Menopause Update

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- the only large, long-term RCT of HT in women aged 50 to 79 years,
- Drug trail for HT on chronic diseases
- WHI (HT oral, only)
  - one formulation of estrogen (conjugated equine estrogens [CEE], 0.625 mg),
  - one progestogen (medroxyprogesterone acetate [MPA], 2.5 mg)
  - limited enrollment of women with bothersome vasomotor symptoms (VMS; hot flashes, night sweats) who were aged younger than 60 years or who were fewer than 10 years from menopause onset—the group of women for whom HT is primarily indicated

Guide Updates

Benefits are most likely to outweigh risks for symptomatic women who *initiate* HT when aged <60 years or <10 years of menopause onset.

Change from previous position statement: The lowest dose used for the shortest duration needed to manage menopausal symptoms.

New statement: Management should be individualized and patient preference considered to identify the most appropriate:

HT Type , Dose, Formulation, Route of Administration Duration of Use.

Using the best available evidence to maximize benefits and minimize risks

Periodic reevaluation of the benefits and risks of continuing or discontinuing HT

The Women's Health Initiative Randomized Trials: 2017 Update

- Among postmenopausal women, hormone therapy with
  - CEE plus MPA for a median of 5.6 years or
  - CEE alone for a median of 7.2 years
- ***HT was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.***

Manson, J.E., Aragaki, A.K., Jacques E. Rossouw, J.E.,et al. 2017. JAMA. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. 318(10):927-938.

So what does this mean…..

- Estrogen alone showed a nonsignificant ***reduction*** in breast cancer risk after an average of 7.2 years of randomization, with 7 fewer cases of invasive breast cancer per 10,000 person-years, remained for up to a median 13 years'
- The attributable risk of breast cancer (mean age, 63 y) randomized to CEE & MPA is less than 1 additional case of breast cancer diagnosed per 1,000 users annually
  - a risk slightly greater than that observed with one daily glass of wine, less than with two daily glasses,
  - similar to the risk reported with obesity, low physical activity, and other medications

HRT REGIMENS

Tips

- **Estrogen , HRT vs cOCP ?!**
- **Progestogen or micronised progesterone?! Six months?**
- **Orally or transdermally.**
- **Mirena ?** Women who cannot tolerate oral progestins
- **Supplemental testosterone ?!**
- **Vaginal progesterone regimens ?**
- **Conjugated estrogen/bazedoxifene ?**

The "Her-Mones"

Estrogen

Approved Prescription Products for Menopausal Symptoms in the United States and Canada

Oral estrogen products Revised: February 2016

(Providers should check the full prescribing information for appropriate dosages for the indication and any updates or information that is not provided here, such as warnings and contraindications.)

Active Ingredient(s)	Product Name(s)	Dosages (mg/d)
17β-estradiol*	Estrace[1] Generic(s) available	0.5, 1.0, 2.0
Conjugated estrogens	Premarin	0.3, 0.45[2], 0.625, 0.9[2], 1.25
Synthetic conjugated estrogens, B	Enjuvia[2]	0.3, 0.45, 0.625, 0.9, 1.25
Conjugated estrogens, CSD* (synthetic)	C.E.S. pms-Conjugated estrogens, CSD	0.3, 0.625, 0.9, 1.25
Esterified estrogens	Menest[2] Estragyn[3]	0.3, 0.625, 1.25, 2.5 (administer cyclically) 0.3, 0.625
Estropipate	Generic(s) available[2]	0.625 (0.75 estropipate), 1.25 (1.5), 2.5 (3.0)

*Bioidentical: defined as compounds that have the same chemical and molecular structure as hormones that are produced in the body
[1] Available in Canada but not the United States
[2] Available in the United States but not Canada
Product names not marked are available in both the United States and Canada.

Transdermal estrogen products Revised: February 2016

(Providers should check the full prescribing information for appropriate dosages for the indication and any updates or information that is not provided here, such as warnings and contraindications.)

Active Ingredient(s)	Product Name	Dosage (mg E2/day)
Patch, Film		
17β-estradiol*	Alora[1] Climara Estraderm[1] Estradot[2] Minivelle[2] Oesclim[2] Vivelle-Dot[2] Generic(s) available	0.025, 0.05, 0.075, 0.1 twice/wk 0.025, 0.0375,[1] 0.05, 0.06,[1] 0.075, 0.1 once/wk 0.05, 0.1 twice/wk 0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk 0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk 0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk 0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
Transdermal gel		
17β-estradiol*	Divigel EstroGel Elestrin[1]	0.25, 0.5, 1.0 0.75 (US: single approved dose, Canada: adjust to control symptoms) 0.52 (adjust based on clinical response)
Transdermal spray		
17β-estradiol*	Evamist[2]	1.53 (1 spray/d initially, adjust dosage by clinical response)

*Bioidentical: defined as compounds that have the same chemical and molecular structure as hormones

Difference CEE and E2

- **Both CEE and estradiol are rapidly metabolized into weaker estrogens such as estrone**
- **Meta-analysis of FDA-approved estrogen trials found no evidence of a significant difference in effectiveness between estradiol and CEE in treating VMS**
- **Adverse events (AEs) were inconsistent, despite more hepatic protein production with CEE**
- **there were differences in cognitive outcomes between types of estrogen and the brain serotonergic system, with estradiol providing more robust anxiolytic and antidepressant effects**

Estrogen Dosing

- **1st line: suggest transdermal 17-beta estradiol for many women starting HT**
- **The appropriate, often lowest, effective dose of systemic ET consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal**
- **Conjugated estrogen 0.625 mg/day and 17-beta estradiol (oral 1 mg/day or transdermal 0.05 mg/day) appeared to be equally effective for the treatment of hot flashes**
- **The appropriate dose of progestogen is added to provide endometrial protection if a woman has a uterus, unless CEE is combined with Bazedoxifene.**

Progestogen indication: need for endometrial protection

- primary menopause-related indication for progestogen use is to prevent endometrial overgrowth and the increased risk of endometrial cancer during ET use
- Progestins commonly used include
  - medroxyprogesterone acetate (MPA)
  - norethindrone acetate,
  - micronized progesterone (MP)
  - Levonorgestrel

Progestin "Pro Pregnancy"

primary menopause-related indication for progestogen use is to prevent endometrial overgrowth and the increased risk of endometrial cancer during ET use

MPA

Synthetic progestin

Long-term use may ^ your risk of breast cancer, heart attack, stroke, or blood clot.

used to treat conditions such as absent or irregular menstrual periods, or abnormal uterine bleeding and to decrease the risk of endometrial hyperplasia

- With CEE
  - 0.3mg/1.5mg
  - 0.45mg/1.5mg
  - 0.625mg/5mg

Micronized Progesterone

- Natural progesterone
- In peanut oil
- Helps w hot flashes, insomnia and bone health
- 200-400 mg HS
- increased deep sleep by approximately 15 %
- stimulates formation of new bone

Other

- suggest off-label use of the lower dose levonorgestrel-releasing intrauterine device (IUD) when no other oral progestagen is tolerated

Oral Micronized Progesterone

- first-line progestin because it is effective for endometrial hyperplasia, is metabolically neutral, and does not appear to increase the risk of either breast cancer or CHD
- ^ flow through small blood vessels in a similar way as in pregnancy. It decreases blood pressure
- ^ our basal body temperature to burn about 300 more calories a day
- And it blocks the production of dihydrotestosterone, the male hormone that causes acne and unwanted facial hair growth

Medroxyprogesterone Acetate (MPA)

- Long-term use of MPA may increase your risk of breast cancer, heart attack, stroke, or blood clot.

Progesterone Dosing

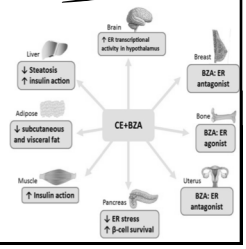
- The appropriate formulation/dose/route of administration of progestogen is needed to counter the proliferative effects of systemic estrogen on the endometrium
- EPT daily was associated with a risk of endometrial cancer = placebo
- ^ incidence of breast cancer was seen in the WHI for EPT compared with placebo, but a reduced incidence with ET alone
- Progestogen dosing-regimen options that provide for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose

Progesterone dosing (cont)

- Observational studies suggest the risk of breast cancer may be less with the use of micronized progesterone (MP) compared with synthetic progestogens
- Different types and doses of progestogens, routes of administration, and types of regimen (sequential or continuous-combined) may have different health outcome
- Progestogen dosing-regimen for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose

Tissue-selective estrogen complex: Bazedoxifene

- Selective estrogen receptor modulator (SERM); (**Duavee**).
- estrogen-like effects on bone (increase bone density) and lipids (decrease LDL); antiestrogenic in uterus and breast (reduces risk of endometrial hyperplasia that can occur with conjugated estrogens).
- The combination provides endometrial protection without the need for a progestogen.
- Indicated for 1) vasomotor symptoms associated with menopause and 2) for prevention of postmenopausal osteoporosis in non-hysterectomized women
  - 20 mg/0.45 mg (1 tablet) PO qDay May take with or without food
- If dose not satisfactory to relieve VMS, do not add additional estrogen. ****Change Rx*****.



Potential risks of HT JAMA, 2017

- a median of six to seven years were no more, nor less, likely to die of any cause over the study's duration than were women who had been assigned to receive a placebo treatment.
- women who got synthetic estrogen and progesterone hormones to replace their naturally declining levels were no more (nor less) likely than those who got a placebo to die of stroke or heart failure.
- And they were neither more nor less likely to die of cardiovascular disease or cancer.
  - JAMA. 2017;318(10):927-938. doi:10.1001/jama.2017.11217

Hot flashes

Initiation of HT

- The safety profile of HT is most favorable when it is initiated by women aged younger than 60 years or within 10 years of menopause onset.
- In general, initiation by older menopausal women aged >65 years requires careful consideration of all individual health benefits and risks
- Vaginal estrogen (and systemic if required) or other non-estrogen therapies may be used at any age for prevention or treatment of GSM

Discontinuation of HT

- Considerations for long-term (or extended) use of HT include persistent VMS, QOL issues, or prevention of osteoporosis in women at elevated risk of fracture.
- Vasomotor symptoms persist on average 7.4 years and for many for more than 10 years.
- In a study of Swedish women aged older than 85 years, 16% reported hot flashes at least several times per week
- HT *does not* need to be routinely discontinued in women >60 and can be considered for continuation beyond age 65 years for persistent VMS, QOL issues, or prevention of osteoporosis after appropriate evaluation and counseling of benefits and risks
- Recommendation using the "Beers" criteria to routinely discontinue systemic HT in women >65 yo is not supported by data.

REFERENCES
The 2017 hormone therapy position statement of: The North American Menopause Society 2.Study of Women,s Health Across the Nation (SWAN). Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med 2015;175:531-539. 3. Gartoulla P, Worsley R, Bell RJ, Davis SR. Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years. Menopause 2015;22:XXX-XXX. 4. Kaunitz AM. Extended duration use of menopausal hormone therapy. Menopause 2012;19:679-681. 5. ACOG Practice Bulletin No. 141: management of menopausal symptoms. Obstet Gynecol 2014;123:202-216.

Contraindication

unexplained vaginal bleeding,
severe active liver disease,
prior estrogen-sensitive breast or endometrial cancer,
coronary heart disease (CHD),
stroke
dementia,

Personal hx or inherited high risk of thromboembolic disease
hypertriglyceridemia,
concern that endometriosis might reactivate,
migraine headaches may worsen,
leiomyomas may grow.

Compounded bioidentical HT

should be avoided, given concerns about safety, including the possibility of over or under dosing, lack of efficacy and safety studies, and lack of a label providing risks. (Level I)

If compounded bioidentical HT is prescribed, concerns about safety should be discussed, and the indication for prescribing compounded rather than government approved bioidentical HT should be documented (allergy, medical need for lower-than-available dose, different preparation). (Level III)

Hormone therapy: type, dose, regimen, and duration of use

The type of HT, specific options, dose, and regimen should be
- **individualized, using shared decision making and determined on the basis of known AE profiles and safety information,**

along with an individual woman's health risks and personal preferences. (Level III)

Lowering doses and/or changing to transdermal HT may be appropriate as women age or in those with metabolic syndromes such as hypertriglyceridemia with risk of pancreatitis or fatty liver. (Level III)

Endometrial protection

- – For women with a uterus using systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen or use of the combination CEE with bazedoxifene. (Level I)
- Progestogen therapy is **not** recommended with low-dose vaginal ET, but appropriate evaluation of the endometrium should be performed if vaginal bleeding occurs, given the limits of safety data. (Level I)

FDA-APPROVED INDICATIONS for HT

- VASOMOTOR SYMPTOMS (LEVEL I)
- PREVENTION OF BONE LOSS (LEVEL I)
- PREMATURE HYPOESTROGENISM (HYPOGONADISM, POI, OR PREMATURE SURGICAL MENOPAUSE WITHOUT CONTRAINDICATIONS) (LEVEL II)
- GENITOURINARY SYMPTOMS (LEVEL I)

Vasomotor symptoms

HT has been shown in double-blind RCTs to relieve hot flashes,

approved as first-line therapy for relief of menopause symptoms in appropriate candidates.

associated with diminished sleep quality, irritability, difficulty concentrating, reduced quality of life (QOL),41 and poorer health status

Vasomotor symptoms return in approximately 50% of women when HT is discontinued.

There is no consensus about whether stopping ''cold turkey'' or tapering is preferable.

Vasomotor

- persisted on average 7.4 years in the (SWAN) and appear to be linked to cardiovascular (CV), bone, and cognitive risks
- Lower doses of HT
  - (oral: CEE 0.3 mg, 17b-estradiol 0.5 mg; or estradiol patch 0.025 mg) may take 6 to 8 weeks to provide adequate symptom relief
- Compared with placebo, ET / EPT was found to
  - reduce weekly symptom frequency by 75%
  - significantly reduce symptom severity
  - no other pharmacologic or alternative therapy found to provide more relief.

Prevention of bone loss

- RCT and observational studies show that HT reduces
  - postmenopausal osteoporotic fractures,
  - (including hip, spine, and all non-spine fractures)
  - with 6 fewer fractures per 10,000 person-years overall,
  - even in women without osteoporosis

Premature hypoestrogenism

HT is approved for women with hypogonadism, POI, or premature surgical menopause without contraindications

with health benefits for menopause symptoms, prevention of bone loss, cognition and mood issues, and in observational studies, heart disease

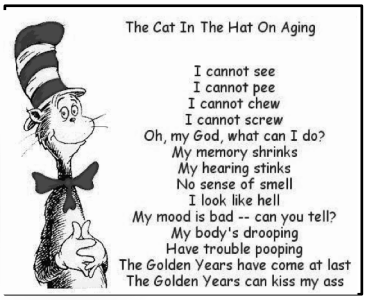
For women whose ovaries are retained at the time of hysterectomy, there is a two-fold increased risk of ovarian failure, and 20% or more of these women may develop symptoms of diminished ovarian reserve within 1 year, with reduced anti-mullerian hormone.

Health risks of early natural menopause and POI

- Women with early menopause and POI have health risks that may include persistent VMS, bone loss, VVA, mood changes, and increased risk of heart disease, dementia, stroke, Parkinson disease, ophthalmic disorders, and overall mortality
- Hormone therapy such as transdermal estradiol in higher doses with adequate endometrial protection may be superior to oral contraceptive therapy to restore or maintain bone mineral density (BMD).

Genitourinary Syndrome of Menopause

- HT has been shown in RCTs to effectively
  - restore genitourinary tract anatomy,
  - increase superficial vaginal cells,
  - reduce vaginal pH,
  - treat symptoms of vulvovaginal atrophy (VVA).



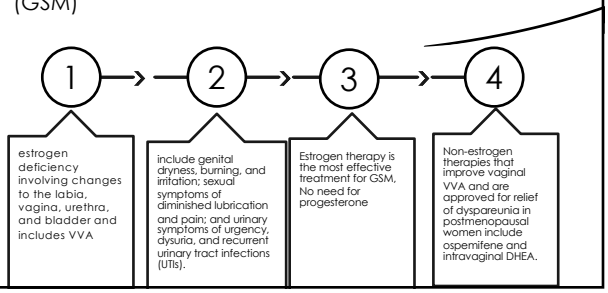
MENOPAUSE SYMPTOMS: BENEFITS AND RISKS

- SLEEP DISTURBANCES
- THE GENITOURINARY SYNDROME OF MENOPAUSE (VAGINAL SYMPTOMS)
- URINARY TRACT SYMPTOMS (INCLUDING PELVIC FLOOR DISORDERS)
- SEXUAL FUNCTION

Sleep disturbances

- HT in the form of low dose estrogen or progestogen could improve chronic insomnia in menopausal women, with 14 of the 23 studies reviewed showing positive result
- Oral progesterone has mildly sedating effects, reducing wakefulness without affecting daytime cognitive functions

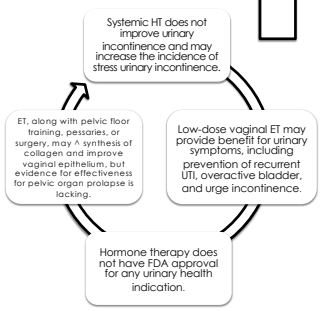
The Genitourinary Syndrome of menopause (GSM)



Breast cancer and vaginal therapy

- Because of the potential risk of small increases in circulating estrogens, the decision to use low-dose vaginal ET in women with breast cancer should be made in conjunction with their oncologists
- although no increased risk was seen in an observational trial of survivors of breast cancer on tamoxifen or aromatase inhibitors (AIs) with low-dose vaginal ET during 3.5 years' mean follow-up.

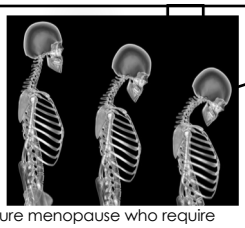
Urinary tract symptoms (including pelvic floor disorders)



Sexual function

- Both systemic HT and low-dose vaginal estrogen increase lubrication, blood flow, and sensation of vaginal tissues.
- Systemic HT generally does not improve sexual function, sexual interest, arousal, or orgasmic response in women without menopause symptoms.
- If sexual function or libido are concerns; transdermal ET may be preferable over oral ET because of less effect on sex hormone-binding globulin and free testosterone levels.
- Low-dose vaginal ET improves sexual function in postmenopausal women with GSM (symptomatic VVA).

Osteoporosis

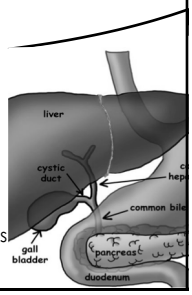


- Hormone therapy prevents bone loss in healthy postmenopausal women, with dose-related effects.
- Unless contraindicated, women with premature menopause who require prevention of bone loss are best served with HT or oral contraceptives (which are less effective than HT) rather than other bone-specific treatments until the average age of menopause, when treatment may be reassessed.
- Hormone therapy effectively prevents postmenopausal osteoporosis and fractures,
- some formulations of ET, EPT, and CEE combined with bazedoxifene are approved for this indication.

Osteoporosis (cont)

1	2	3	4
Women in the ET and EPT cohorts in the WHI intervention trial overall had significant reductions in hip fracture.	For women with VMS aged <60 years or <10 years of menopause onset, HT (ET, EPT, or CEE combined with bazedoxifene) is probably the most appropriate bone-active therapy in the absence of contraindications.	When alternate osteoporosis therapies are not appropriate or cause AEs, the extended use of HT is an option for women who are at high risk of osteoporotic fracture.	The decision to stop HT should be made on the basis of extraskeletal benefits and risks.

GALLBLADDER AND LIVER

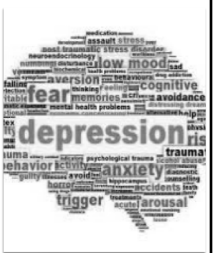


- Cholelithiasis, cholecystitis, and cholecystectomy occur more frequently in women who take oral estrogen, presumably because of the first-pass hepatic effect after oral ingestion.
- lower risk with transdermal HT than with oral
- An association of HT with slower fibrosis progression in hepatitis C and with fatty liver has been observed, but randomized trials are needed

DIABETES MELLITUS, METABOLIC SYNDROME, AND BODY COMPOSITION

- combined HT (EPT) reduced type 2 DM incidence almost 40%, with lower fasting glucose levels and levels of hemoglobin A1c. but it is not US-government approved for this purpose.
- CEE-alone cohort, there was a reduction of 14% in onset of DM
- The EPT either has no effect on weight or is associated with less weight gain in women who are using it than in women who are not

MOOD, DEPRESSION, & COGNITION



- HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia
- ET was effective in improving clinical depression in perimenopausal but not postmenopausal women.
- timing of HT initiation is a significant determinant of Alzheimer disease risk, with early initiation lowering risk and later initiation associated with increased risk.
- Progestins may contribute to mood disturbance.

MOOD, DEPRESSION, AND COGNITION

- HT does not improve memory or other cognitive abilities and that CEE + MPA may be harmful for memory when initiated in women >65
- CEE +MPA doubled the risk of all-cause dementia (23 cases per 10,000 women) when initiated in women aged older than 65 years,164 whereas CEE alone did not significantly increase the risk of dementia
- ET may have positive cognitive benefits when initiated immediately after early surgical menopause, but HT in the early natural post menopause period has neutral effects on current cognitive function

CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

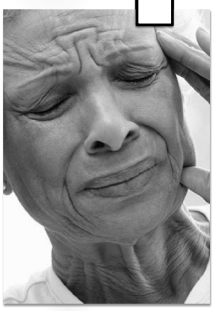
- For healthy symptomatic women <60 years/<10 years of menopause onset, the more favorable effects of HT on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke.
- Hormone therapy is not FDA indicated for primary or secondary cardioprotection.

Coronary heart disease

- HT represents a safe and effective option for the treatment of menopause symptoms when initiated in healthy postmenopausal women aged younger than 60 years or are within 10 years of menopause onset;
- however, the effects of HT on CHD may vary depending on when HT is initiated in relation to a woman's age and/or time since menopause onset. Studies suggest reduced risk of CHD in women who initiate HT when<60 years and/or <10 years of menopause onsetonset.

Stroke

- RCTs of women who initiate HT <60 /<10, found
  - no ^ risk of stroke in women whereas observational study findings are mixed.
  - ^ in women on CEE alone who were within 10 years of menopause onset.
  - A meta-analysis of RCTs found an ^ rare, absolute risk of stroke risk of stroke in women who initiate HT when >60 /10+.
  - Studies suggest that compared with standard-dose oral HT, lower-dose oral and lower-dose transdermal therapy has less effect on risk of stroke, although RCT data are lacking.



CHD/Venous thromboembolism

- Initiation 10+ years from menopause onset, and clearly by 20 years, there is potential for ^ risk of CHD.
- both ET & EPT^ risk of CHD, with potentially greater risk with CEE + MPA, which was significant when initiated in women who were 20 + years from menopause
- ^ risk of VTE with oral ET and EPT, with higher risk seen in the first 1 to 2 years.
- For women who initiated HT when aged <60 years, the absolute risk of VTE was rare but significantly increased

Cancers

BREAST CANCER
ENDOMETRIAL CANCER
OVARIAN CANCER
COLORECTAL CANCER
LUNG CANCER

BREAST CANCER

- The effect of HT on breast cancer risk may depend on the type of HT, dose, duration of use, regimen, route of administration, prior exposure, and individual characteristics
- ET alone showed a nonsignificant reduction in breast cancer risk after an average of 7.2 years of randomization, with 7 fewer cases of invasive breast cancer per 10,000 than placebo remained up to a median 13 years' cumulative follow-up
- EPT: in increased risk of breast cancer (a rare absolute risk of breast cancer), with 9 additional breast cancer cases per 10,000

Cancer

Breast

HT use does **not** further increase risk of breast cancer in women with a family history of breast cancer or in women after oophorectomy for BRCA 1 or 2 gene mutation

low-dose vaginal ET, with minimal systemic absorption, may be considered after a failed trial of nonhormone therapies and in consultation with an oncologist.

There is a concern even with low-dose vaginal ET for women on AIs because of suppressed estradiol levels.

Endometrial

Use of HT may be considered in symptomatic women with surgically treated, early stage endometrial cancer (low risk) if other options are not effective, particularly in women with early surgical menopause who are at higher risk of health consequences related to estrogen loss.

Nonhormone therapies are recommended for women with more advanced cancer or higher-risk endometrial cancer.

OVARIAN

If an association between HT and ovarian cancer exists, the absolute risk is likely to be rare (< 1/1,000) or very rare (< 0.01/1,000) and more likely with longer durations of use.

Limited observational data have not found an increased risk of ovarian cancer in women with a family history or a BRCA mutation who use EPT.

Concern has been raised regarding HT in tumors that are likely to contain ERs, but data are limited.

no increased risk of recurrence or death in women receiving HT after treatment for ovarian cancer

Other Cancers

- Colon:
  - Observational studies suggest a reduced incidence of colorectal cancer with HT, particularly if initiated early in menopause.
  - The use of EPT across all ages reduced colorectal cancer incidence during treatment.
  - Further analysis of the WHI data and postintervention data found no strong evidence of a protective effect of ET or EPT risk of colorectal cancer.
- Lung
  - In the WHI, after a median 13 years' cumulative follow-up, the incidence of lung cancer did not differ significantly between placebo and treatment with either ET or EPT.

Take Home

- HT does **not** need to be routinely dc'd in women aged >60 or 65 years and can be considered for continuation beyond age 65 years for persistent VMS, QOL issues, or prevention of osteoporosis after appropriate evaluation and counseling of benefits and risks.
- Decisions about duration of HT require individualization, including consideration of personal preferences, balancing potential ongoing benefits and risks, and decisions to continue HT for preventive and/or QOL purposes. (Level III)

2017 Hormone Therapy Position Statement of the North American Menopause Society

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