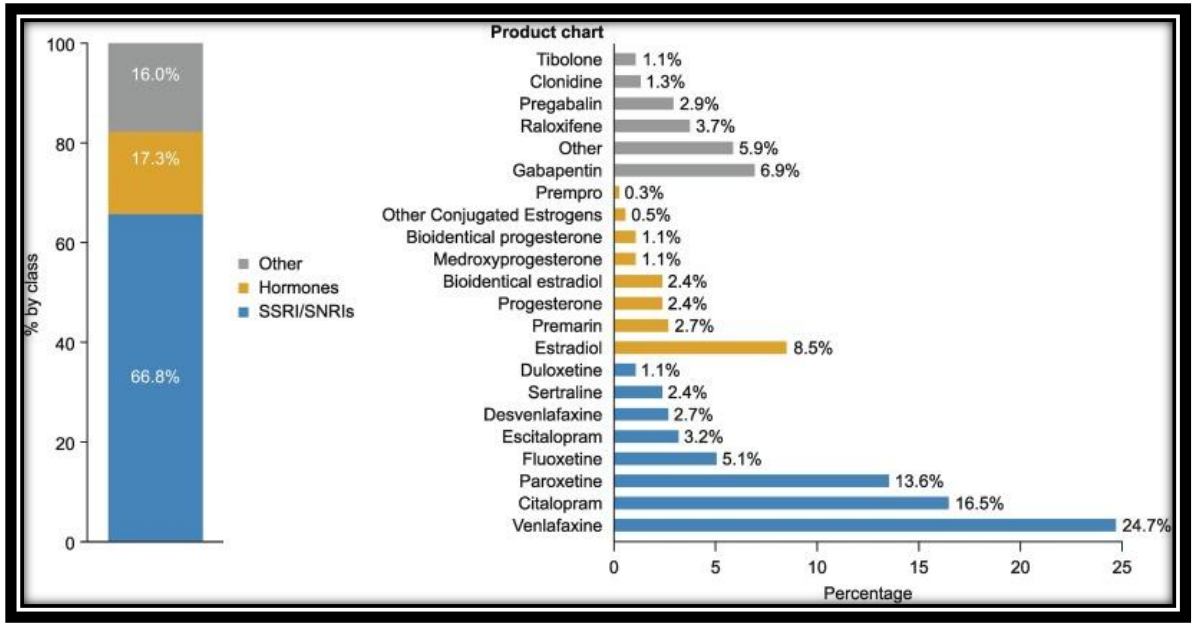
Breast cancer types. Breast cancer encompasses a spectrum of diseases with differing biologic characteristics and prognoses. For instance, ductal carcinoma in situ rarely exhibits distant recurrence. Recurrence (local and distant) is most common in triple-negative breast cancer or in those with estrogen receptor (ER)-negative/human epidermal growth factor receptor 2 (HER2)-positive disease, often occurring within the first 5 years. Recurrences in ER-positive/HER2-negative disease are most prevalent within the first 5 years but can occur 10 to 15 years later.[3] The ER-positive/HER2-positive disease has variable biology, and its recurrence risk is less predictable.

https://menopause.org/wp-content/uploads/default-document-library/Practice-Pearl-Hormone-Therapy-and-Breast-Cancer.pdf

What is happening in the REAL WORLD?

REALISE TRIAL (US and Europe)

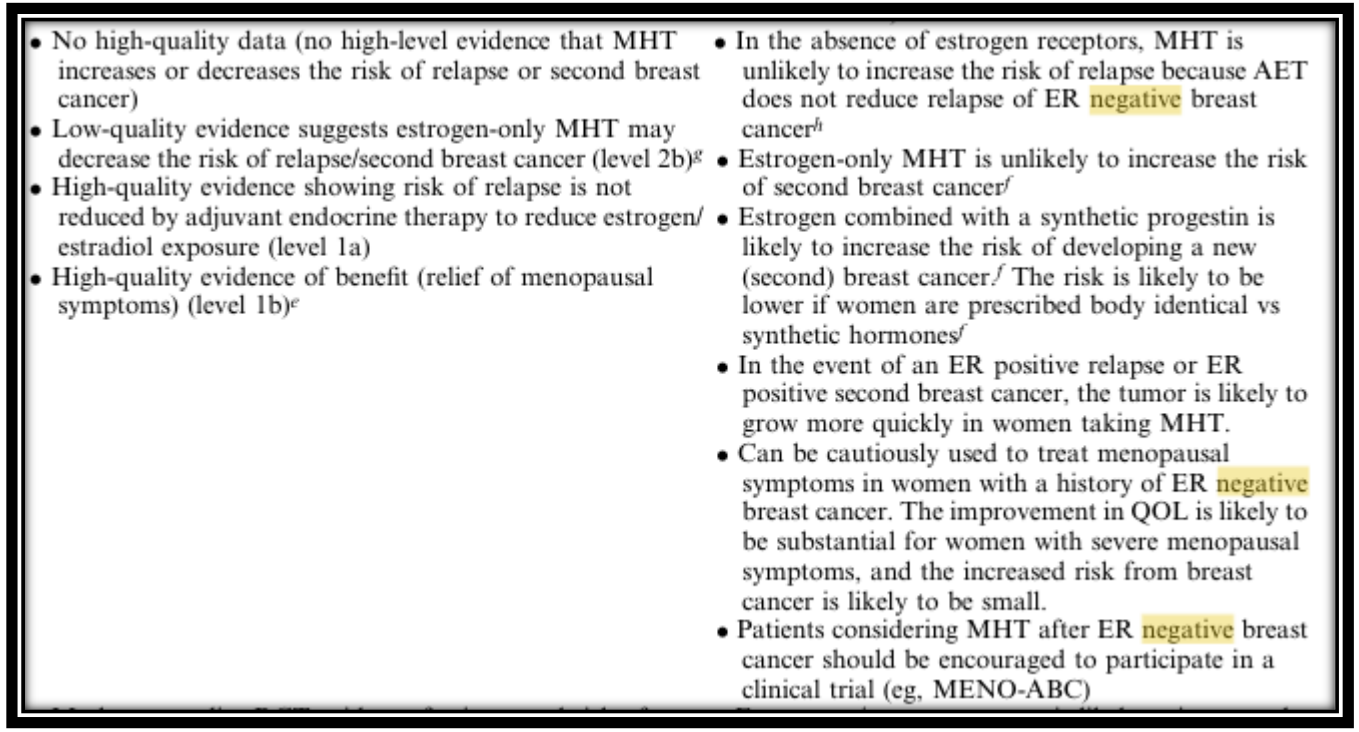
- Nearly 1/3 breast cancer survivors taking endocrine therapy who were experiencing vasomotor symptoms were receiving no treatment for them.
- Nearly 1/5 breast cancer survivors were currently prescribed hormone therapy.
- >50% of hormone therapies were non-vaginal (15.2% of all prescriptions)
- Over 3/4 patients used lifestyle changes (exercise, diet, relaxation) to manage their vasomotor symptoms.
- Over 60% used over-the-counter products (soy and black cohosh were the most popular)



Triple negative breast cancer

- Negative receptor status does not mean NO receptors
- TNBC cells can still interact with estrogens and progestogens via alternative mechanisms (such as ER-beta, GPER activation, and RANK/RANKL paracrine growth)
- Lower or more individualized risk of recurrence in ER-negative or TNBC cases compared to ER-positive breast cancer
- Treatment should be individualized

Systemic MHT after ER negative breast cancer



- No high-quality data (no high-level evidence that MHT increases or decreases the risk of relapse or second breast cancer)
- Low-quality evidence suggests estrogen-only MHT may decrease the risk of relapse/second breast cancer (level 2b)[g]
- High-quality evidence showing risk of relapse is not reduced by adjuvant endocrine therapy to reduce estrogen/estradiol exposure (level 1a)
- High-quality evidence of benefit (relief of menopausal symptoms) (level 1b)[e]
- In the absence of estrogen receptors, MHT is unlikely to increase the risk of relapse because AET does not reduce relapse of ER negative breast cancer[h]
- Estrogen-only MHT is unlikely to increase the risk of second breast cancer[f]
- Estrogen combined with a synthetic progestin is likely to increase the risk of developing a new (second) breast cancer.[f] The risk is likely to be lower if women are prescribed body identical vs synthetic hormones[f]
- In the event of an ER positive relapse or ER positive second breast cancer, the tumor is likely to grow more quickly in women taking MHT.
- Can be cautiously used to treat menopausal symptoms in women with a history of ER negative breast cancer. The improvement in QOL is likely to be substantial for women with severe menopausal symptoms, and the increased risk from breast cancer is likely to be small.
- Patients considering MHT after ER negative breast cancer should be encouraged to participate in a clinical trial (eg, MENO-ABC)

Glynne S, Simon J, Branson A, Payne S, Newson L, Manyonda I, Cleator S, Douek M, Usiskin S, Tobias JS, Vaidya JS. Menopausal hormone therapy for breast cancer patients: what is the current evidence? Menopause. 2026 Jan 1;33(1):88-117. doi: 10.1097/GME.0000000000002627. PMID: 41025376; PMCID: PMC12727074.

Registry or International Trial

- Given that many women are choosing to take the risk of using MHT, we should collect prospective data to inform future guidance
- Upcoming MENO-ABC trial will be an RCT
- Non-hormonal therapies remain first line



MENO-ABC trial

The MENO-ABC trial

MENopausal hormone therapy Outcomes After Breast Cancer

Many women after having been treated for breast cancer can suffer from menopausal symptoms, which can include vasomotor symptoms such as hot flushes (flashes), sleep disturbance, fatigue, mood swings, cognitive dysfunction ('brain fog'), muscle and joint aches and pains, skin dryness, loss of libido and genitourinary symptoms including vaginal dryness.

As it has been well established that for patients with ER positive breast cancer, reducing the exposure to oestrogen improves survival, use of menopausal hormone therapy (also known as HRT or MHT) which usually includes oestrogens and progestogens is expected to increase the chances of relapse of breast cancer. Therefore HRT is not considered advisable after diagnosis of breast cancer.

However, there is an increasing recognition that some women may like to have the opportunity to carefully consider the balance between the potential improvement in quality of life they can expect by taking HRT, and the higher risk of relapse and death from breast cancer. If robust quantification of these risks and benefits is available, it would greatly facilitate decisions about taking HRT after breast cancer. However, such data are not currently available, especially for the newer body-identical HRT drugs, for individual stages and types of breast cancer, and current treatments.

Therefore, further research is urgently needed to quantify the risks and benefits of oestrogen supplementation (especially with body-identical versions) for patients who have had breast cancer. The best way to quantify the risks and benefits would be in a randomised clinical trial. We propose the MENO-ABC (MENopausal hormone therapy Outcomes After Breast Cancer) Trial. We recommend that participation in this study is made mandatory for any patient with breast cancer who are considering taking MHT / HRT.

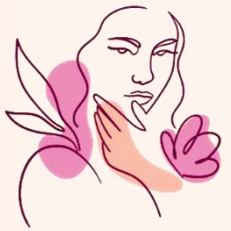
Our **full paper** "Menopausal Hormone therapy for breast cancer patients: what is the current evidence?" published on 30 September 2025 in the Menopause Journal explores the current evidence and gives the rationale for the MENO-ABC trial.

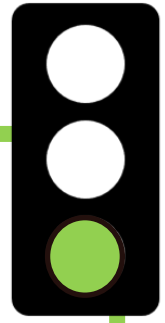
Covered by The Telegraph: https://www.telegraph.co.uk/health-fitness/conditions/cancer/doctors-changing-minds-breast-cancer-hrt/ **PDF: Why doctors are changing their mind about breast cancer and HRT**

UCL press release: Experts call for change of heart on hormone replacement therapy after breast cancer

https://www.londonbreastcancer.com/meno-abc-trial

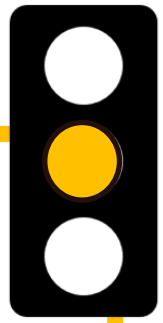
Menopausal hormone therapy recommendations by patient risk





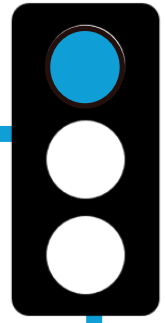
Low-risk MHT

- Recent menopause
- Normal weight
- Normal blood pressure
- Physically active
- 10-year ASCVD risk <5%
- Low risk for breast cancer



Intermediate-risk MHT

- Diabetes
- Smoking
- Hypertension
- Obesity
- Sedentary/limited mobility
- Autoimmune disease
- Hyperlipidemia
- Metabolic syndrome
- 10-yr ASCVD risk ≥5%–10%
- Increased risk for breast cancer



High-risk MHT*

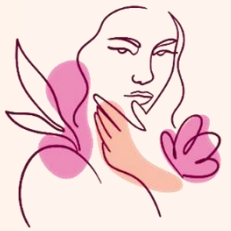
- Congenital heart disease
- ASCVD/CAD/PAD
- VTE or PE
- Stroke/TIA or MI
- History of breast cancer
- 10-year ASCVD risk ≥10%*

*Generally advised to avoid systemic MHT. Consider alternative therapy and if severe VSM persists, individualized, shared decision-making recommended. All women are candidates for low-dose vaginal estrogen therapy for GSM.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; GSM, genitourinary symptoms of menopause; MHT, menopause hormone therapy; MI myocardial infarction; PAD, peripheral arterial disease; PE, pulmonary embolism; TIA transient ischemic attack; VMS, vasomotor symptoms; VTE, venous thromboembolism.

Adapted from Cho L, et al. Circulation. 2023;147(7):597-610.

2023 NAMS Position Statement: Treatment recommendations for nonhormone therapies for VMS



Recommended (level of evidence)

Prescription
SSRI/SNRI (1)
Gabapentin (1)
Oxybutynin (1–2)
Fezolinetant* (1)

Mind–body techniques
Cognitive-behavioural therapy (1)
Hypnosis (1)

Recommended (lower evidence)

Lifestyle
Weight loss (2–3)

Other treatments/ technologies
Stellate ganglion block (2–3)

Not recommended (due to lack of evidence for effectiveness)

Lifestyle
Exercise/yoga (2)
Cooling techniques (2)
Dietary modifications (3)
Avoiding triggers (2)

Mind–body techniques
Paced respiration (1)
Relaxation (2)
Mindfulness-based stress reduction (2)

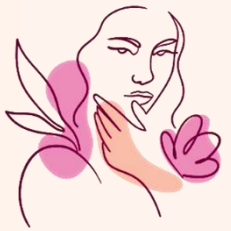
Prescription
Suvorexant (2)
Clonidine (1–3)
Pregabalin (3)

Dietary supplements
Soy foods and soy extracts (2)
Soy metabolites equol (2)
Cannabinoids (2)
Supplements/herbal remedies (1–3)

Other treatments/technologies
Acupuncture (2)
Calibration of neural oscillations (2)
Chiropractic intervention (2)

*** PrVEOZAH® (fezolinetant) Product Monograph. Astellas Pharma Canada Inc. Approved by Health Canada on Dec. 2, 2024.**
Note: SSRIs, SNRIs, and gabapentin are not approved by Health Canada for menopausal symptoms and are used off-label.
Levels of evidence: Level 1 – Good and consistent evidence; Level 2 – Limited or inconsistent scientific evidence; Level 3 – Consensus and expert opinion.
EMA, European Medicines Agency; FDA, Food and Drug Administration; NAMS, North American Menopause Society; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; VMS, vasomotor symptoms. Adapted from 1. NAMS 2023 Position Statement. Menopause. 2023;30,573-590.

2023 NAMS Position Statement: Key points on non-hormonal therapies



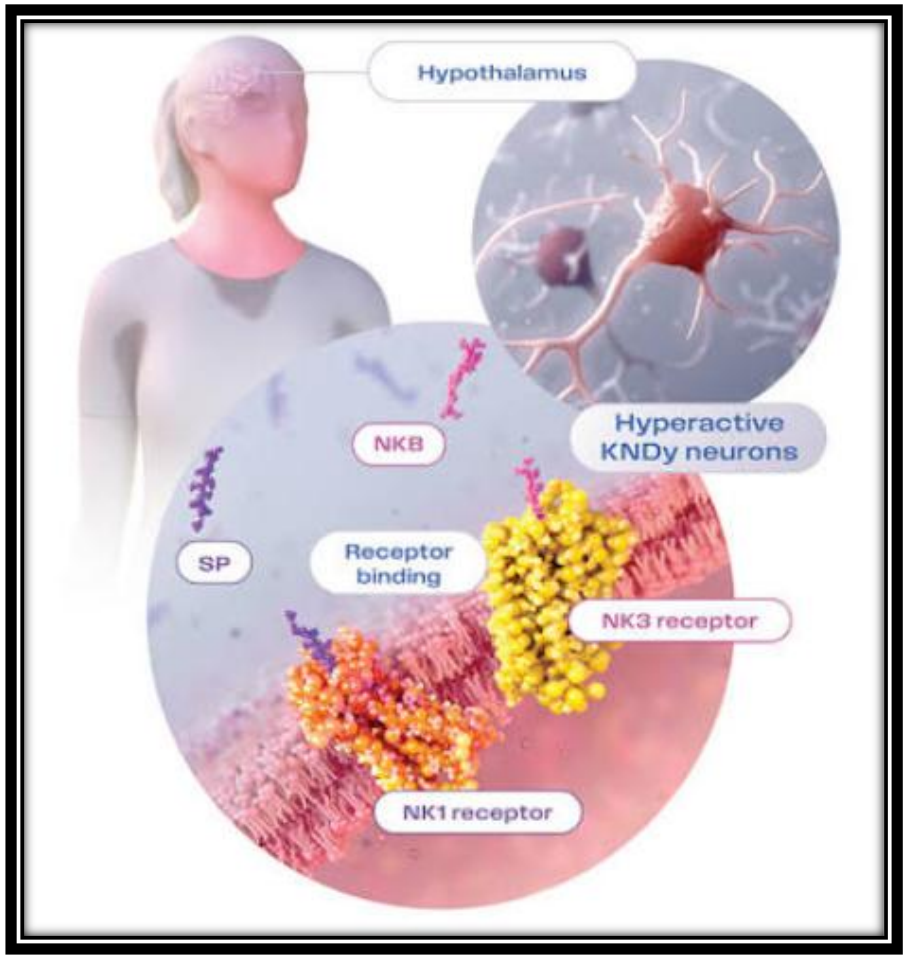
Drug	Commentary on why it is recommended
SSRIs and SNRIs	Mild-to-moderate improvements in VMS
Gabapentin	Improvements in frequency and severity of VMS
Oxybutynin	Reduces moderate-to-severe VMS In older adults, long-term use may be associated with cognitive decline
Fezolinetant*	First-in-class neurokinin B antagonist that is Health Canada-approved for management of VMS

Drug	Commentary on why it is not recommended
Pregabalin	Due to AEs**
Clonidine	Significant AEs** and no recent studies showing greater benefit than placebo
Suvorexant	Limited data

***PrVEOZAH® (fezolinetant) Product Monograph. Astellas Pharma Canada Inc. Approved by Health Canada on Dec. 2, 2024.**
****See speaker notes and individual product monographs for details on AEs.**
Note: SSRIs, SNRIs, gabapentin, oxybutynin, pregabalin, and suvorexant are not approved by Health Canada for menopausal symptoms and are used off-label.
Levels of evidence: Level 1 – Good and consistent evidence; Level 2 – Limited or inconsistent scientific evidence; Level 3 – Consensus and expert opinion.
AEs, adverse events; FDA, Food and Drug Administration; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; VMS, vasomotor symptoms.
Adapted from: 1. NAMS 2023 Position Statement. Menopause. 2023;30:573-590.

What are fezolinetant and elinzanetant?

- Oral pills that inhibit the action of NKB at the NK3 receptor (and NK1 for Eli)
- Both treatments were found to reduce the frequency of vasomotor symptoms by 50% or more
- Studies in breast cancer patients are complete for Eli and in progress for Fezo
- Daily pill with or without food
- Not covered by plan NP



On label treatment for VMS from endocrine therapy…

IMS 2025:
"Elinzanetant is a dual NK1 and NK3 receptor antagonist, shown to be effective in phase 3 clinical trials, with multiple key government approvals for VMS and shown to be effective for endocrine therapy-associated VMS in women with breast cancer." ⊕⊕⊕⊕ A

Panay, N., Fenton, A., Hamoda, H., Hillard, T., Islam, R., … Pedder, H. (2025). International Menopause Society (IMS) recommendations and key messages on women's midlife health and menopause. *Climacteric*, *28*(6), 634–656. https://doi.org/10.1080/13697137.2025.2585487

The NEW ENGLAND JOURNAL of MEDICINE

Elinzanetant for Vasomotor Symptoms from Endocrine Therapy

A Research Summary based on Cardoso F et al. | 10.1056/NEJMoa2415566 | Published on June 2, 2025

WHY WAS THE TRIAL DONE?

For women with hormone receptor (HR)–positive breast cancer, guidelines recommend endocrine therapy for at least 5 years, which has been shown to substantially reduce disease recurrence and mortality. Vasomotor symptoms (also known as hot flashes) are common adverse reactions to endocrine therapy that can negatively affect quality of life and lead to nonadherence. In previous trials, elinzanetant — a neurokinin-targeted therapy — was shown to be effective in treating vasomotor symptoms associated with menopause.

HOW WAS THE TRIAL CONDUCTED?

Women who were receiving endocrine therapy to treat or prevent HR-positive breast cancer and had moderate-to-severe vasomotor symptoms were randomly assigned to receive either 120 mg of elinzanetant once daily for 52 weeks or placebo once daily for 12 weeks followed by 120 mg of elinzanetant once daily for 40 weeks. The primary end points were the change in the mean daily frequency of moderate-to-severe vasomotor symptoms at week 4 and week 12.

TRIAL DESIGN

- Phase 3
- Randomized
- Double-blind
- Placebo-controlled
- Location: 90 sites in Europe, Canada, Israel, and Kazakhstan

RESULTS

At weeks 4 and 12, treatment with elinzanetant resulted in greater decreases in the daily frequency of vasomotor symptoms than placebo. The frequency of adverse events was similar in the two groups, and most events were mild or moderate in severity.

LIMITATIONS AND REMAINING QUESTIONS

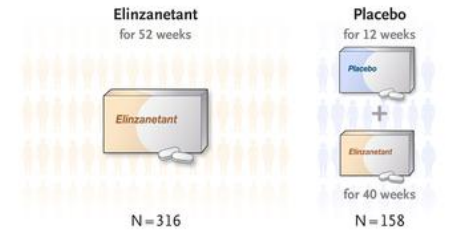
- Most of the participants were White.
- Because only one participant received elizanetant for prevention of breast cancer, conclusions regarding its efficacy in this population cannot be drawn.
- Survival and recurrence of breast cancer were not prespecified outcomes in this trial.

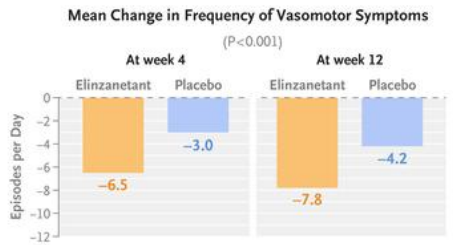
CONCLUSIONS

Among women who were receiving endocrine therapy for HR-positive breast cancer, elinzanetant significantly reduced the frequency of moderate-to-severe vasomotor symptoms.

NEJM QUICK TAKE | EDITORIAL





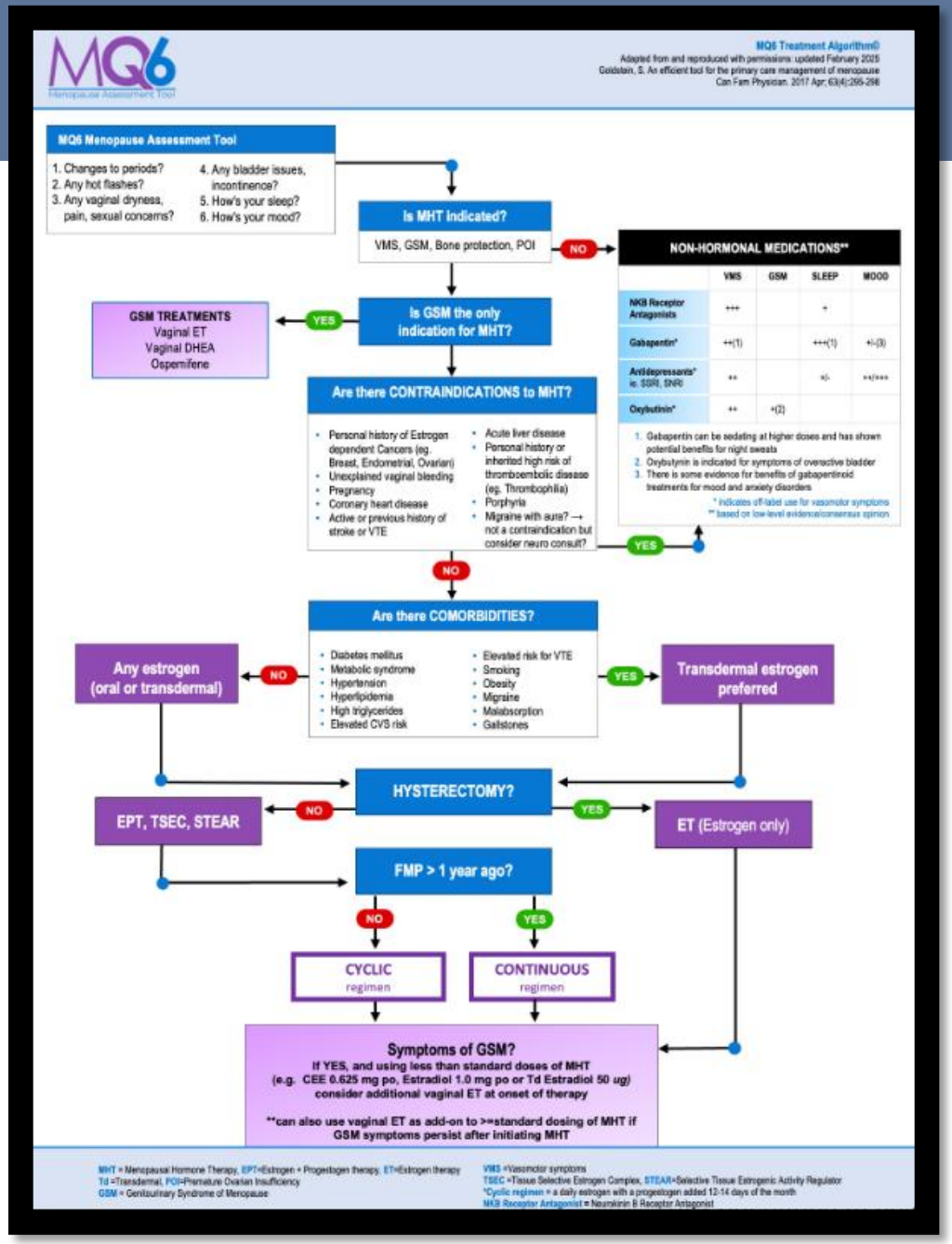




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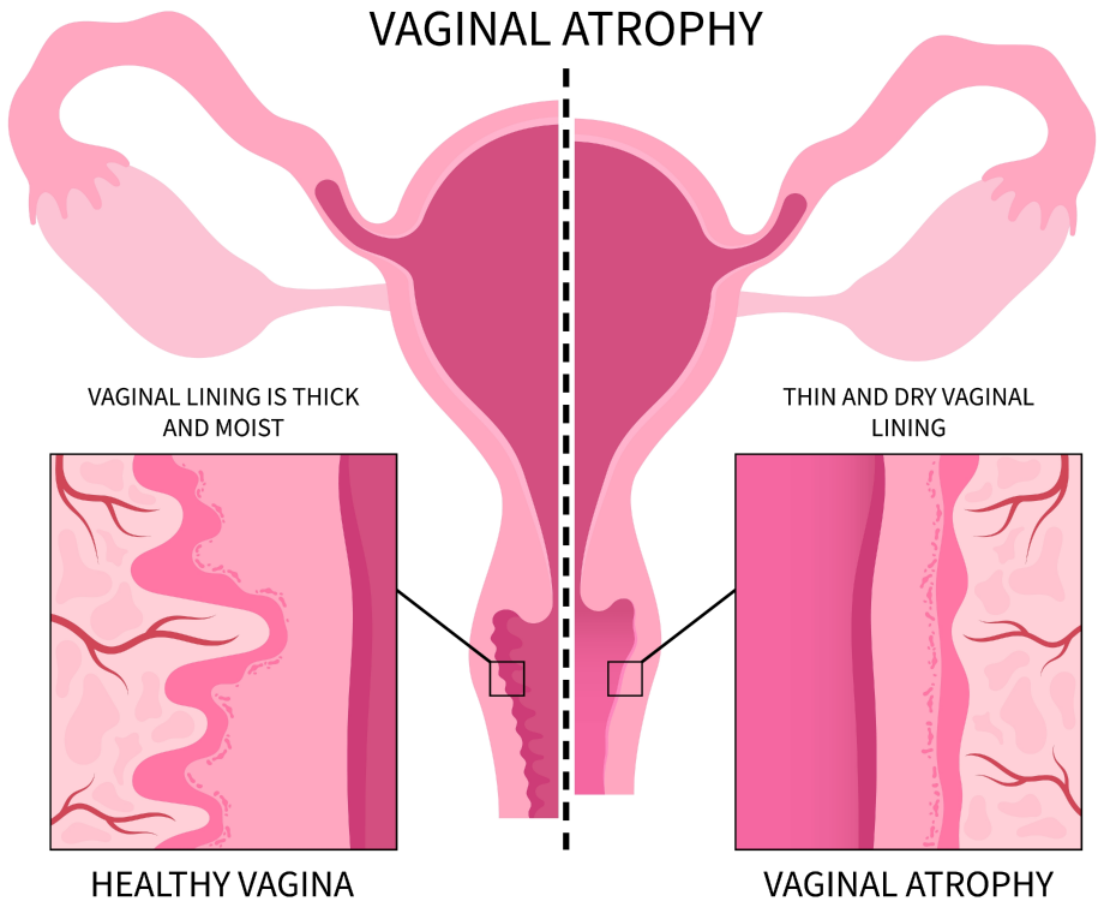
Treatment algorithm:

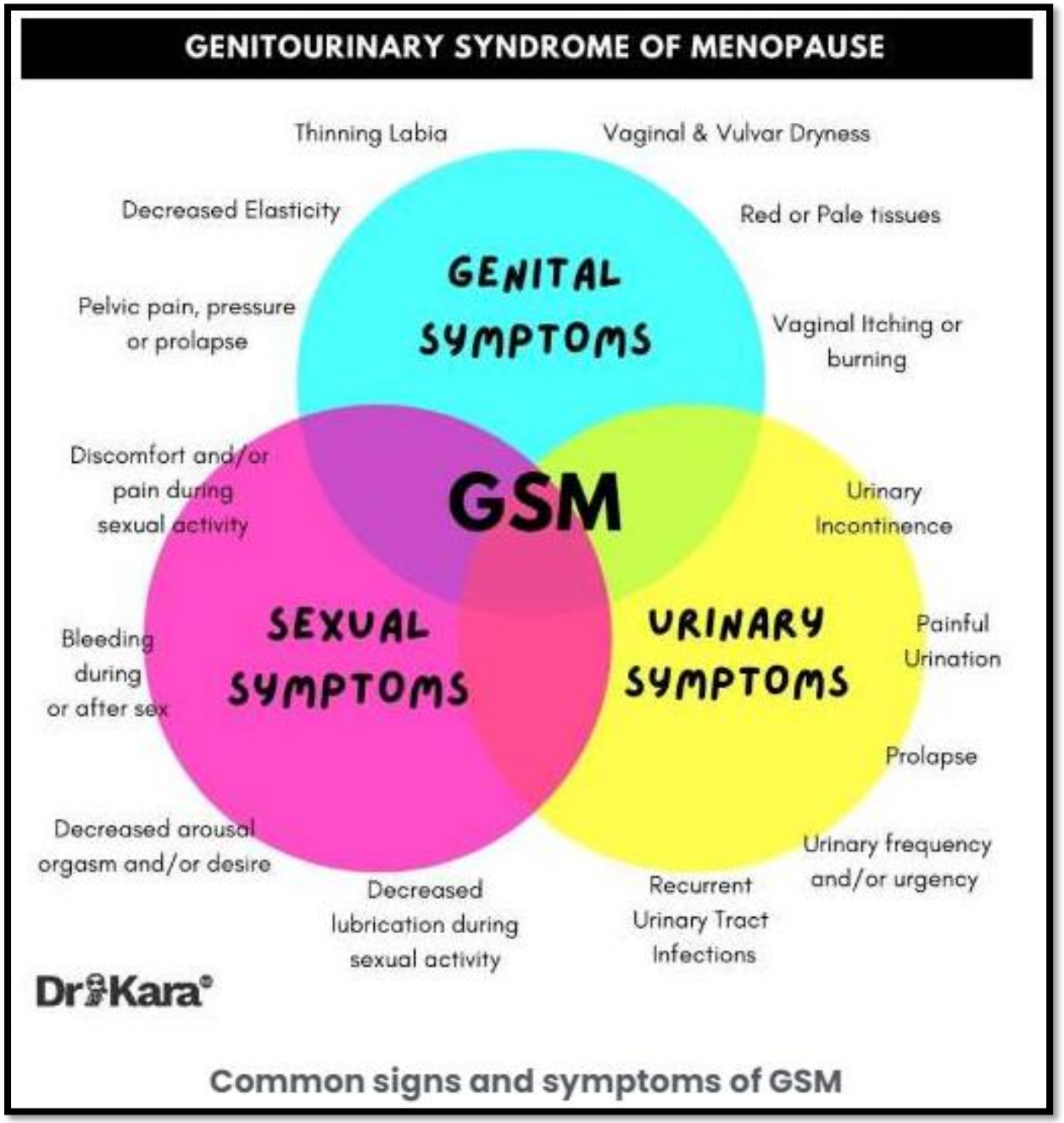
MQ6.ca



Managing GSM

In patients with or without breast cancer





What is GSM?

- Genitourinary syndrome of menopause (GSM) describes symptoms and signs resulting from the effects of estrogen deficiency on the female genitourinary tract
- GSM tends to worsen over time and is unlikely to improve without treatment
- Affects over 80% of women
- Worsened by AI and any estrogen restriction

Many Symptoms Associated With GSM

Genital Symptoms



- Vaginal dryness
- Irritation, burning, itching
- Vaginal discharge
- Vaginal/pelvic pain
- Bulging/pressure (from prolapse)

Sexual Symptoms



- Dyspareunia
- Reduced lubrication
- Post-coital bleeding
- Decreased arousal
- Loss of libido
- Dysorgasmia

Urinary Symptoms



- Dysuria / recurrent urinary tract infection
- Urinary frequency and urgency
- Urinary incontinence
- Bleeding with wiping (urethral prolapse)

Women may present with some or all signs and symptoms
Symptoms may be intermittent but are **usually progressive**
Women who are not having penetrative sex may also have symptoms

Portman DJ, Gass ML. *Menopause*. 2014;21(10):1063-1068; The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause*. 2020;27(9):976-992; Angelou K, et al. *Cureus*. 2020 Apr 8;12(4):e7586; Johnston S, et al. *J Obstet Gynaecol Can*. 2021;43(11):1301-1307.e1.

GSM Treatment Modalities – Non-Pharmacologic and Non-Hormonal Options



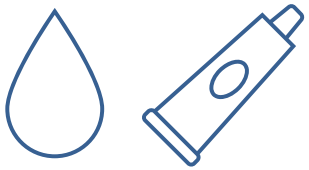
Lifestyle modifications:

- Smoking cessation
- Caffeine reduction
- Weight reduction
- Identifying irritants (soaps, detergents, chlorine, spermicides from condoms)



Activity modifications:

- Regular sexual activity (coitus, masturbation)
- Self-stimulators
- Dilators
- Pelvic floor muscle physiotherapy



Over-the-counter options:

- Lubricants
  - Used as needed by both partners upon sexual activity to reduce friction
  - Water-based (KY gel) or silicone-based (Pink), products are preferred; oil-based (olive oil, coconut oil)
- Moisturizers
  - Used regularly (2–3x/week) irrespective of sexual activity to reduce daily symptoms of GSM and facilitate comfortable sexual activity
  - Moisturizers (Replens, RepaGyn) mimic normal vaginal secretions and can reduce vaginal pH

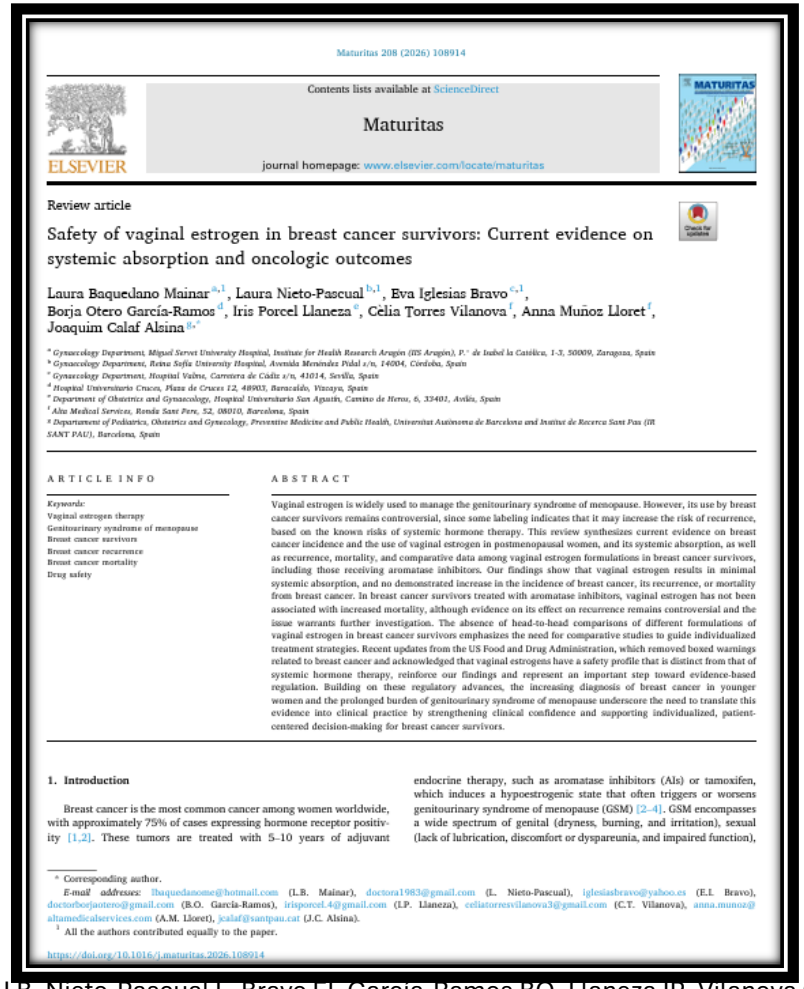


Topical lidocaine:

- Can be helpful before vaginal intercourse
  - Male partner should wear a condom to prevent numbing of the penis

The NAMS 2020 GSM Position Statement Editorial Panel. *Menopause*. 2020;27(9):976-992; Johnston S, et al. *J Obstet Gynaecol Can*. 2021;43(11):1301-1307.e1; Lim J, et al. The Genitourinary Syndrome of Menopause. Gynaecology Quality Improvement Collaboration: v03.08.2023 https://gynqi.com/wp-content/uploads/2023/04/M3-Genitourinary-Syndrome-Menopause-v03.08.2023.pdf

For patients with marked symptoms and with recurrent UTI, vaginal estrogen remains an option…



Maturitas 208 (2026) 108914

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Safety of vaginal estrogen in breast cancer survivors: Current evidence on systemic absorption and oncologic outcomes

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ARTICLE INFO

Keywords:
Vaginal estrogen therapy
Genitourinary syndrome of menopause
Breast cancer survivors
Breast cancer recurrence
Breast cancer mortality
Drug safety

ABSTRACT

Vaginal estrogen is widely used to manage the genitourinary syndrome of menopause. However, its use by breast cancer survivors remains controversial, since some labeling indicates that it may increase the risk of recurrence, based on the known risks of systemic hormone therapy. This review synthesizes current evidence on breast cancer incidence and the use of vaginal estrogen in postmenopausal women, and its systemic absorption, as well as recurrence, mortality, and comparative data among vaginal estrogen formulations in breast cancer survivors, including those receiving aromatase inhibitors. Our findings show that vaginal estrogen results in minimal systemic absorption, and no demonstrated increase in the incidence of breast cancer, its recurrence, or mortality from breast cancer. In breast cancer survivors treated with aromatase inhibitors, vaginal estrogen has not been associated with increased mortality, although evidence on its effect on recurrence remains controversial and the issue warrants further investigation. The absence of head-to-head comparisons of different formulations of vaginal estrogen in breast cancer survivors emphasizes the need for comparative studies to guide individualized treatment strategies. Recent updates from the US Food and Drug Administration, which removed boxed warnings related to breast cancer and acknowledged that vaginal estrogens have a safety profile that is distinct from that of systemic hormone therapy, reinforce our findings and represent an important step toward evidence-based regulation. Building on these regulatory advances, the increasing diagnosis of breast cancer in younger women and the prolonged burden of genitourinary syndrome of menopause underscore the need to translate this evidence into clinical practice by strengthening clinical confidence and supporting individualized, patient-centered decision-making for breast cancer survivors.

1. Introduction

Breast cancer is the most common cancer among women worldwide, with approximately 75% of cases expressing hormone receptor positivity [1,2]. These tumors are treated with 5–10 years of adjuvant endocrine therapy, such as aromatase inhibitors (AIs) or tamoxifen, which induces a hypoestrogenic state that often triggers or worsens genitourinary syndrome of menopause (GSM) [2–4]. GSM encompasses a wide spectrum of genital (dryness, burning, and irritation), sexual (lack of lubrication, discomfort or dyspareunia, and impaired function),

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[1] All the authors contributed equally to the paper.

https://doi.org/10.1016/j.maturitas.2026.108914

Mainar LB, Nieto-Pascual L, Bravo EI, García-Ramos BO, Llaneza IP, Vilanova CT, Lloret AM, Alsina JC. Safety of vaginal estrogen in breast cancer survivors: Current evidence on systemic absorption and oncologic outcomes. Maturitas. 2026 May;208:108914. doi: 10.1016/j.maturitas.2026.108914. Epub 2026 Mar 12. PMID: 41864136.



Urology 215 (2026) 43–48

Contents lists available at ScienceDirect

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Female Urology, Urodynamics, Incontinence and Pelvic Floor

Vaginal Estrogen Prescription is Associated with Reduced Risk of Serious Adverse Outcomes in Women of All Age Groups with Recurrent Urinary Tract Infection: An Epic Cosmos Database Analysis

Justin LaClair[a,b,*], Joseph Visingardi[c], Brennan Wells[d], Paul Feustel[a,e], Joseph Deckert[f], Elise J.B. De[b]

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[f] Epic Systems, Verona, WI

ABSTRACT

Objective: To explore rates of serious adverse outcomes (sepsis, hospital admission, and death) in women with rUTI who were prescribed vs not prescribed vaginal estrogen.
Methods: We used the Epic Cosmos database to identify women with rUTI, which we defined as 2 separate coded UTIs within 1-6 months. Vaginal estrogen prescription classification was either (1) never received or (2) received within 2 months of the second UTI. Outcomes were assessed within 8 years of inclusion (second UTI with or without a documented prescription) and included sepsis, hospital admission, and all-cause mortality. Age-stratified odds ratios (OR) with 95% confidence intervals (CI) were calculated.
Results: Of 1,891,956 females with rUTI, 97,109 (5.1%) received a prescription within 2 months and 1,794,847 (94.9%) did not. Across age groups (20-39, 40-54, 55-69, and 70-99 years), vaginal estrogen prescription was associated with lower odds of sepsis, hospitalization, and death. Sepsis occurred in 4.2%-10.4% of estrogen recipients vs 8.5%-24.1% of nonrecipients (OR 0.2-0.5 across age groups). Hospitalization occurred in 7.5%-12.0% of recipients compared with 15.7%-27.5% of nonrecipients (OR 0.3-0.6). Mortality increased with age in both groups but remained lower among estrogen recipients at 0.3%-3.9% vs 0.8%-9.6% in nonrecipients (OR 0.2-0.4 across age groups).
Conclusion: Vaginal estrogen prescription within 2 months of rUTI diagnosis is associated with lower odds of serious adverse outcomes across age groups.

Recurrent urinary tract infections (rUTI), defined as two acute UTIs within 6 months or three or more within a year,[1] pose a significant healthcare burden, with $6 billion spent on complicated UTIs in 2011. The majority of these costs stemmed from inpatient care, where the median admission was approximately $10,000.[2] The incidence of rUTI is particularly pronounced among postmenopausal women, and occurs among other symptoms that comprise the genitourinary syndrome of menopause (GSM).

Randomized controlled trials focused on local vaginal estrogen use have shown its efficacy for the treatment of GSM and multiple studies have reported its safety in postmenopausal women.[3,4] The current literature has focused on the use of vaginal estrogen for improving bothersome symptoms involving vulvovaginal dryness, burning, irritation, urinary urgency and frequency, dyspareunia, arousal and orgasm, and for prevention of rUTI.[5] Data is lacking regarding outcomes of vaginal estrogen replacement in GSM beyond these quality-of-life concerns, specifically with respect to serious adverse outcomes of rUTI such as sepsis, hospital admission, and mortality.

Globally, 404,610,000 cases of urinary tract infection and 236,790 deaths were estimated in 2019, with an age-standardized mortality rate (ASMR) of 3.13/100,000. Rates have not been published specific to recurrent UTI. Using the Epic Research Cosmos Database, we investigated the rates of sepsis, admission, and death in female patients with rUTI prescribed vs not prescribed vaginal estrogen. Our hypothesis was that the prescription of vaginal estrogen would be associated with reduced serious adverse events (SAEs) in those with GSM and rUTI.

METHODS

Ethics Statement

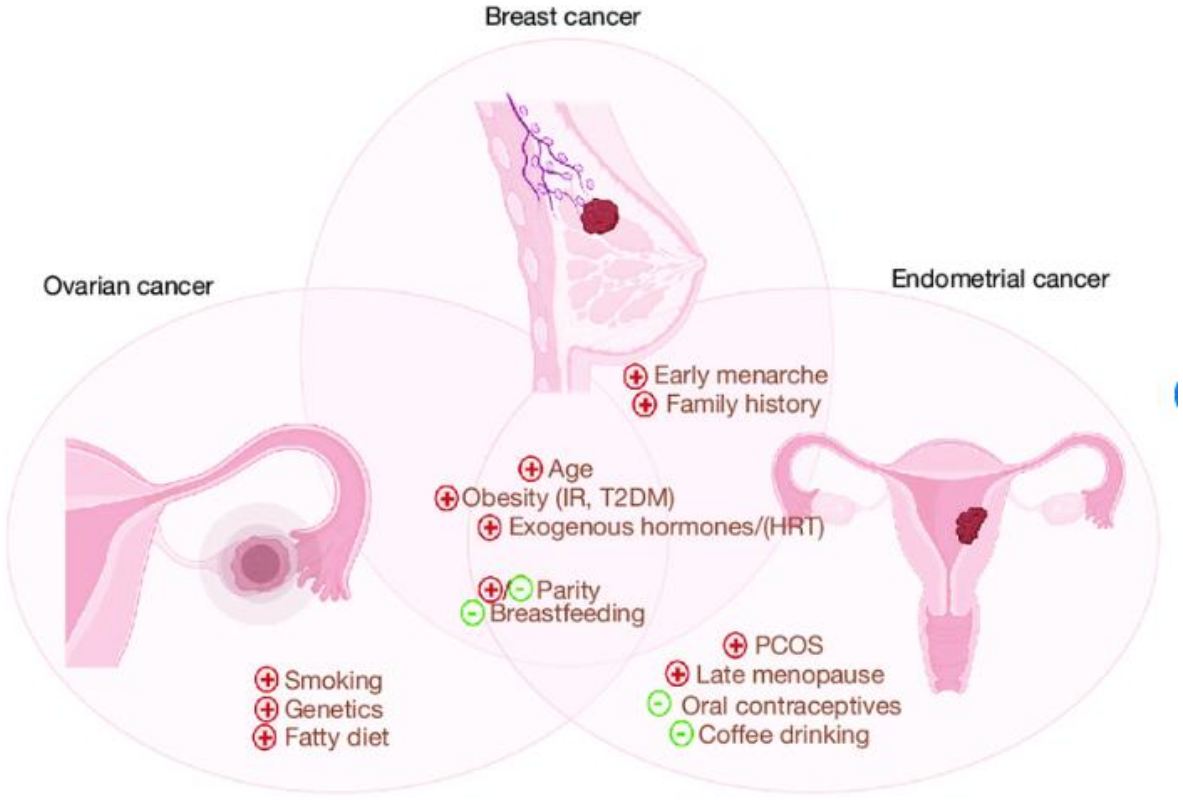
This study used the Epic Cosmos platform, a HIPAA-compliant, de-identified, aggregate-level cloud-based database of electronic health records from participating healthcare organizations. The data have

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https://doi.org/10.1016/j.urology.2026.06.004
Received 15 March 2026; Accepted 4 June 2026
0090-4295/© 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

LaClair J, Visingardi J, Wells B, Feustel P, Deckert J, De EJB. Vaginal Estrogen Prescription is Associated with Reduced Risk of Serious Adverse Outcomes in Women of All Age Groups with Recurrent Urinary Tract Infection: An Epic Cosmos Database Analysis. Urology. 2026 Sep;215:43-48. doi: 10.1016/j.urology.2026.06.004. Epub 2026 Jun 10. PMID: 42269780.

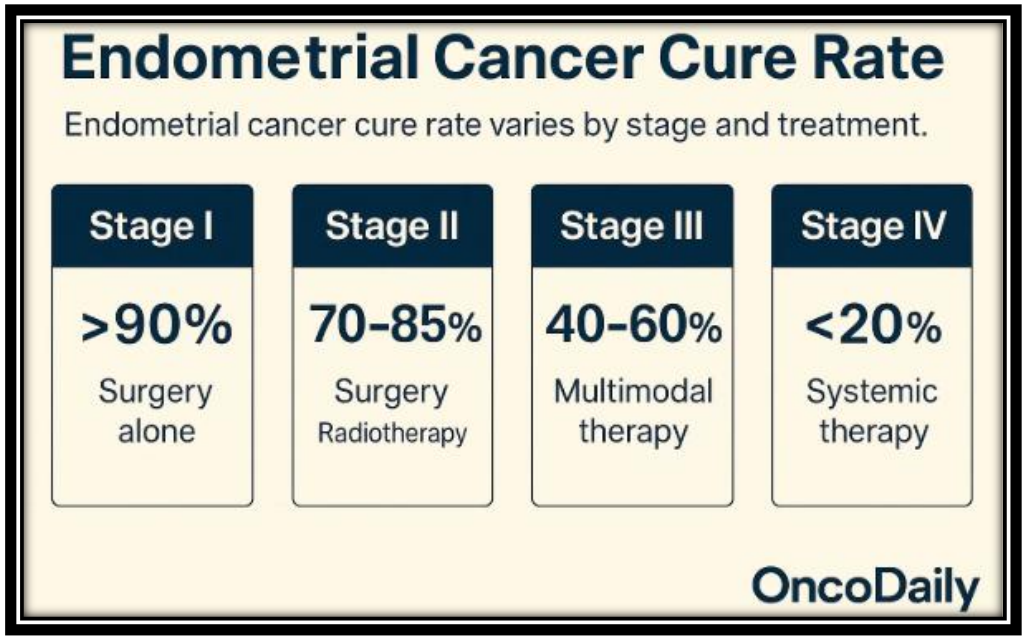
Endometrial Cancer



Systemic factors overlap in promoting breast, endometrial, and ovarian cancer. This Venn diagram shows systemic factors generally considered in the literature to correlate with one or more of the tumor types examined in this review. +, indicates factors demonstrated to increase cancer incidence and/or worsen prognosis; while −, indicates factors that have been shown to have protective effects. Figure created

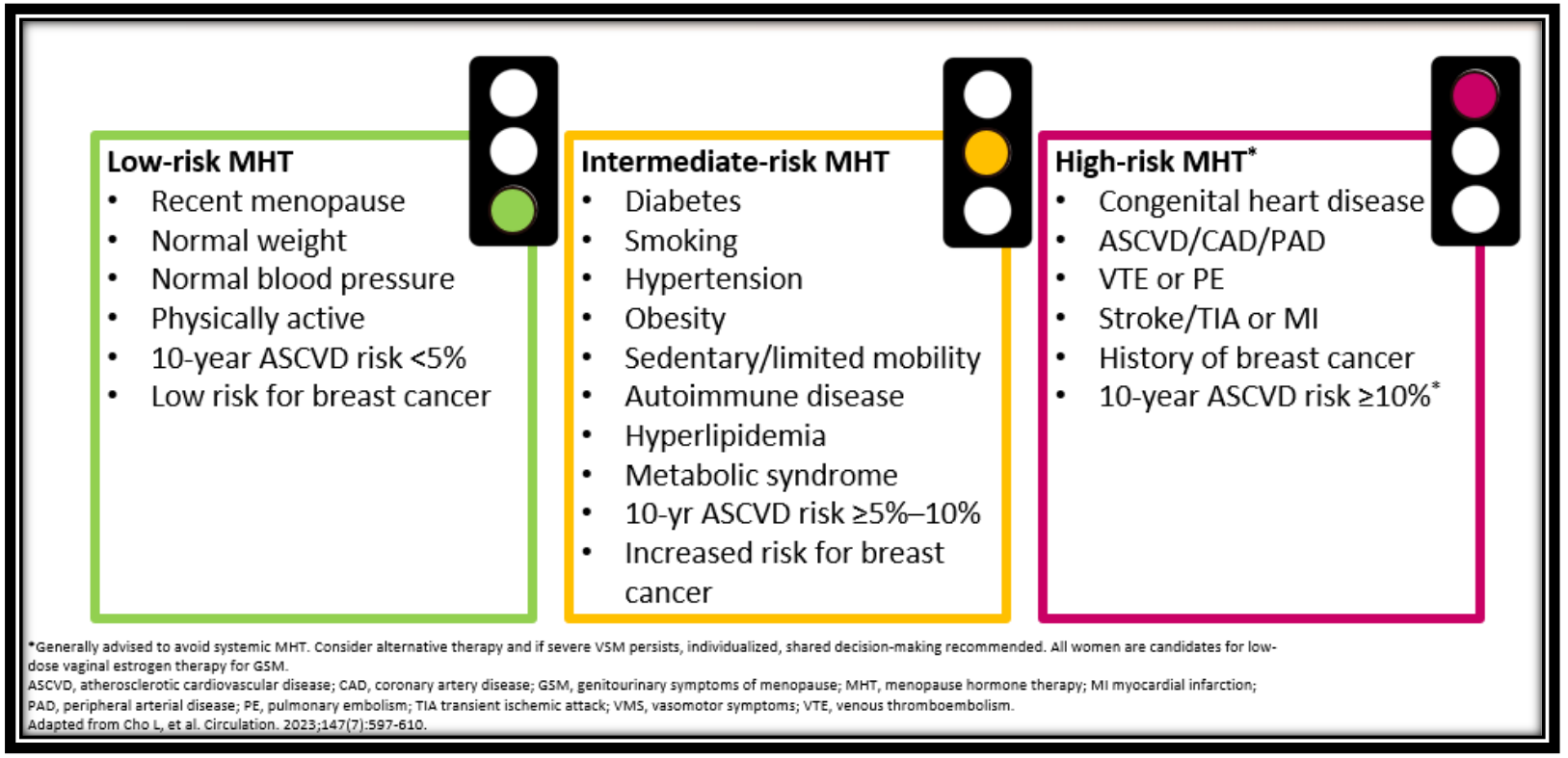
Factors in managing post EC patients

- Risk depends on stage, grade, histology
- Early-stage survivors can safely use MHT
- Progestogen required if uterus intact
- Vag E2: Minimal systemic absorption, No recurrence signal

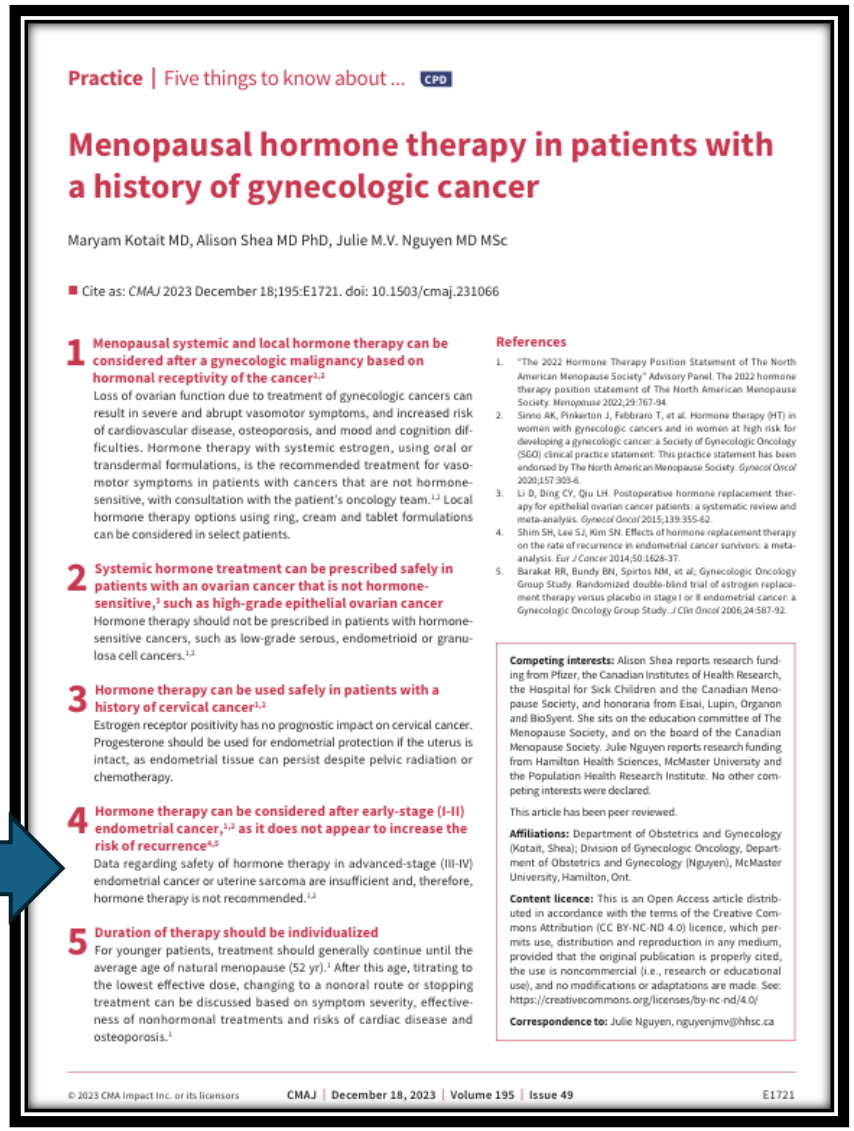


Factors in managing post EC patients

- Factors that increase EC risk may also increase risks of MHT use, eg: obesity, DM
- Common co-morbidities with EC also increase MHT risks



Canadian guidance on post EC MHT



Practice | Five things to know about ... CPD

Menopausal hormone therapy in patients with a history of gynecologic cancer

Maryam Kotait MD, Alison Shea MD PhD, Julie M.V. Nguyen MD MSc

Cite as: *CMAJ* 2023 December 18;195:E1721. doi: 10.1503/cmaj.231066

1 Menopausal systemic and local hormone therapy can be considered after a gynecologic malignancy based on hormonal receptivity of the cancer[1,2]

Loss of ovarian function due to treatment of gynecologic cancers can result in severe and abrupt vasomotor symptoms, and increased risk of cardiovascular disease, osteoporosis, and mood and cognition difficulties. Hormone therapy with systemic estrogen, using oral or transdermal formulations, is the recommended treatment for vasomotor symptoms in patients with cancers that are not hormone-sensitive, with consultation with the patient's oncology team.[1,2] Local hormone therapy options using ring, cream and tablet formulations can be considered in select patients.

2 Systemic hormone treatment can be prescribed safely in patients with an ovarian cancer that is not hormone-sensitive,[3] such as high-grade epithelial ovarian cancer

Hormone therapy should not be prescribed in patients with hormone-sensitive cancers, such as low-grade serous, endometrioid or granulosa cell cancers.[1,2]

3 Hormone therapy can be used safely in patients with a history of cervical cancer[1,2]

Estrogen receptor positivity has no prognostic impact on cervical cancer. Progesterone should be used for endometrial protection if the uterus is intact, as endometrial tissue can persist despite pelvic radiation or chemotherapy.

4 Hormone therapy can be considered after early-stage (I-II) endometrial cancer,[1,2] as it does not appear to increase the risk of recurrence[4,5]

Data regarding safety of hormone therapy in advanced-stage (III-IV) endometrial cancer or uterine sarcoma are insufficient and, therefore, hormone therapy is not recommended.[1,2]

5 Duration of therapy should be individualized

For younger patients, treatment should generally continue until the average age of natural menopause (52 yr).[1] After this age, titrating to the lowest effective dose, changing to a nonoral route or stopping treatment can be discussed based on symptom severity, effectiveness of nonhormonal treatments and risks of cardiac disease and osteoporosis.[1]

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Competing interests: Alison Shea reports research funding from Pfizer, the Canadian Institutes of Health Research, the Hospital for Sick Children and the Canadian Menopause Society, and honoraria from Eisai, Lupin, Organon and BioSyent. She sits on the education committee of The Menopause Society, and on the board of the Canadian Menopause Society. Julie Nguyen reports research funding from Hamilton Health Sciences, McMaster University and the Population Health Research Institute. No other competing interests were declared.

This article has been peer reviewed.

Affiliations: Department of Obstetrics and Gynecology (Kotait, Shea); Division of Gynecologic Oncology, Department of Obstetrics and Gynecology (Nguyen), McMaster University, Hamilton, Ont.

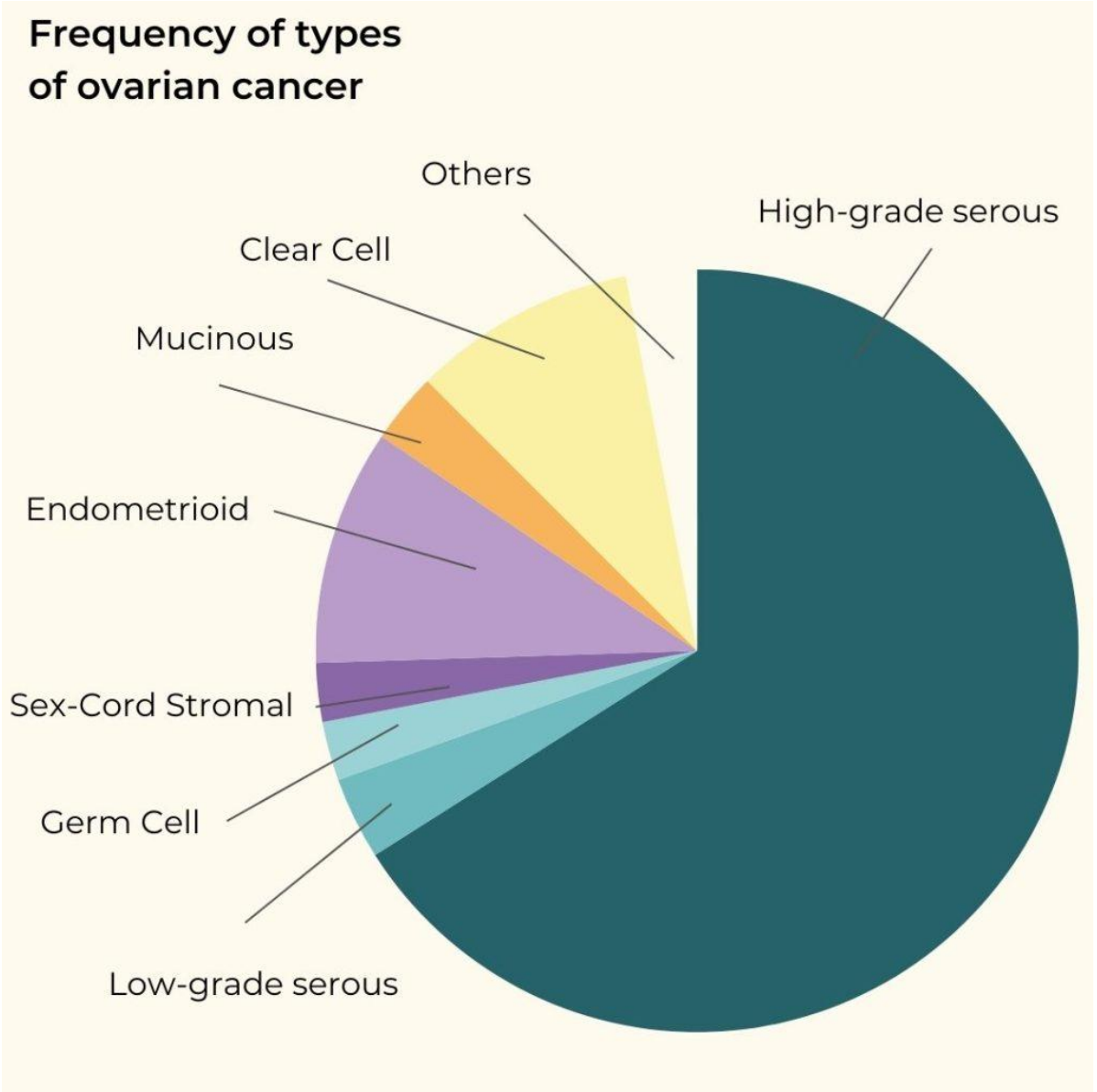
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Correspondence to: Julie Nguyen, nguyenjmv@hhsc.ca

Taken together, the existing evidence suggests that HRT appears safe in women with low-grade, early-stage endometrial cancer after hysterectomy. However, since most available data are derived from surgically treated stage I cohorts with limited use of adjuvant radiotherapy or systemic therapy, the oncologic safety of HRT in women receiving adjuvant treatment remains insufficiently studied, warranting a cautious approach.

Gobrecht-Keller, & Vetter,. (2026). Hormone Replacement Therapy After Endometrial Cancer: Current Evidence and Treatment Recommendations. healthbook TIMES Oncology Hematology. 10.36000/HBT.OH.2026.27.203.

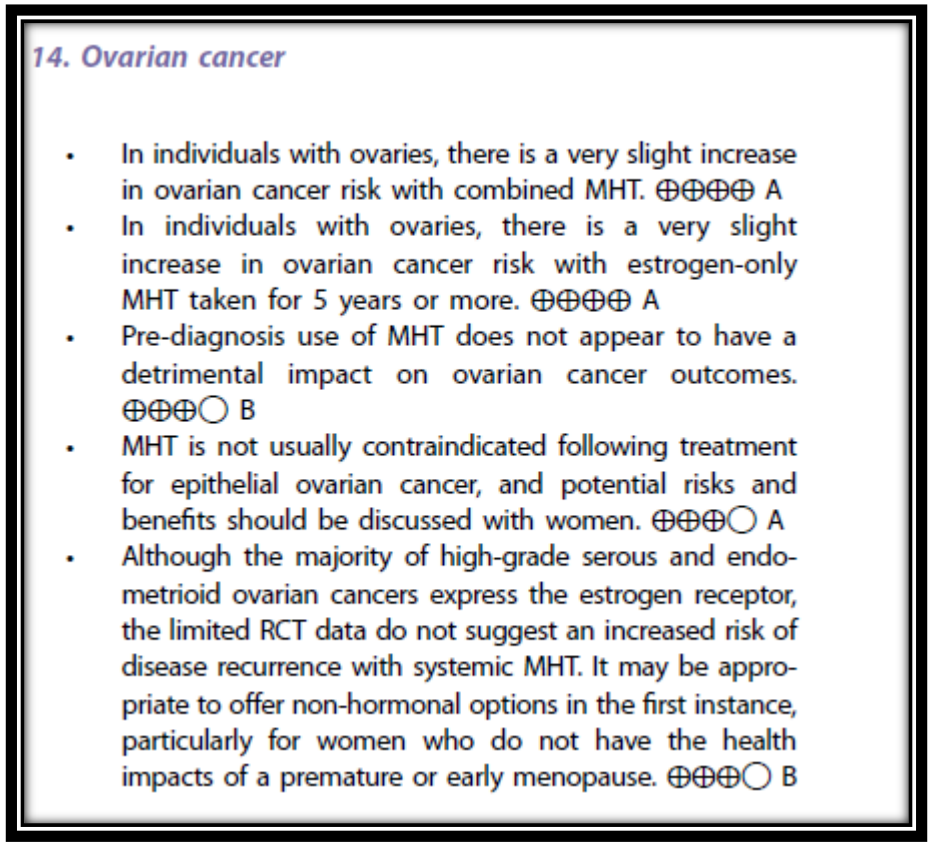
Ovarian Cancer



https://ovariancancerfoundation.org.nz/about-ovarian-cancer/

Managing menopause in OC patients

- Epithelial ovarian cancer is the most common
- Careful consideration for MHT should be used especially if treatment has caused premature menopause
- Hormone therapy should not be prescribed in patients with hormone sensitive cancers, such as low-grade serous, endometrioid or granulosa cell cancers.

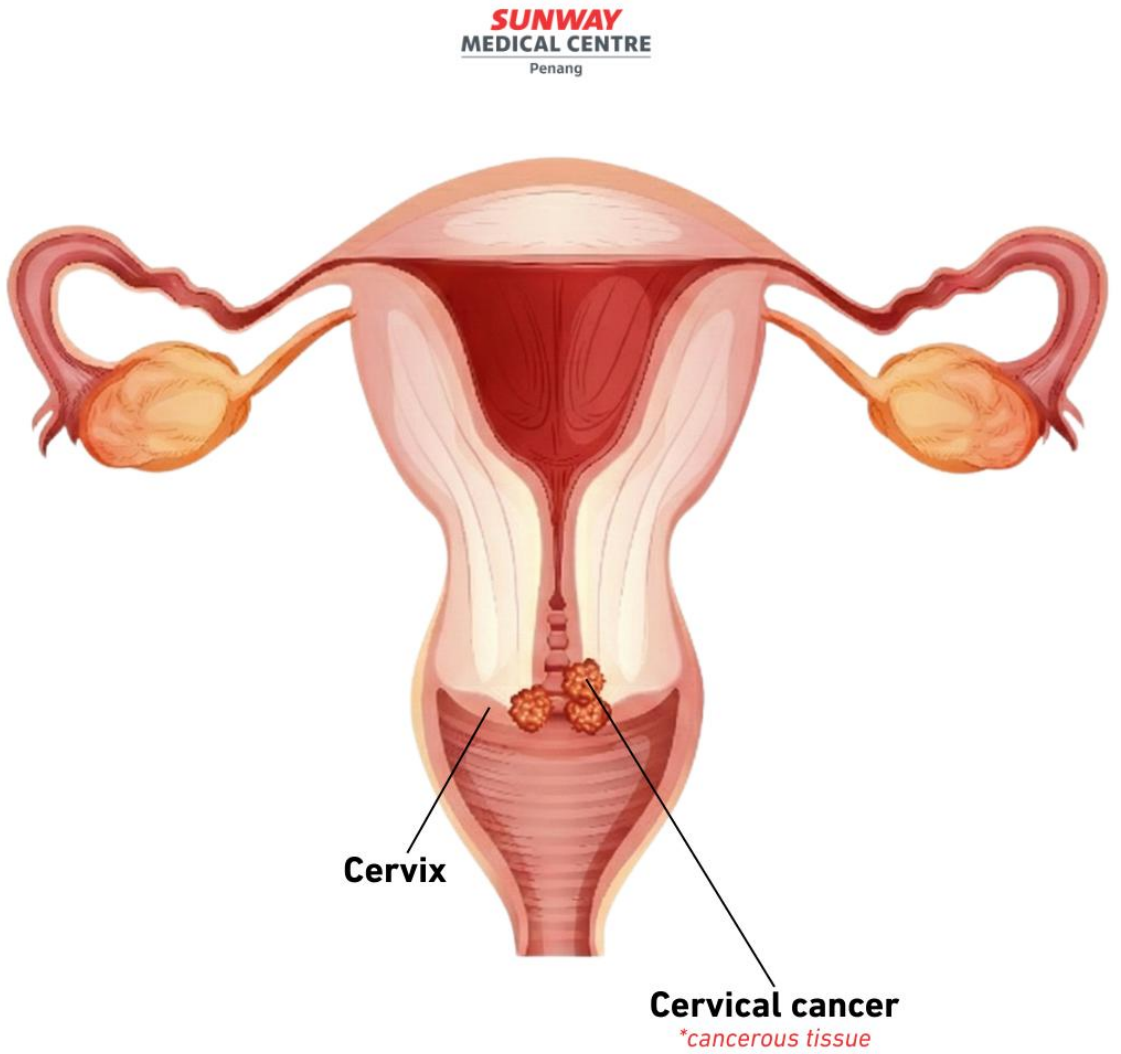


14. Ovarian cancer

- In individuals with ovaries, there is a very slight increase in ovarian cancer risk with combined MHT. ⊕⊕⊕⊕ A
- In individuals with ovaries, there is a very slight increase in ovarian cancer risk with estrogen-only MHT taken for 5 years or more. ⊕⊕⊕⊕ A
- Pre-diagnosis use of MHT does not appear to have a detrimental impact on ovarian cancer outcomes. ⊕⊕⊕◯ B
- MHT is not usually contraindicated following treatment for epithelial ovarian cancer, and potential risks and benefits should be discussed with women. ⊕⊕⊕◯ A
- Although the majority of high-grade serous and endometrioid ovarian cancers express the estrogen receptor, the limited RCT data do not suggest an increased risk of disease recurrence with systemic MHT. It may be appropriate to offer non-hormonal options in the first instance, particularly for women who do not have the health impacts of a premature or early menopause. ⊕⊕⊕◯ B

Panay, N., Fenton, A., Hamoda, H., Hillard, T., Islam, R., … Pedder, H. (2025). International Menopause Society (IMS) recommendations and key messages on women's midlife health and menopause. *Climacteric*, *28*(6), 634–656. https://doi.org/10.1080/13697137.2025.2585487

Cervical Cancer



Key information about cervical cancer

- Average age at diagnosis is currently 47 in Canada
- There is a trend towards increased rates in 35- 44-year-olds
- While there are significant risks to premature menopause, hormone replacement rates remain low across Canada

Lee J, Wasim A, Karreman E et al., Hormone Therapy Use Among Young Patients with Cervical Cancer in Southern Saskatchewan JOGC, 2022; 44, 757-761

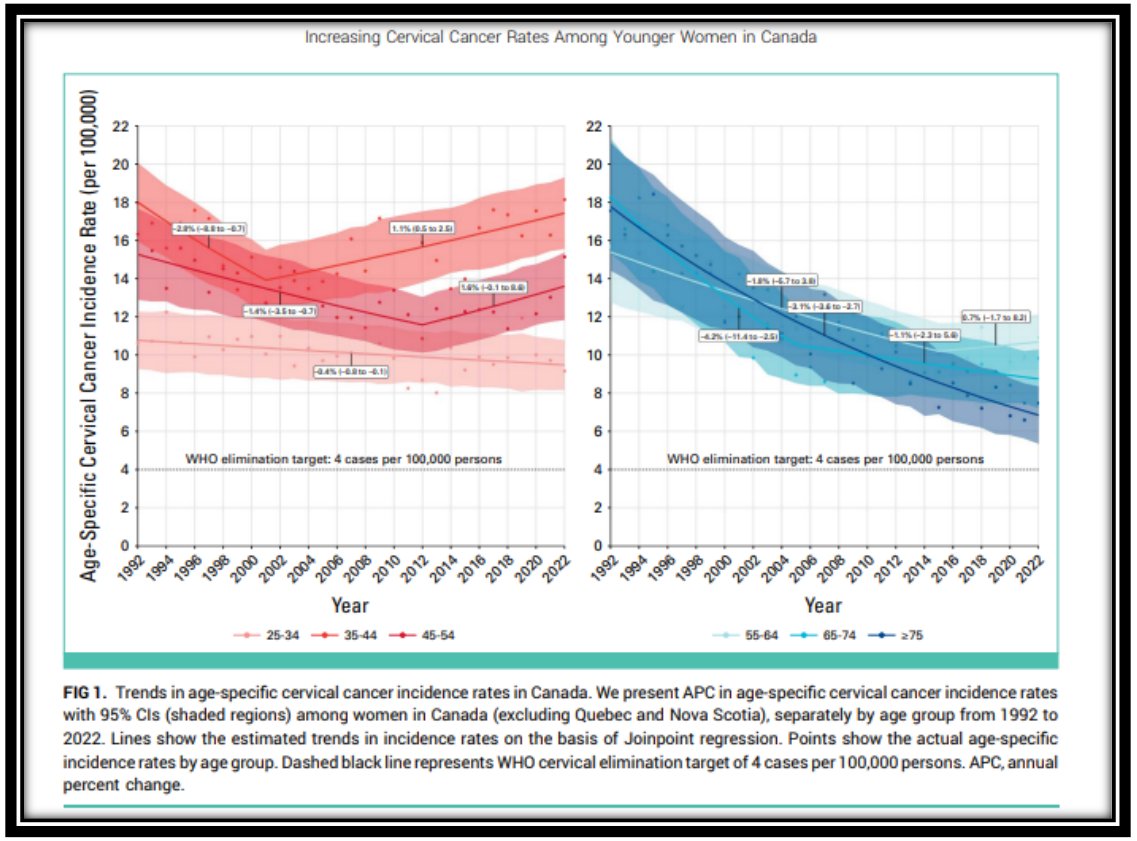
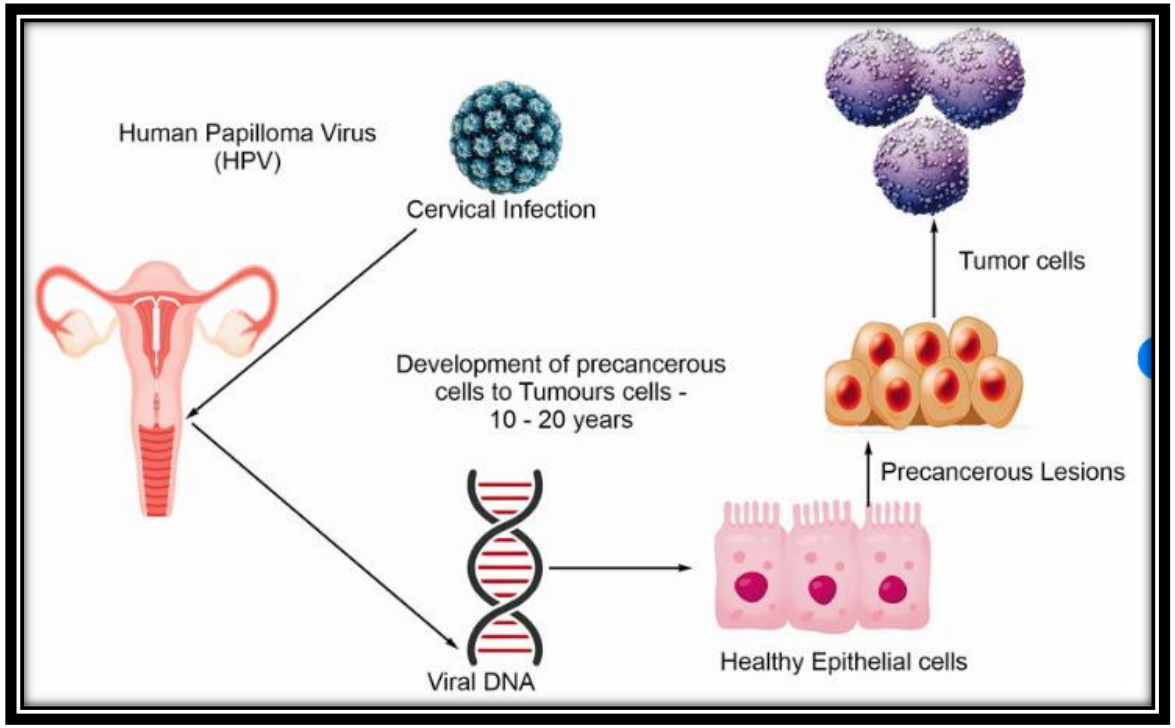


FIG 1. Trends in age-specific cervical cancer incidence rates in Canada. We present APC in age-specific cervical cancer incidence rates with 95% CIs (shaded regions) among women in Canada (excluding Quebec and Nova Scotia), separately by age group from 1992 to 2022. Lines show the estimated trends in incidence rates on the basis of Joinpoint regression. Points show the actual age-specific incidence rates by age group. Dashed black line represents WHO cervical elimination target of 4 cases per 100,000 persons. APC, annual percent change.

Nicolau IA, Warkentin MT, Graff K, Doll C, Bryant H, Brenner DR. Increasing Cervical Cancer Rates Among Women Age 35-54 Years in Canada: Age-Specific Cervical Cancer Incidence Trends in Canada, 1992-2022. JCO Oncol Adv. 2025 Jul 9;2(1):e2400101. doi: 10.1200/OA-24-00101. PMID: 40667567; PMCID: PMC12258797.

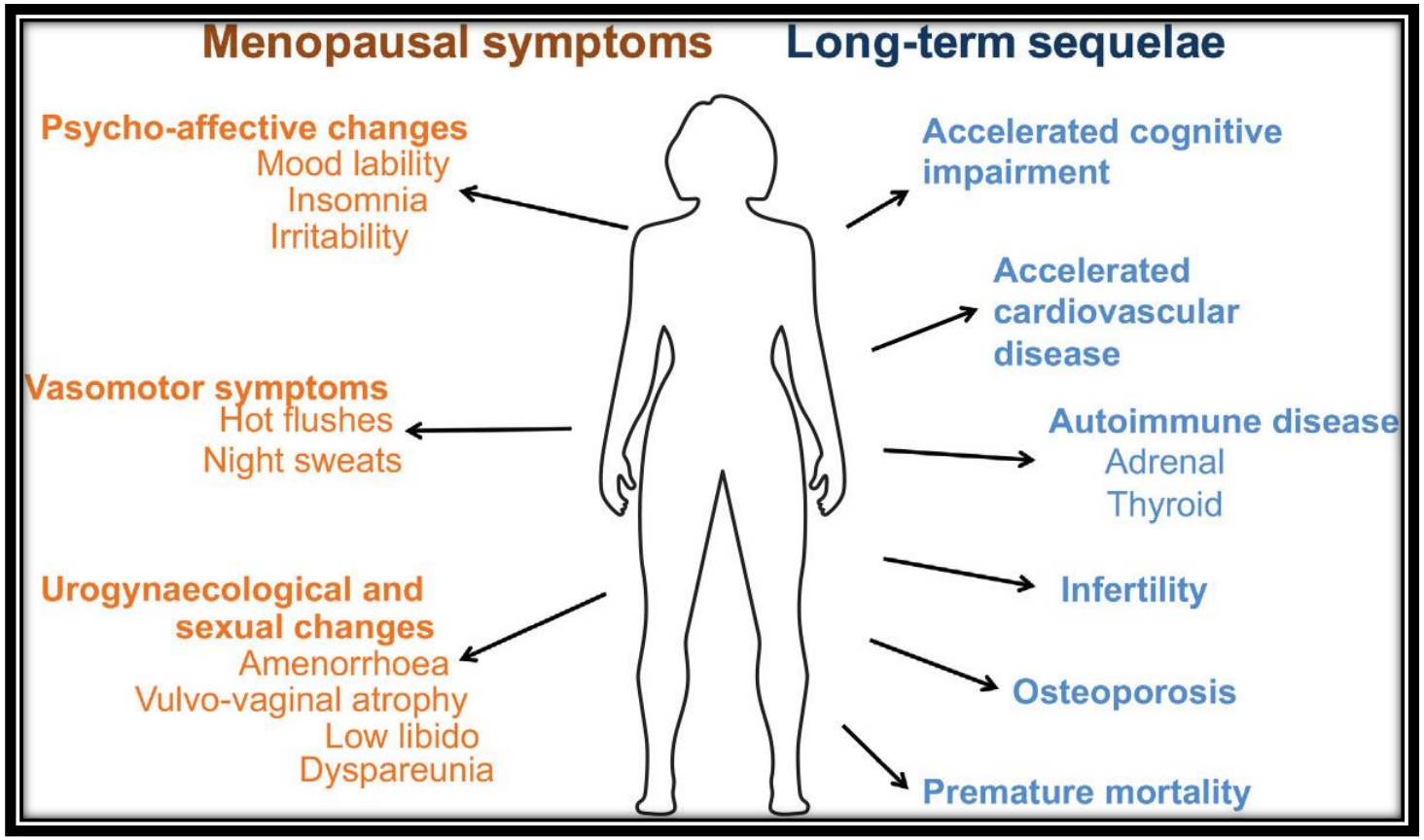
Key information about cervical cancer

- Estrogen receptor positivity has no prognostic impact on cervical cancer.
- Estrogen and E+P therapy do not alter prognosis
- Progesterone should be used for endometrial protection if the uterus is intact, as endometrial tissue can persist despite pelvic radiation or chemotherapy.



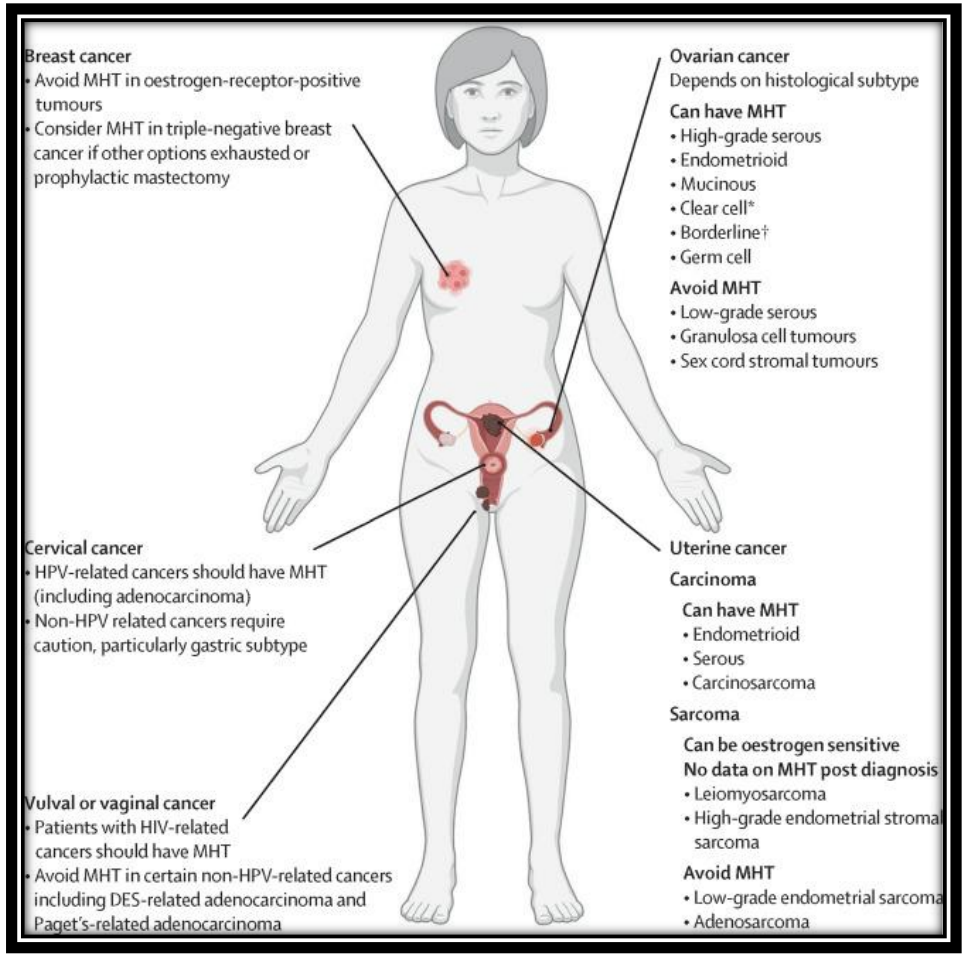
Risks of not treating young patients with menopause…

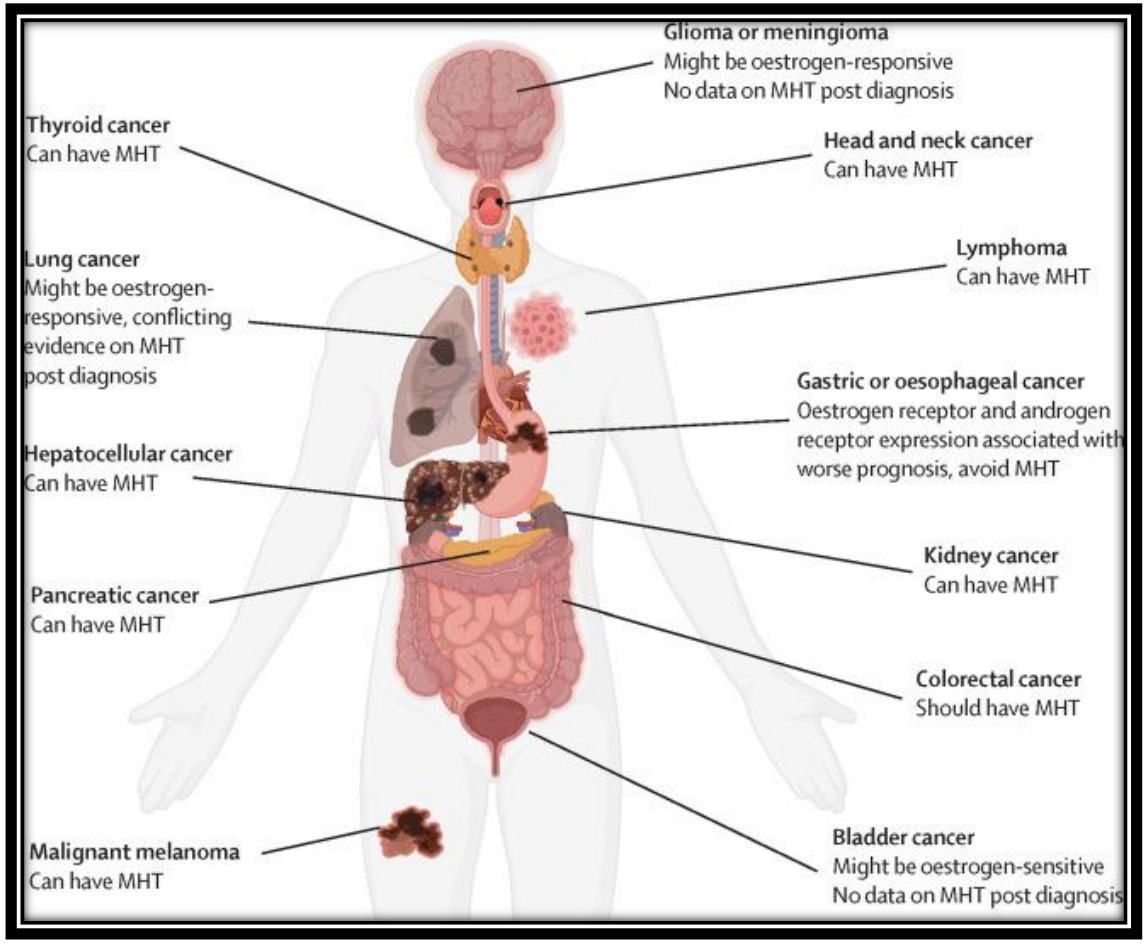
- We should not withhold HRT for patients with menopause due to cervical cancer
- In particular, patients with premature menopause face serious consequences including earlier death



https://www.racgp.org.au/afp/2017/june/premature-ovarian-insufficiency-in-general-practic

Other Cancers...



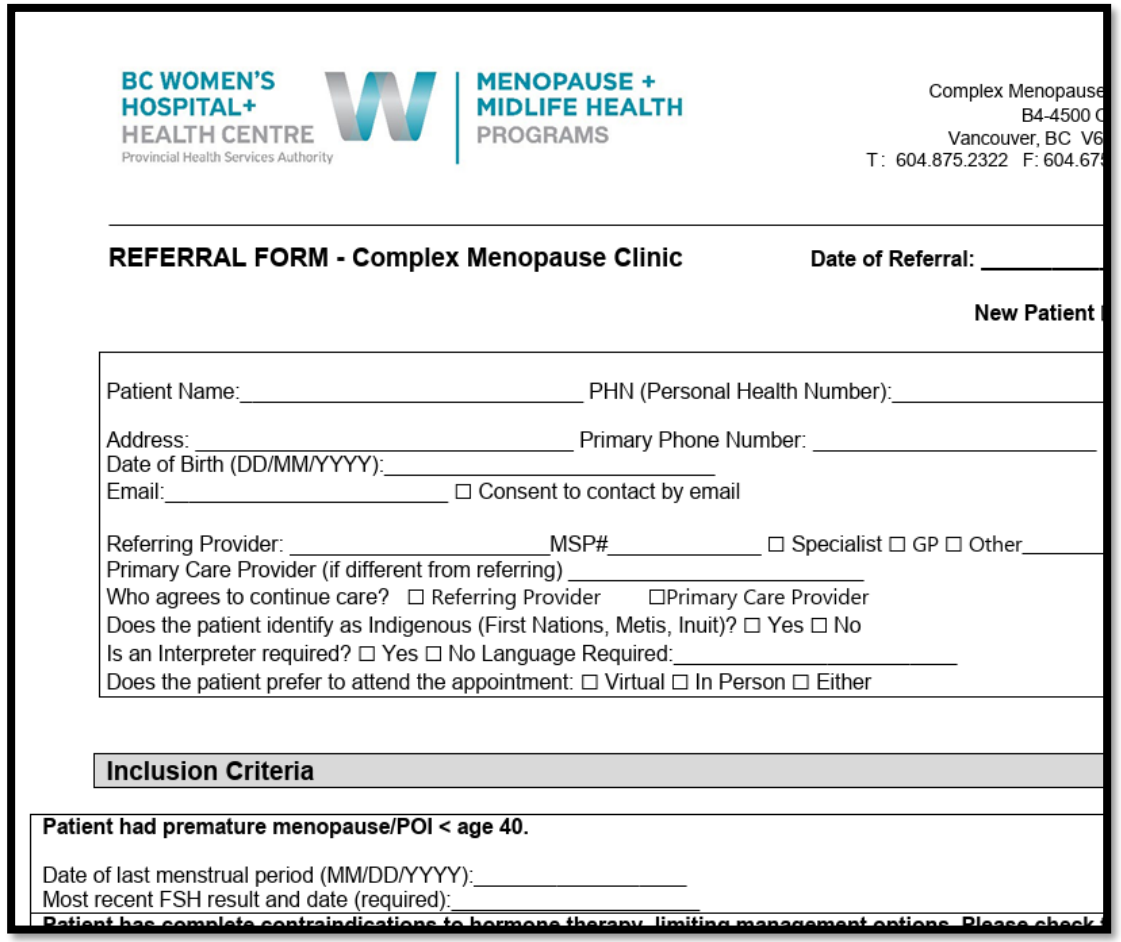


Hickey M, Basu P, Sassarini J et al. **Managing menopause after cancer** The Lancet, 2024; 403, 984-996

Summary

- Many gynecologic cancer intersect with menopause and management should consider this
- Breast cancer patients should generally avoid MHT
- Effective non hormonal options are available
- GSM treatment should be offered to all women
- Early stage endometrial cancer patients can use MHT, with awareness of co-morbidities
- Most ovarian cancers are not hormone sensitive and care should be individualized
- Cervical cancer does not contraindicate MHT and HRT should be offered to all patients who have been put into premature menopause

Managing Complex Patients: BCWH



BC WOMEN'S HOSPITAL+ HEALTH CENTRE
Provincial Health Services Authority

MENOPAUSE + MIDLIFE HEALTH PROGRAMS

Complex Menopause
B4-4500 C
Vancouver, BC V6
T: 604.875.2322 F: 604.67

REFERRAL FORM - Complex Menopause Clinic **Date of Referral:** _____

New Patient

Patient Name:_____ PHN (Personal Health Number):_____

Address:_____ Primary Phone Number: _____
Date of Birth (DD/MM/YYYY):_____
Email:_____ ☐ Consent to contact by email

Referring Provider: _____MSP#_____ ☐ Specialist ☐ GP ☐ Other_____
Primary Care Provider (if different from referring) _____
Who agrees to continue care? ☐ Referring Provider ☐Primary Care Provider
Does the patient identify as Indigenous (First Nations, Metis, Inuit)? ☐ Yes ☐ No
Is an Interpreter required? ☐ Yes ☐ No Language Required:_____
Does the patient prefer to attend the appointment: ☐ Virtual ☐ In Person ☐ Either

Inclusion Criteria

Patient had premature menopause/POI < age 40.

Date of last menstrual period (MM/DD/YYYY):_____
Most recent FSH result and date (required):_____
Patient has complete contraindications to hormone therapy, limiting management options. Please check

- All providers are MSCP
- For patients with medical complexity or who have not responded or tolerated attempts at usual management
- 1 hour consultation
- May also access eCase via dr2dr platform:

dr2dr secure messaging

Thank you

Questions?

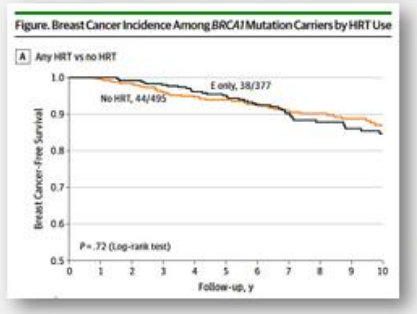


https://www.nfcr.org/blog/national-womens-health-week-time-health-now/

BrCa1 Pre-vivors

JAMA Oncology | Original Investigation

Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among *BRCA1* Mutation Carriers



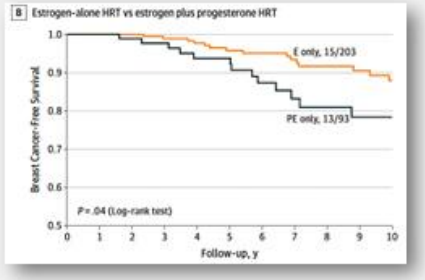
In the sub-group of carriers taking estrogen alone, there was no increase in risk of subsequent breast cancer compared with controls.

- **Overall HRT was not associated with an increased risk of breast cancer at a median follow-up of 7.6 years (hazard ratio [HR] 0.97, 95% CI 0.62-1.52, *P* = .89)**

Kotsopoulos J, Gronwald J, Karlan BY, Jacobson MR, et al. Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers. JAMA Oncol 2018; 4:1059.

JAMA Oncology | Original Investigation

Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among *BRCA1* Mutation Carriers



However, in the sub-group taking combination HRT, the 10-year actuarial risk of breast cancer was 22% as compared with: 12% percent in those taking estrogen alone (absolute difference, 10%; log rank *P* = 0.04).

Kotsopoulos J, Gronwald J, Karlan BY, Jacobson MR, et al. Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers. JAMA Oncol 2018; 4:1059.

Tibolone

LIVIAL INTERVENTION FOLLOWING BREAST CANCER: EFFICACY, RECURRENCE, AND TOLERABILITY ENDPOINTS

- Multinational, placebo-controlled, randomized study of women with vasomotor symptoms who had had breast cancer surgically treated within the previous 5 years
- Upon finding an excess of breast cancers in the treated group, the sponsor canceled the trial 5 months early w median duration of participation 3 years (weeks to 5y)
- 1556 women in the treated group and 1542 in the placebo group age under 40 to 79, with a mean age of 52.7 years
- 57.8% had positive lymph nodes and 70% had a tumor stage of IIA or higher
- HR for recurrent breast cancer in the tibolone-treated women was 1.40 (CI = 1.14–1.70)
- AR for tibolone was 51 cancers per 1000 women per year, and 36 in the placebo group. **The increase occurred only in women with estrogen receptor-positive tumors.**
- No difference in mortality rates between the two groups during the 5-year study period