DR. HYMAN+

The FM Approach to Menopause and HRT

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Do mid-life women need to be medicated for menopause?

Yes...

“I’m restless, nervous, tired all the time and always nagging…And sometimes I think I don’t like being married.”

- 1960’s advertisement for tricyclic antidepressant

“Menopause is a hormone deficiency and totally preventable. Now, almost every woman, regardless of age, can safely live a full sex life her entire life.”

- Self help book for women, 1966

Or No?

Combined Hormone Therapy and Breast Cancer

A Single-Edged Sword

Altering a menopausal woman's hormones for decades is fraught with hazard.

Gann PH, Morrow M. Combined hormone therapy and breast cancer: a single-edged sword. JAMA. 2003 Jun 25;289(24):3304-6.

Long-term hormone therapy for peri-menopausal and postmenopausal women A Cochrane Review

2012: 23 studies including 42,830 women. Conclusion: HT **is not indicated** as a primary or secondary prevention strategy against cardiovascular disease or dementia in postmenopausal women.

2017: 22 studies including 43,637 women. Conclusion: HT **is not indicated** for preventing cardiovascular disease or dementia.

- Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2012 Jul 11;(7):CD004143. doi: 10.1002/14651858.CD004143.pub4. Review.
- Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev*. 2017;1(1):CD004143. Published 2017 Jan 17. doi:10.1002/14651858.CD004143.pub5

USPSTF - November 2022

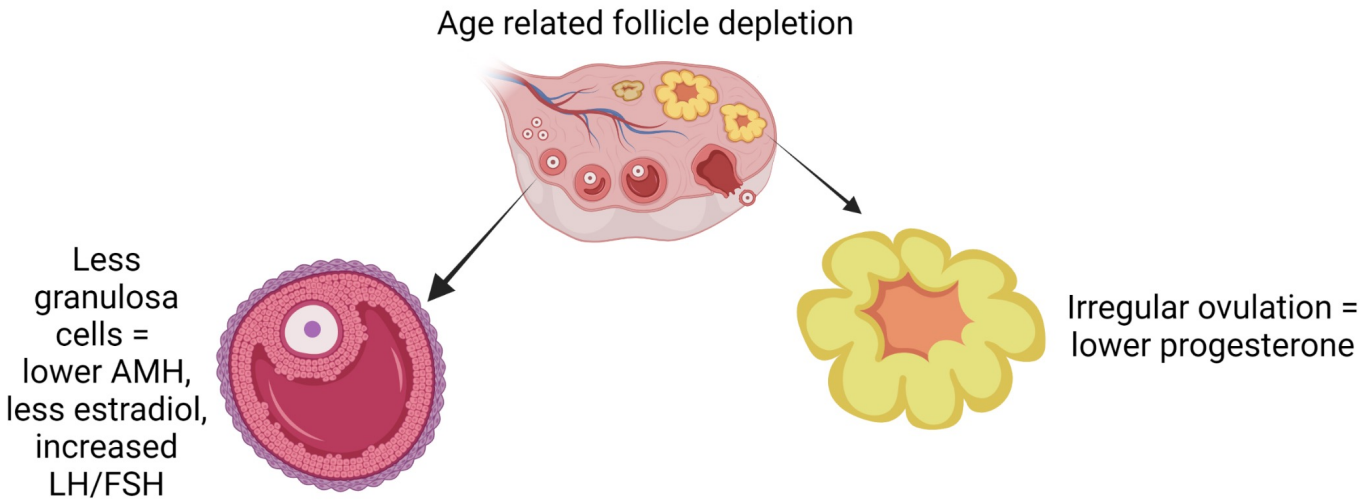
The USPSTF recommends against the use of combined estrogen and progestin or estrogen alone for the primary prevention of chronic conditions in postmenopausal persons.

US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(17):1740-1746. doi:10.1001/jama.2022.18625

Don’t give HRT?
Really?

The IFM HRT Decision Tree

Biology of The Menopausal Transition



Legato MJ, ed. *Principles of Gender-Specific Medicine: Gender in the Genomic Era*. 3rd ed. Amsterdam: Academic Press; 2017.

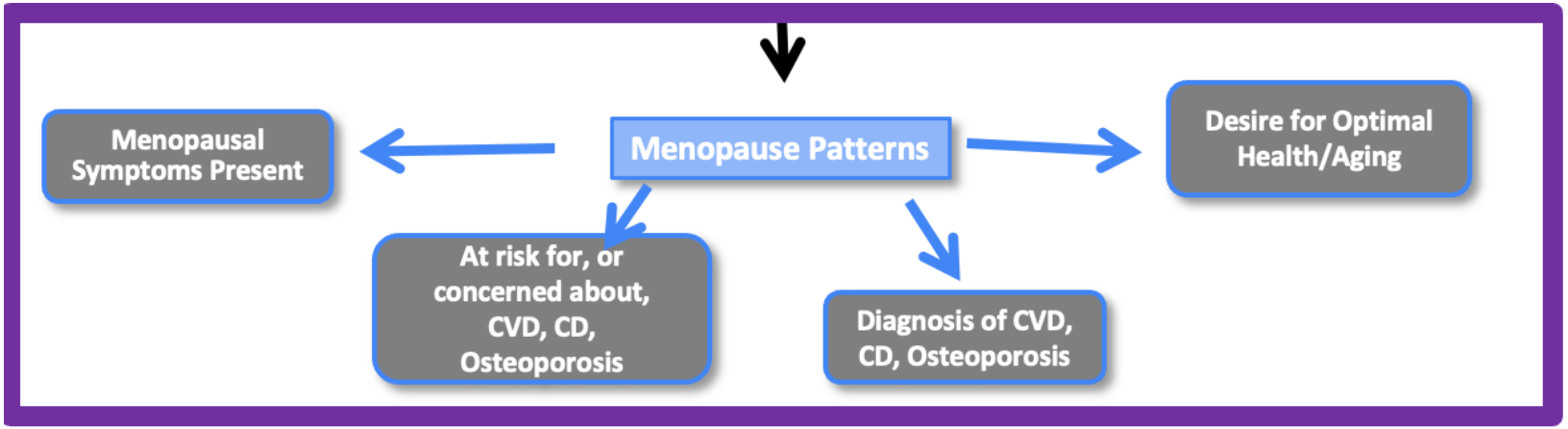
If you wonder about the importance of how women in family transitioned into menopause, it matters….

Familial menopause stories matter!

There is good correlation between menopausal age in mothers and daughters and between sisters, suggesting that **genetic factors play an important role in determining menopausal age.**

Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility. Lippincott Williams & Wilkins. 2012:1144

Common Categories of Menopausal Women Seeking Care



Personalize by Addressing Each Box With or Without Hormones

Women spend one-third of their lives in menopause

Therefore, we are obligated to determine the degree to which declining estrogen levels mediate the age-related decline in so many health parameters.

Hara Y et al. Estrogen Effects on Cognitive and Synaptic Health Over the Lifecourse. *Physiological Reviews.* 2015;95(3):785-807. doi:10.1152/physrev.00036.2014.

Menopausal/Postmenopausal Stage:

The Major Physiologic Considerations

- **Cardiovascular disease implications**
- Osteoporosis / osteopenia
- Cognitive decline
- Skin, hair and beyond

Cardiovascular Implications are Critical

- Heart disease is the #1 killer of women.
- Young women who have undergone early or surgical menopause also have a higher risk for heart disease independent of conventional CVD risk factors.

1. Centers for Disease Control and Prevention. Women and heart disease. Updated October 14, 2022. Accessed December 1, 2022. https://www.cdc.gov/heartdisease/women.htm
2. Gallons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. Menopause. 2012;19(10):1081-1087. doi:10.1097/gme.0b013e3182517bd0

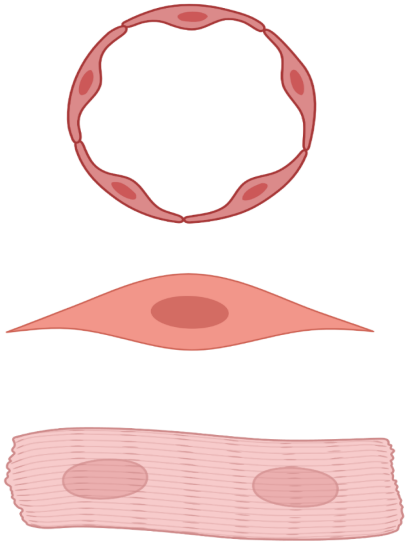
Estrogen protects the CV system

Estrogens are potent ***vasoactive*** hormones:

- **Estradiol Reduces Inflammation:**
  - 17β-estradiol inhibits expression and/or action of C-reactive protein (CRP) in injured arteries
- **Estradiol Reduces Oxidative Stress:**
  - Modulates oxidative stress in arteries and vascular smooth muscle cells

1. Cossette É, Cloutier I, Tardif K, DonPierre G, Tanguay JF. Estradiol inhibits vascular endothelial cells pro-inflammatory activation induced by C-reactive protein. *Mol Cell Biochem*. 2013;373(1-2):137-147. doi:10.1007/s11010-012-1482-9
2. Xing D, Nozell S, Chen YF, Hage F, Oparil S. Estrogen and mechanisms of vascular protection. *Arterioscler Thromb Vasc Biol*. 2009;29(3):289-295. doi:10.1161/ATVBAHA.108.182279

Estrogen Action in the Heart

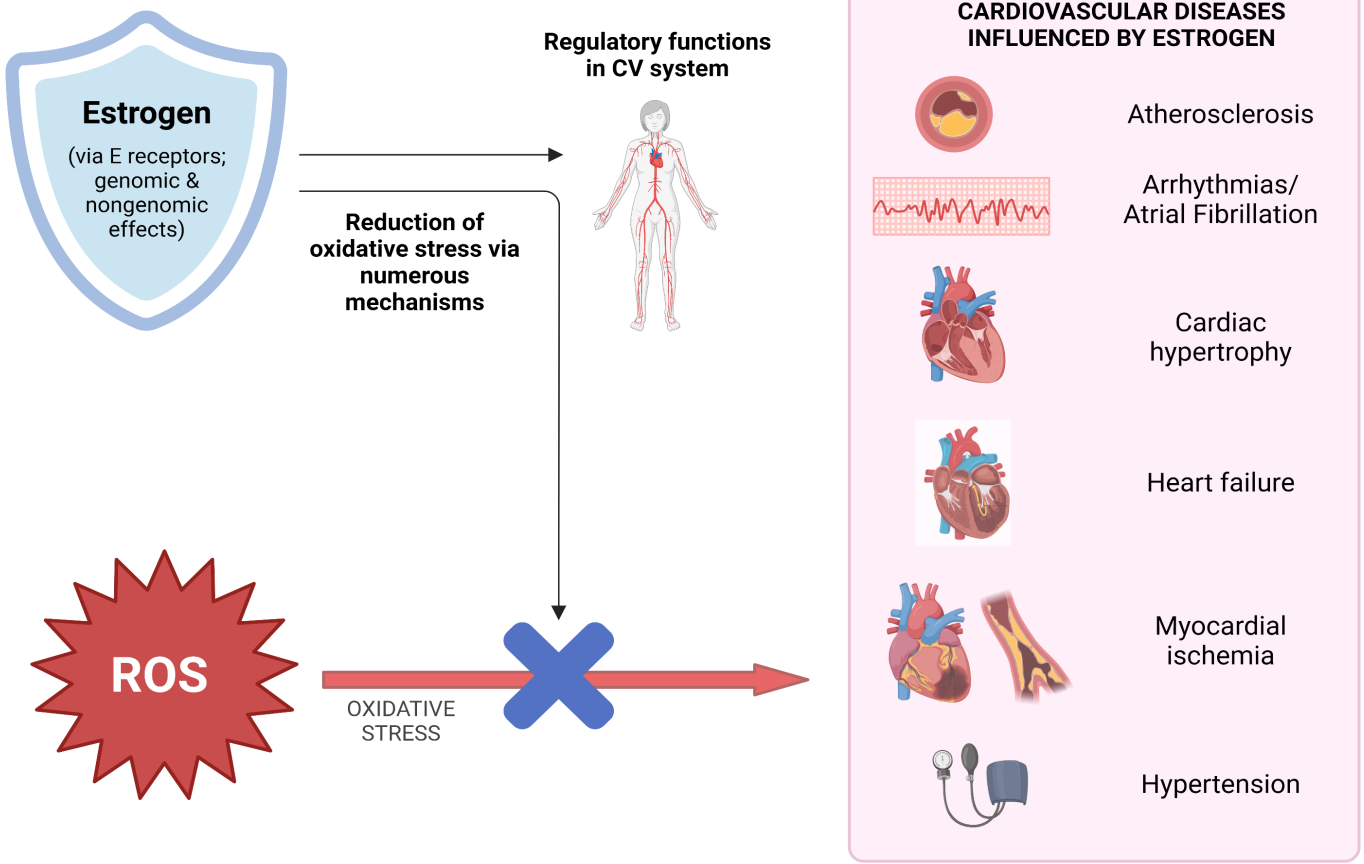


↑ vasodilation in vascular endothelium

↓ cell migration & proliferation in smooth muscle

↓LDL oxidation, insulin resistance, cardiac hypertrophy in cardiomyocytes

Menazza S, Murphy E. The Expanding Complexity of Estrogen Receptor Signaling in the Cardiovascular System. *Circ Res.* 2016;118(6):994-1007. doi:10.1161/CIRCRESAHA.115.305376



Xiang D, Liu Y, Zhou S, Zhou E, Wang Y. Protective Effects of Estrogen on Cardiovascular Disease Mediated by Oxidative Stress. Oxid Med Cell Longev. 2021;2021:5523516. Published 2021 Jun 28. doi:10.1155/2021/5523516

Table 1: The mechanisms of estrogen inhibiting oxidative stress.

Mechanisms	The changes in oxidative stress	References
E_2 decreased MAPK activity	The cardiomyocyte apoptosis and ROS production were reduced	[74, 77, 143, 180]
Estrogen decreased serum lipid peroxides	Overall antioxidant status was upregulated	[92, 150, 173, 181]
E_2 inhibited NOX subunit p47phox	The reduction of superoxide anion production was inhibited	[155, 160]
E_2 decreased NOX subunits $gp91^{phox}$, $p22^{phox}$, and $p67^{phox}$ induced by Ang II	ROS production was reduced	[143, 158, 182, 183]
E_2 upregulated the expression and activity of SOD induced by Ang II	ROS production wad reduced	[167, 184–190]
Estrogen restored antioxidant enzymes GPX1 and GPX4 expression levels	Oxidative stress balance was maintained	[158, 181, 189]
Estrogen increased the expression of the glutathione rate-limiting enzyme γ-glutamylcysteine synthetase	Oxidative stress balance was maintained	[168, 190, 191]
Estrogen maintained the bioavailability of NO by increasing the expression of eNOS mRNA and protein	The production of NO increased and oxidative stress was reduced	[84, 192–195]
ERα activated eNOS through the PI3/AKT signal pathway	The production of NO increased and oxidative stress was reduced	[175, 189, 195]
Estrogen increased the intracellular availability of the eNOS cofactor BH4 and prevented the uncoupling of eNOS	The production of eNOS-dependent ROS was reduced	[177, 178]

Xiang D, Liu Y, Zhou S, Zhou E, Wang Y. Protective Effects of Estrogen on Cardiovascular Disease Mediated by Oxidative Stress. *Oxid Med Cell Longev*. 2021;2021:5523516. Published 2021 Jun 28. doi:10.1155/2021/5523516

Menopause Occurs As CV Risk Factors Are Increasing

- Changes in body fat distribution
- Reduced glucose tolerance
- Abnormal plasma lipids
- Increased blood pressure
- Increased sympathetic tone
- Endothelial dysfunction
- Vascular inflammation

Rosano GM, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. Climacteric. 2007 Feb;10 Suppl 1:19-24.

Menopause increases both CV risk and CVD disease.

The questions now become:

Does estrogen replacement reduce CV risk?

If it does reduce CV risk, is the risk/benefit a net positive?

Does HRT prevent cardiovascular disease in menopause?

USPSTF - November 2022

Observational evidence has suggested that there **might** be a protective effect of menopausal hormone therapy on coronary heart disease; however, the WHI and other trials of menopausal hormone therapy have not demonstrated such an effect.

US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(17):1740-1746. doi:10.1001/jama.2022.18625

But we need to look more closely…

Let’s look at the new recommendation statement from the USPSTF:

A pooled analysis showed no difference in risk of coronary heart disease events in persons treated with estrogen **plus progestin**

US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(17):1740-1746. doi:10.1001/jama.2022.18625

What about estrogen alone?

Let’s look at the new recommendation statement from the USPSTF:

Similarly, a pooled analysis of 3 trials found no significant difference in coronary events between persons taking estrogen alone.

US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(17):1740-1746. doi:10.1001/jama.2022.18625

What is the Committee Opinion from ACOG?

The ACOG Committee Opinion on hormone therapy and heart disease, released in 2013 and reaffirmed in 2020, advises that **menopausal hormone therapy should not be used for primary or secondary prevention of coronary heart disease.**

ACOG Committee Opinion No. 565: Hormone therapy and heart disease. American College of Obstetricians and Gynecologists. Updated 2020. Accessed December 1, 2022. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/06/hormone-therapy-and-heart-disease https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/06/hormone-therapy-and-heart-disease

How about the current 2022 position statement from NAMS?

- For healthy women who are within 10 years of the menopause transition and who have bothersome menopause symptoms, the benefits of hormone therapy (ET or EPT) outweigh its risks, with fewer CVD events in younger versus older women.

- Initiating hormone therapy in women aged 60 years or older or after 10 years since menopause had no effect on CHD or all-cause mortality but was associated with higher risk of stroke and VTE.

The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

NAMS 2022 SUMMARY STATEMENT

Hormone therapy is not government approved for primary or secondary cardioprotection.

The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

NAMS 2022 SUMMARY STATEMENT

Yet…

Data show a reduced risk of CHD in women who initiate hormone therapy when aged younger than 60 years or within 10 years of menopause.

The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

NAMS 2022 SUMMARY STATEMENT

- The risk of breast cancer related to hormone therapy use is low, (less than one additional case per 1,000 women per year of hormone therapy use or three additional cases per 1,000 women when used for 5 years with CEE plus MPA).

The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

NAMS 2022 SUMMARY STATEMENT

- Different types of estrogen or progestogen, as well as different formulations, timing of initiation, duration of therapy, and **patient characteristics**, may play a role in the effects of hormone therapy on the breast.

The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

What About HRT and Diabetes?

- EPT reduced incidence of metabolic syndrome.
- Incidence of type 2 DM was decreased by 30%.
- A second, smaller meta-analysis confirmed these findings and reported that women with type 2 DM using ET or EPT had better glycemic control.
- The benefit reverses when hormone therapy is discontinued. For these reasons, hormone therapy can be considered for symptomatic menopausal women with type 2 DM.

The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

My Conclusion of Professional Society Recommendations:

Contradictory!!
Confusing!!
Not Very Helpful!!

In order to safely and effectively utilize HRT, we need to look closer at the nuances of the research...

Enter...The Timing Hypothesis

Looking back on the Committee Opinion from ACOG: #565 June 2013, reaffirmed 2020

Initial statement

Do not use menopausal hormone therapy for the primary or secondary prevention of coronary heart disease at the present time…

However…

…the "timing hypothesis," which states that cardiovascular benefit may exist when estrogen therapy or hormone therapy is used close to the onset of menopause, **has supporting evidence**.

ACOG Committee Opinion No. 565: Hormone therapy and heart disease. American College of Obstetricians and Gynecologists. Reaffirmed 2023 Accessed July, 5, 2023. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/06/hormone-therapy-and-heart-disease

NAMS also recognized a timing component as early as 2014

Initial statement

"Available evidence **does not support** the use of systemic hormone therapy for the prevention or treatment of CVD"…

However…

…"However, age and time since menopause are critical modifiers of the effect of systemic hormone therapy on CVD, with more **favorable effects observed for women ages 50-59 years and within 10 years of menopause at treatment initiation."**

Shifren JL, Gass ML; NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause*. 2014;21(10):1038-1062. doi:10.1097/GME.0000000000000319

Q: Does timing of HRT matter in the prevention of heart disease?

- Estrogen signaling may be altered in older women, converting effects from anti-inflammatory/ vasoprotective to pro-inflammatory/vasotoxic effects

- Early menopause is associated with adverse cardiovascular disease outcomes; starting HT in the perimenopausal/early menopausal period reduces these outcomes

To summarize: As women age and/or there is an estrogen deficiency, the vasoprotective effects of estrogen diminish.

Hage FG, Oparil S. Ovarian hormones and vascular disease. *Curr Opin Cardiol*. 2013;28(4):411-416. doi:10.1097/HCO.0b013e32836205e7

Biologic Plausibility for Timing Hypothesis

- Early in the atherosclerotic disease process: Estrogen exerts **protective effects on the endothelium and retards plaque formation.**
- Late in the process: Estrogen **causes plaque erosion or rupture with subsequent thrombosis and acute coronary events.**

Santen RJ. Use of cardiovascular age for assessing risks and benefits of menopausal hormone therapy. *Menopause*. 2017;24(5):589-595. doi:10.1097/GME.0000000000000847

Further support for the “timing hypothesis” from the ELITE Trial

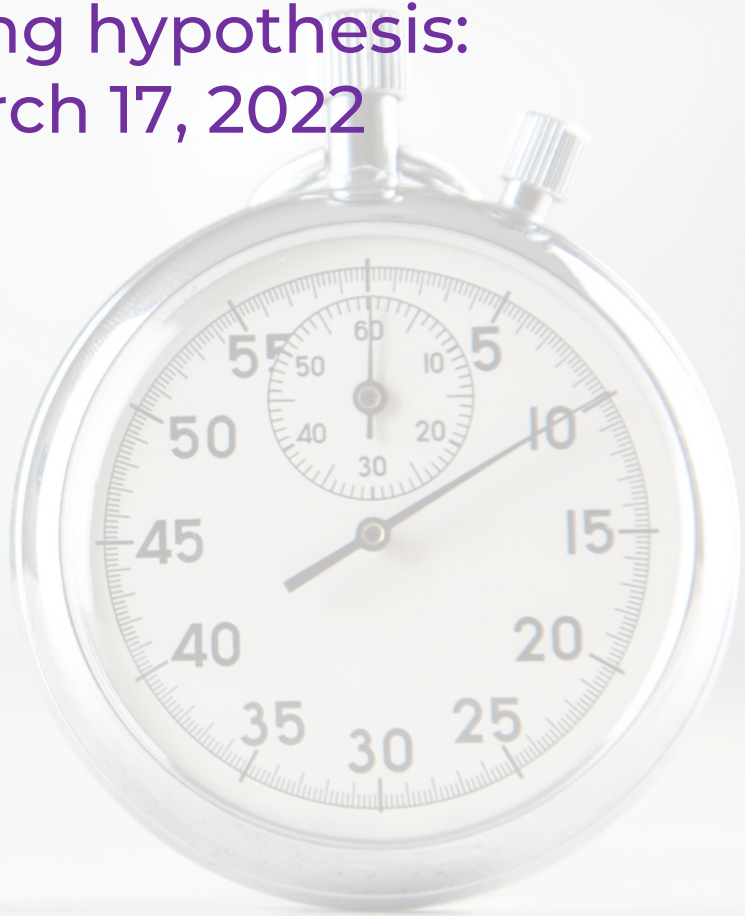
- Over a follow up period of 6 years, the women taking estradiol, who were less than 6 years from menopause onset, had slower progress of atherosclerosis. The women more than 10 years from menopause did not show this effect.

The results from ELITE trial suggests that **when HRT is initiated at the time of menopause or early (within 6 years) after menopause that there is a significant reduction in CVD** relative to no effect when initiated more than 10 years after menopause onset.

Manson JA. ELITE Trial Supports "Timing Hypothesis" for estrogen therapy - https://www.medscape.com/viewarticle/837535. Accessed March 25, 2019.
Hodis H, Mack W, Shoupe D. Testing the Menopausal Hormone Therapy Timing Hypothesis: The Early versus Late Intervention Trial with Estradiol. *Circulation*. March 2018

The latest on the timing hypothesis: In the press on March 17, 2022

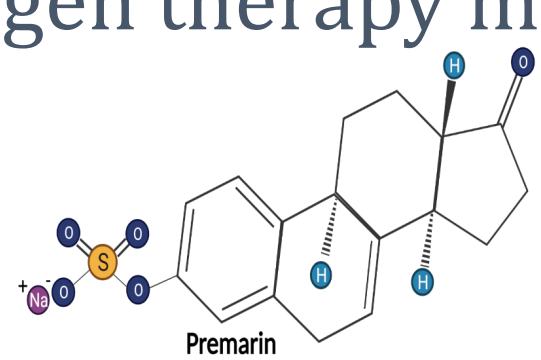
- There is recent research (ELITE trial) on the *timing* of HT initiation.
- HT possibly has a benefit for cardiovascular health, depending on the timing of initiation.
- Conclusion: The overall risk-benefit profile is such that HRT is not indicated for the promotion of heart health alone.

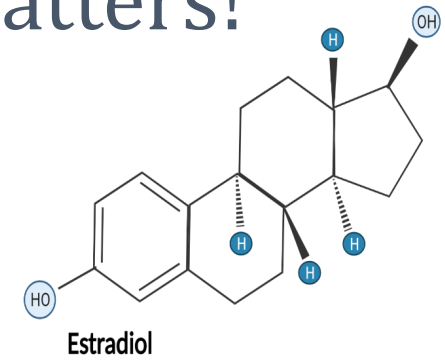


Nash Z, Al-Wattar BH, Davies M. Bone and heart health in menopause [published online ahead of print, 2022 Mar 17]. *Best Pract Res Clin Obstet Gynaecol*. 2022;S1521-6934(22)00041-4. doi:10.1016/j.bpobgyn.2022.03.002

The form of estrogen therapy matters!

- Estradiol-based protocols may have a different risk-benefit ratio than CEE.[1]





A 2017 review encompassing data from USA and Europe concluded that the **use of estradiol-based HT** was not associated with cardiovascular risk, but rather reduced the prevalence of coronary artery disease.[2]

1. Mikkola TS, Tuomikoski P, Lyytinen H, Korhonen P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O. Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. *Menopause*. 2015 Sep;22(9):976-83. doi: 10.1097/GME.0000000000000450

2. Mikkola TS, Savolainen-Peltonen H, Venetkoski M, Ylikorkala O. New evidence for cardiac benefit of postmenopausal hormone therapy. *Climacteric*. 2017 Feb;20(1):5-10. doi: 10.1080/13697137.2016.1262839

Image created with BioRender.com

In a large study including 489,104 women who used hormone therapy from 1994-2009:

- Risk of CHD death was significantly **reduced by 18%** to 54%
- Risk of stroke death was **reduced by 18%** to 39%
- Risk of ***all-cause mortality*** was **reduced by 12%** to 38%

However…

There was no significant difference in risk reduction in women initiating HT before or after age 60.

Mikkola TS, Tuomikoski P, Lyytinen H, Korhonen P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O. Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. Menopause. 2015 Sep;22(9):976-83. doi: 10.1097/GME.0000000000000450.

HRT & Cardiovascular Disease

CLINICAL TAKEAWAYS

- There is biologic plausibility that ERT helps prevent CVD and Type II DM.
- The intervention **data is most supportive for estradiol.**
- The timing hypothesis data makes me most likely to start HRT for CVD prevention **5 or fewer (certainly less than 10) years into menopause.**
- **I recommend HRT for CVD prevention in women at high risk for CVD and low risk of breast cancer.**
- I continue it up to 10 years but work to reduce CV risk at the same time so I can consider stopping HRT sooner.

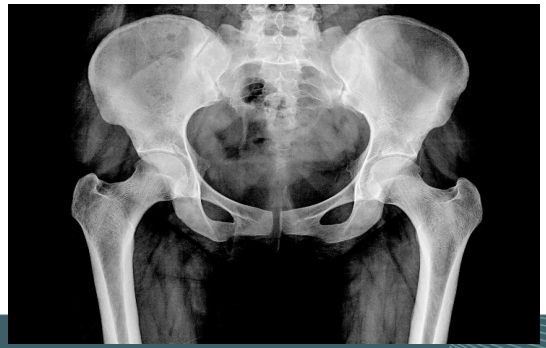
Menopausal/Postmenopausal Stage: Additional Physiologic Considerations

- Cardiovascular disease implications
- **Osteoporosis / osteopenia**
- Cognitive decline
- Skin, hair and beyond

Bone Health is Important

Menopause: Osteoporosis

- **Osteoporosis**: characterized by low bone mineral density (BMD) resulting in bone fragility & **increased fracture risk**
- Of the estimated 10 million Americans with osteoporosis, about eight million or 80% are women.
- Worldwide, 1 in 3 women over age 50 will experience osteoporotic fractures
- A woman's risk of breaking a hip is equal to her combined risk of breast, uterine and ovarian cancer.



1. What Women Need to Know - National Osteoporosis Foundation. National Osteoporosis Foundation. 2017. Available at: https://www.nof.org/preventing-fractures/general-facts/what-women-need-to-know/. Accessed April 13, 2017.
2. Iofbonehealth.org. (2017). Facts and Statistics | International Osteoporosis Foundation. [online] Available at: https://www.iofbonehealth.org/facts-statistics [Accessed 27 Jun. 2017].

Osteoporosis: What it is

- BMD measured by **dual X-ray absorptiometry (DXA, DEXA)** is the gold standard to diagnose osteoporosis
  - osteoporosis is defined as the T-score of less or equal to -2.5
  - osteopenia as the T-score between -1.0 and -2.5.

1. Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. Chronic Diseases and Translational Medicine. 2015; 1(1): 9-13
2. Nelson HD et al. Osteoporosis in Postmenopausal Women: Diagnosis and Monitoring: Summary. 2001 Feb. In: AHRQ Evidence Report Summaries. Rockville (MD): Agency for Healthcare Research and Quality (US); 1998-2005. 28.

Relationship to Menopause

- At menopause, the normal bone turnover cycle is impaired by estrogen deficiency.
- Osteoclast-mediated bone **resorption is increased** relative to osteoblast-mediated bone formation.
- After 4–8 years, a second phase is caused by **reduced bone formation.**

Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. *Chronic Dis Transl Med*. 2015;1(1):9-13. Published 2015 Mar 21. doi:10.1016/j.cdtm.2015.02.006

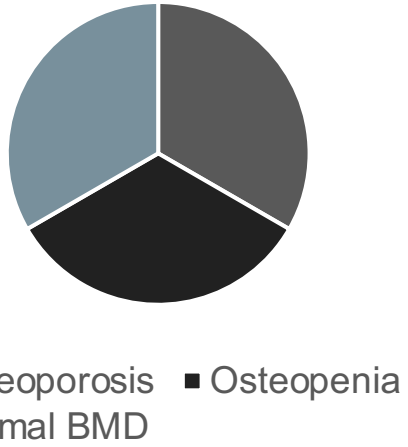
Osteoporosis and celiac disease

In CD patients, metabolic bone disease has been observed and reported in the literature for more than 70 years.

Greater Malabsorption → Greater Bone Loss

- When compared to healthy controls, even sub-clinical CD cases have lower bone mineral density.

Upon diagnosis, roughly 1/3 of adults with celiac disease already have osteoporosis, and 1/3 have osteopenia. Low bone mass has also been observed in children at CD diagnosis.



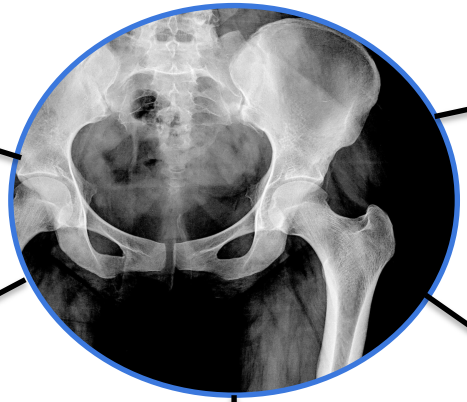
Fouda MA, Khan AA, Sultan MS, Rios LP, McAssey K, Armstrong D. Evaluation and management of skeletal health in celiac disease: position statement [published correction appears in Can J Gastroenterol Hepatol. 2017;2017:1323607]. *Can J Gastroenterol*. 2012;26(11):819-829. doi:10.1155/2012/823648 -829.

Osteoporosis Rx

Hormones?

How Estrogen Benefits Bones

Lowers the sensitivity of bone mass to PTH (parathyroid hormone), thus **reducing bone resorption**



Accelerates calcium resorption by the intestine

Increases the production of calcitonin, thus **inhibiting bone resorption**

Direct binding to **estrogen receptors**

Reduces the calcium excretion from the kidney

Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. Chronic Diseases and Translational Medicine. 2015; 1(1): 9-13

HRT & Osteoporosis Prevention

- **Estrogen is effective in the prevention of osteoporosis**
- **Menopause Hormone Therapy (MHT) has long been known to significantly increase BMD.**
  - In a meta-analysis of 57 trials (both prevention and treatment trials) which included about 10,000 women, the combined results imply that on average, the change in bone density is significantly higher in the MHT group (both opposed and unopposed estrogen) at all measurement sites.

Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. Chronic Diseases and Translational Medicine. 2015; 1(1): 9-13

It’s effective.

But should we use it?

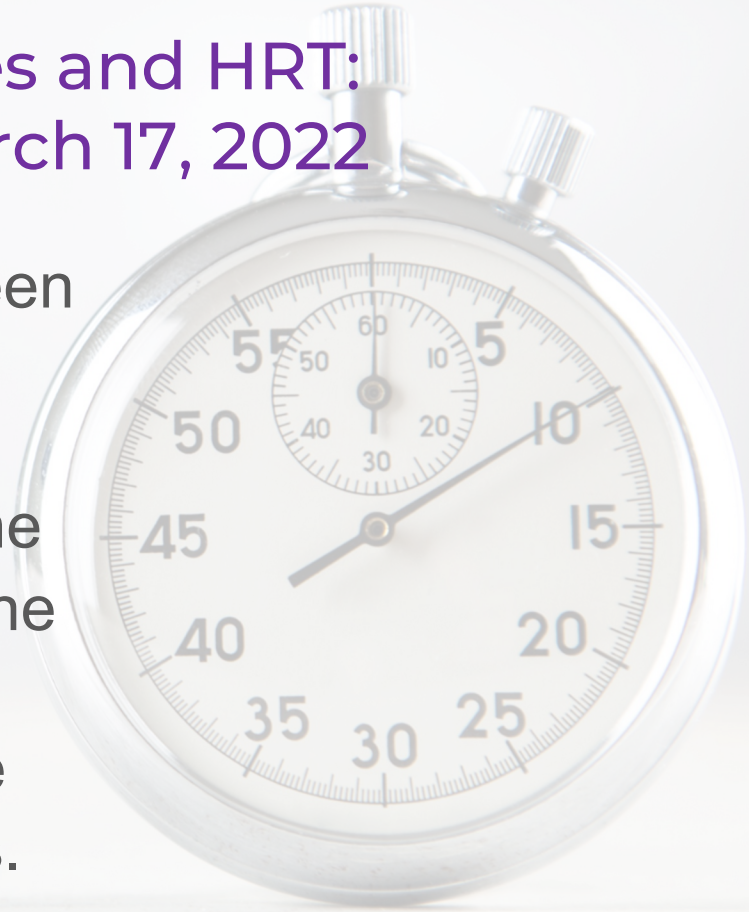
Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis?

- We provide an evidence base and guidance for the use of menopausal hormone therapy (MHT) for the maintenance of skeletal health and prevention of future fractures in recently menopausal women
- Overall, the benefit-risk profile supports MHT treatment in women who:
  - Have recently (< 10 years) become menopausal
  - Have menopausal symptoms and who are less than 60 years old with a low baseline risk for adverse events.

Rozenberg S, Al-Daghri N, Aubertin-Leheudre M, Brandi ML, Cano A, Collins P, Cooper C, Genazzani AR, Hillard T, Kanis JA, Kaufman JM, Lambrinoudaki I, Laslop A, McCloskey E, Palacios S, Prieto-Alhambra D, Reginster JY, Rizzoli R, Rosano G, Trémollieres F, Harvey NC. Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? Osteoporos Int. 2020 Dec;31(12):2271-2286. doi: 10.1007/s00198-020-05497-8.

The latest on Bones and HRT: In the press on March 17, 2022

- Estrogen Replacement has been shown to reduce the risk of fracture.
- There is strong evidence for the beneficial effect of HRT on bone health.
- However, the benefits must be considered alongside the risks.



Nash Z, Al-Wattar BH, Davies M. Bone and heart health in menopause [published online ahead of print, 2022 Mar 17]. *Best Pract Res Clin Obstet Gynaecol*. 2022;S1521-6934(22)00041-4. doi:10.1016/j.bpobgyn.2022.03.002

It’s not just about estrogen…

Hormones and Osteoporosis in Women

- Decreasing E2 levels lead to **increased bone loss.**
- Progesterone leads to **increased bone formation.**
  - Progesterone sits on specific osteoblast receptors and stimulates new osteoblasts to be made also stimulates osteoblasts to create more bone matrix. It is women's bone formation-stimulating hormone.
- Testosterone stimulates bone formation.
- Cortisol, in high levels both increases bone resorption and paralyzes bone formation by inhibiting osteoblast progesterone and testosterone effects.

Prior JC. Progesterone for treatment of symptomatic menopausal women. *Climacteric*. 2018;21(4):358-365. doi:10.1080/13697137.2018.1472567

HRT & Osteoporosis

CLINICAL TAKEAWAYS

- Estrogen is not the only hormone involved in bone health:
  - Progesterone
  - Testosterone
  - Cortisol
- Medications have side effects but are probably better than hormones in the TREATMENT of severe osteoporosis. (Opinion, JME 2023).
- Hormones are probably better than medications for the PREVENTION of osteoporosis and TREATMENT of osteopenia (Opinion, JME 2023).

Bone Support: The Role of Inflammation

Increase in C-Reactive Protein Predicts Increase in Rate of Bone Mineral Density Loss: The Study of Women's Health Across the Nation

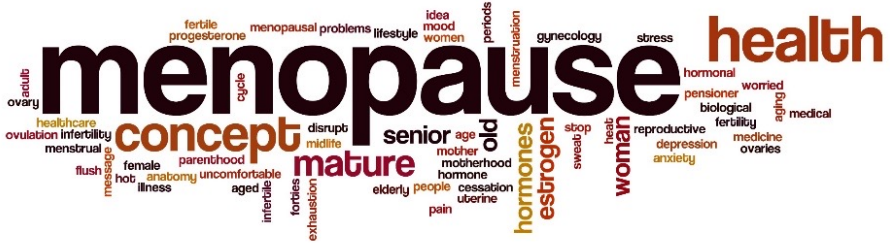
- Do larger increases in C-reactive protein predict greater amounts of subsequent bone loss in women going from pre-menopause to post-menopause?

- Increases in CRP predict faster BMD decline in the next ~2 years, but the magnitude of CRP's effect is small.
- Another reason to decrease inflammation (JME 2023)

Greendale GA, Jackson NJ, Han W, et al. Increase in C-Reactive Protein Predicts Increase in Rate of Bone Mineral Density Loss: The Study of Women's Health Across the Nation. JBMR Plus. 2021;5(4):e10480. Published 2021 Mar 16. doi:10.1002/jbm4.10480

Menopausal/Postmenopausal Stage: Additional Physiologic Considerations

- Cardiovascular disease implications
- Osteoporosis / osteopenia
- **Cognitive decline**
- Skin, hair and beyond



The Complex and Multi-Faceted Role of Estrogen and Cognition

Does estrogen deficiency cause cognitive decline?

- Human studies: many inconsistent results
- Animal studies demonstrate strong correlations between estrogen deficiency and cognitive parameters

Whether lack of estrogen is a <u>MAIN</u> contributor to age-related learning and memory losses is, at this time, not fully known

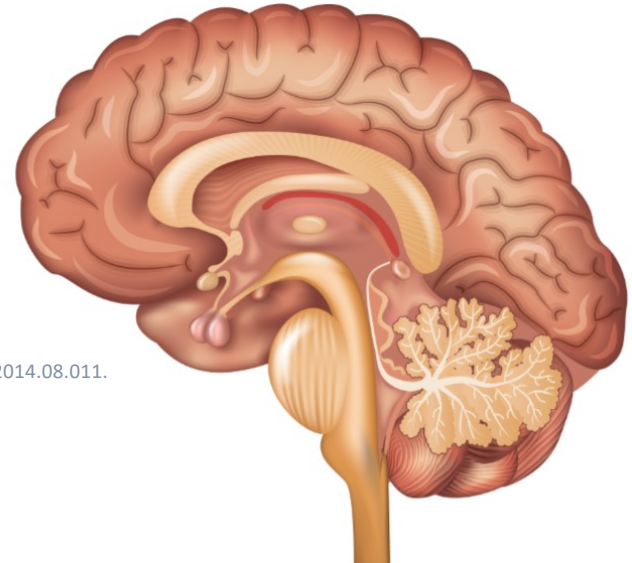
Luine VN. Estradiol and cognitive function: Past, present and future. *Hormones and behavior.* 2014;66(4):602-618. doi:10.1016/j.yhbeh.2014.08.011.

Estrogen mediation in the brain

Cognitive effects of estradiol are mediated at many sites that regulate higher order brain function

the cerebral cortex,
basal forebrain,
hippocampus and striatum

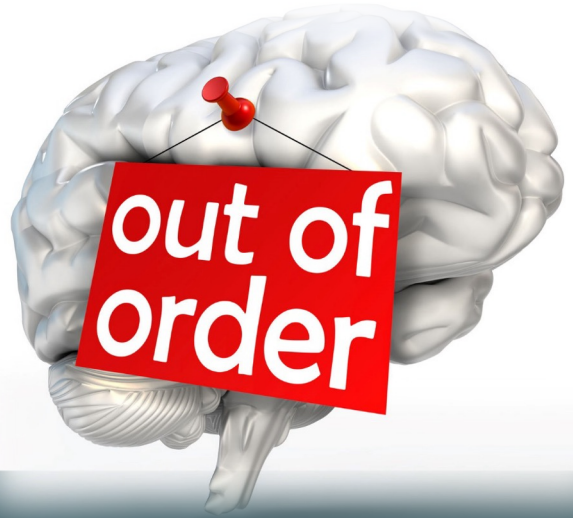
through binding to classical nuclear receptors (ERα & ERβ) in the medial prefrontal cortex and hippocampus



Luine VN. Estradiol and cognitive function: Past, present and future. *Hormones and behavior.* 2014;66(4):602-618. doi:10.1016/j.yhbeh.2014.08.011.

Estrogen affects cognition in 3 main ways

- **Classic genomic mechanisms**
- **Intra-cellular signaling mechanisms**
- **Neurosteroids**



Luine VN. Estradiol and cognitive function: Past, present and future. *Hormones and behavior.* 2014;66(4):602-618. doi:10.1016/j.yhbeh.2014.08.011.

How does estrogen affect cognition?

- **Classic genomic mechanisms:** Hormone binding to specific receptors leads to effects in target areas in the brain.
- **Intra-cellular signaling mechanisms**: More recently established that hormones, (including estradiol) can act at membrane receptors to alter cellular function.
- **Neurosteroids:** Neurons contain aromatase and can produce potent steroidal compounds (neurosteroids).
    - Accumulating, but still controversial, evidence suggests that estradiol, synthesized within the hippocampus and prefrontal cortex, may also contribute to memory consolidation

Estradiol changes brain morphology and biochemistry

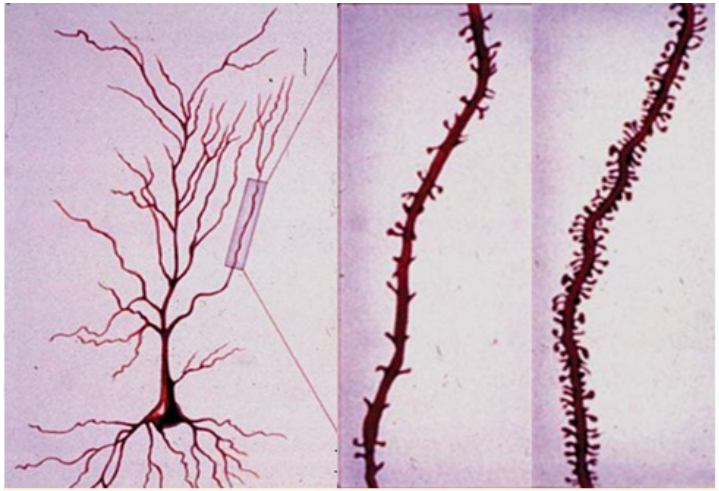
- Brain-derived neurotrophic factor (BDNF) improves memory function and increases number, size and complexity of dendritic spines.
- **Estrogens increase BDNF levels** in the PFC and hippocampus (estradiol and BDNF may work in concert to enhance cognition).

Dendritic spines are extremely responsive to both acute and chronic changes in circulating estrogen.

1. Luine V, Frankfurt M. Interactions between estradiol, BDNF and dendritic spines in promoting memory. *Neuroscience*. 2013;239:34-45. doi:10.1016/j.neuroscience.2012.10.019
2. Luine VN. Estradiol and cognitive function: past, present and future. *Horm Behav*. 2014;66(4):602-618. doi:10.1016/j.yhbeh.2014.08.011

Not just biochemistry:
Estradiol changes brain morphology

Estradiol in multiple animal studies has shown both rapid and dramatic **increases in hippocampal dendritic spine density and spine synapse density** (as well as in the **medial prefrontal cortex** of non-human primates)



Increase in rat dendritic spine densities with high estradiol levels

1. IMAGE: Psychological Reviews, Hara, Y., Waters, E. M., McEwen, B. S., & Morrison, J. H., Estrogen Effects on Cognitive and Synaptic Health Over the Lifecourse, vol. 95, 2015, pages 785-807. Prominently displayed in the article or in the figure/image legend.
2. Luine VN. Estradiol and cognitive function: Past, present and future. *Hormones and behavior.* 2014;66(4):602-618. doi:10.1016/j.yhbeh.2014.08.011.

Estrogen has biologic plausibility to be neuroprotective.

Is menopause (estrogen deficiency) neuroproblematic?

SWAN Study (2017)

- Longitudinal data from Study of Women's Health Across the Nation (SWAN); n= 2124
- For women, mental sharpness (particularly processing speed) begins to decline as early as age 50
- Mean decline in scores reflecting **cognitive speed was 5% in 10 years**

1. Anderson P. Cognitive Decline in Women Starts Midlife. *Medscape*. Jan 27 2017. http://www.medscape.com/viewarticle/875015
2. Karlamangla AS et al. Evidence for Cognitive Aging in Midlife Women: Study of Women's Health Across the Nation. Reddy H, ed. *PLoS ONE*. 2017;12(1):e0169008. doi:10.1371/journal.pone.0169008.

SWAN Study

The SWAN data suggests that the decline in estrogen may be a missing factor that contributes to cognitive decline that occurs with aging

1. Anderson P. Cognitive Decline in Women Starts Midlife. *Medscape*. Jan 27 2017. http://www.medscape.com/viewarticle/875015
2. Karlamangla AS et al. Evidence for Cognitive Aging in Midlife Women: Study of Women's Health Across the Nation. Reddy H, ed. *PLoS ONE*. 2017;12(1):e0169008. doi:10.1371/journal.pone.0169008.

Menopause and cognitive complaints: Are ovarian hormones linked with subjective cognitive decline? (2021)

- 19 studies were analyzed.
- Findings: cognitive complaints increased during menopause.
- **Clinicians should be aware of cognitive issues during menopause or after ovarian hormone loss. They might presage future cognitive decline.**

Reuben R, Karkaby L, McNamee C, Phillips NA, Einstein G. Menopause and cognitive complaints: are ovarian hormones linked with subjective cognitive decline? *Climacteric*. 2021;24(4):321-332. doi:10.1080/13697137.2021.1892627

Does replacing estrogen help?

Hormones & the Brain

- Both gonadal and adrenal hormones appear to impact cognition

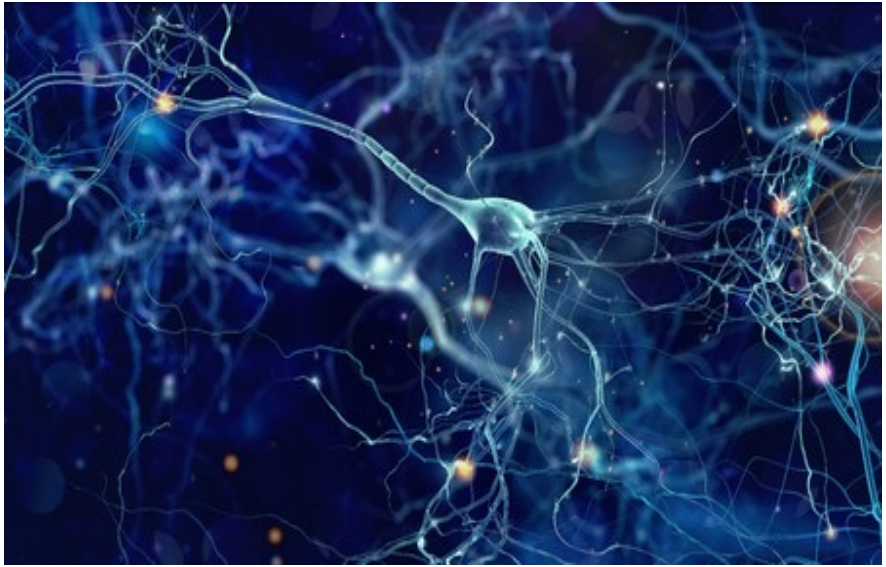
- **Chronic treatments with estrogen alter the major neuronal systems of the brain** including, but not limited to, cholinergic, monoaminergic, GABAnergic and glutaminergic neurons in both animals and humans

Frankfurt M, Luine V. The evolving role of dendritic spines and memory: interaction(s) with estradiol. Hormones and behavior. 2015;74:28-36. doi:10.1016/j.yhbeh.2015.05.004.

Estrogenic and BDNF control of synaptic connectivity

Neuroscience Review (2013)

- The authors hypothesize that dendrite spine formation and stabilization in support of synapse and circuit plasticity occur due to rapid, non-genomic **17β-estradiol and acute BDNF signal working together.**



Srivastava DP, Woolfrey KM, Evans PD. Mechanisms underlying the interactions between rapid estrogenic and BDNF control of synaptic connectivity. Neuroscience. 2013 Jun 3;239:17-33. doi: 10.1016/j.neuroscience.2012.12.004.

During menopause, an interference in estrogen homeostasis leads to the dysregulation of BDNF−5-HT2A signaling and weakens synaptic plasticity.

The combination of these factors **predispose the brain to a susceptible state for depression** (and cognitive impairment?)

Chhibber A, Woody SK, Karim Rumi MA, Soares MJ, Zhao L. Estrogen receptor β deficiency impairs BDNF-5-HT(2A) signaling in the hippocampus of female brain: A possible mechanism for menopausal depression. Psychoneuroendocrinology. 2017 Aug;82:107-116. doi: 10.1016/j.psyneuen.2017.05.016.

Estrogen: Other brain benefits

(METABOLIC, MITOCHONDRIAL, OXIDATIVE)

Estrogen improves cerebral metabolic rate and blood flow.

- Estrogen therapy increased PFC blood oxygenation levels during tests of verbal and spatial working memory, and this increase was associated with fewer errors

Hara Y, Waters EM, McEwen BS, Morrison JH. Estrogen Effects on Cognitive and Synaptic Health Over the Lifecourse. *Physiol Rev*. 2015;95(3):785-807. doi:10.1152/physrev.00036.2014.

Estrogen: Other brain benefits

(METABOLIC, MITOCHONDRIAL, OXIDATIVE)

- **Estradiol reduces formation of reactive oxygen species (ROS)**, which damage DNA, RNA, proteins, and lipids, and can induce cell death.
    - Mitochondrial dysfunction and damage accrued from oxidative stress precede, and may cause, neurodegenerative disorders such as Alzheimer's disease.

Hara Y, Waters EM, McEwen BS, Morrison JH. Estrogen effects on cognitive and synaptic health over the lifecourse. *Physiol Rev*. 2015;95(3):785-807. doi:10.1152/physrev.00036.2014

Is there biologic plausibility that replacing estrogen helps?

YES

The Guidelines

2017 NAMS Update

Initial statement

NAMS recommended against hormone replacement therapy at any age to prevent or treat a decline in cognitive function or dementia

However…

Hormone therapy is approved for women with premature menopause for prevention of bone loss, **cognition** and mood changes, and heart disease.

The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017 Jun 22. doi: 10.1097/GME.0000000000000921.

But let’s dig deeper:

HRT, cognitive decline, & the Critical Period Hypothesis

- Previous studies of HRT in Alzheimer's disease and the WHI study (women aged 65 years and older and at least 15 years past normal menopause), which used conjugated equine estrogens, did not improve cognitive functioning

- Other randomized clinical trials with 17β-estradiol near the onset of menopause have showed beneficial effects of treatment on verbal and working memory

- **Investigators have posited that a critical period or window of opportunity may exist for positive estrogen effects (Critical Period Hypothesis)***

**Results of other studies have not supported the critical period hypothesis, however, CEE was utilized in most*

Sound Similar?

- **Timing Hypothesis**
  - CVD
- **Critical Period Hypothesis**
  - Cognition

Does estradiol treatment at middle age enhance memory in old age?

- **Critical Period Hypothesis**: for estrogens to exert positive effects on neural functioning, hormonal replacements must be given close to the initiation of menopause.
- Some evidence has indicated that even a short period of treatment, given around menopause, might confer long-term benefits.
    - Bagger et al. (2005) found that treatment with **ET for 2 to 3 years around menopause decreased risk of cognitive impairments 5–15 years later by 64%**

1. Bagger YZ et al.; PERF Study Group. Early postmenopausal hormone therapy may prevent cognitive impairment later in life. Menopause. 2005 Jan-Feb;12(1):12-7.
2. Luine VN. Estradiol and cognitive function: Past, present and future. Hormones and behavior. 2014;66(4):602-618. doi:10.1016/j.yhbeh.2014.08.011.

The Menopause and Hormonal Aging Study Group of France and the National College of French Gynecologists and Obstetricians

- **Menopause hormone therapy and cognition. Postmenopausal women management: CNGOF and GEMVi Clinical Practice Guidelines**
  - The WHI reported a doubling of the risk of Alzheimer's disease in women given HRT
  - 17-beta estradiol and bio-identical progesterone are very different from the hormones used in the WHI
  - **It can now be stated that if MHT is started within the window of opportunity (i.e. before the age of 60 or within the first 10 years after the beginning of menopause) no deleterious effect on cognition is observed.**

André G. Traitement hormonal de la ménopause et cognition. RPC Les femmes ménopausées du CNGOF et du GEMVi [Menopause hormone therapy and cognition. Postmenopausal women management: CNGOF and GEMVi clinical practice guidelines]. Gynecol Obstet Fertil Senol. 2021 May;49(5):448-454. French. doi: 10.1016/j.gofs.2021.03.029.

Don’t forget about progesterone.

Progesterone and Brain Function

- Progesterone is neuroprotective, reduces edema and reduces secondary neuronal degeneration after injury. There is some conflicting evidence about its ability to reduce mortality and disability after TBI.
- Progesterone activates MAP-kinase which is anti-apoptotic.
- MPA (medroxyprogesterone acetate) is not only not neuroprotective, but when co-administered cancelled the beneficial effects of estradiol.
- Progesterone promotes myelin.

See References: Progesterone and Brain Function

References: Progesterone and Brain Function

Progesterone is neuroprotective, reduces edema and reduces secondary neuronal degeneration after injury:

1. Deutsch ER, Espinoza TR, Atif F, Woodall E, Kaylor J, Wright DW. Progesterone's role in neuroprotection, a review of the evidence. *Brain Res*. 2013;1530:82-105. doi:10.1016/j.brainres.2013.07.014
2. Ma J, Huang S, Qin S, You C, Zeng Y. Progesterone for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2016;12(12):CD008409. Published 2016 Dec 22. doi:10.1002/14651858.CD008409.pub4

Progesterone activates MAP-kinase which is anti-apoptotic:

1. Peluso JJ, Bremner T, Fernandez G, Pappalardo A, White BA. Expression pattern and role of a 60-kilodalton progesterone binding protein in regulating granulosa cell apoptosis: involvement of the mitogen-activated protein kinase cascade. *Biol Reprod*. 2003;68(1):122-128. doi:10.1095/biolreprod.102.007542
2. Nilsen J, Brinton RD. Impact of progestins on estradiol potentiation of the glutamate calcium response. *Neuroreport*. 2002;13(6):825-830. doi:10.1097/00001756-200205070-00018

Progesterone promotes myelin. This effect is blocked by mifepristone:

1. Ghoumari AM, Baulieu EE, Schumacher M. Progesterone increases oligodendroglial cell proliferation in rat cerebellar slice cultures. *Neuroscience*. 2005;135(1):47-58. doi:10.1016/j.neuroscience.2005.05.023
2. Ghoumari AM, Ibanez C, El-Etr M, et al. Progesterone and its metabolites increase myelin basic protein expression in organotypic slice cultures of rat cerebellum. *J Neurochem*. 2003;86(4):848-859. doi:10.1046/j.1471-4159.2003.01881.x

What about giving P?

Cognitive Effects of Estrogen and Progesterone

RCT, n=29 women ages 45-55 years were given oral estradiol or progesterone counterbalanced with placebo for 12 weeks. Functional MRI and neuropsychological measures used to assess verbal and visual cognitive function.

When compared to placebo

- Estradiol treatment group had greater improvements associated with verbal processing
- Progesterone treatment group had greater improvements in regional brain activation with visual memory.

Conclusion: While not every cognitive task showed statistically significant improvement, progesterone and estrogen HRT may be associated with cognitive benefit in postmenopausal women.

Berent-Spillson A, Briceno E, Pinsky A, et al. Distinct cognitive effects of estrogen and progesterone in menopausal women. *Psychoneuroendocrinology*. 2015;59:25–36. doi:10.1016/j.psyneuen.2015.04.020

Depression and Memory

Hormone replacement therapy improves mood and depression.

Cognitive function can be improved by hormone replacement only in case of an early start (critical window hypothesis, healthy cell bias hypothesis).

On the contrary, at the age over 65, it increases the risk of dementia. The same dependence applies to Alzheimer's disease.

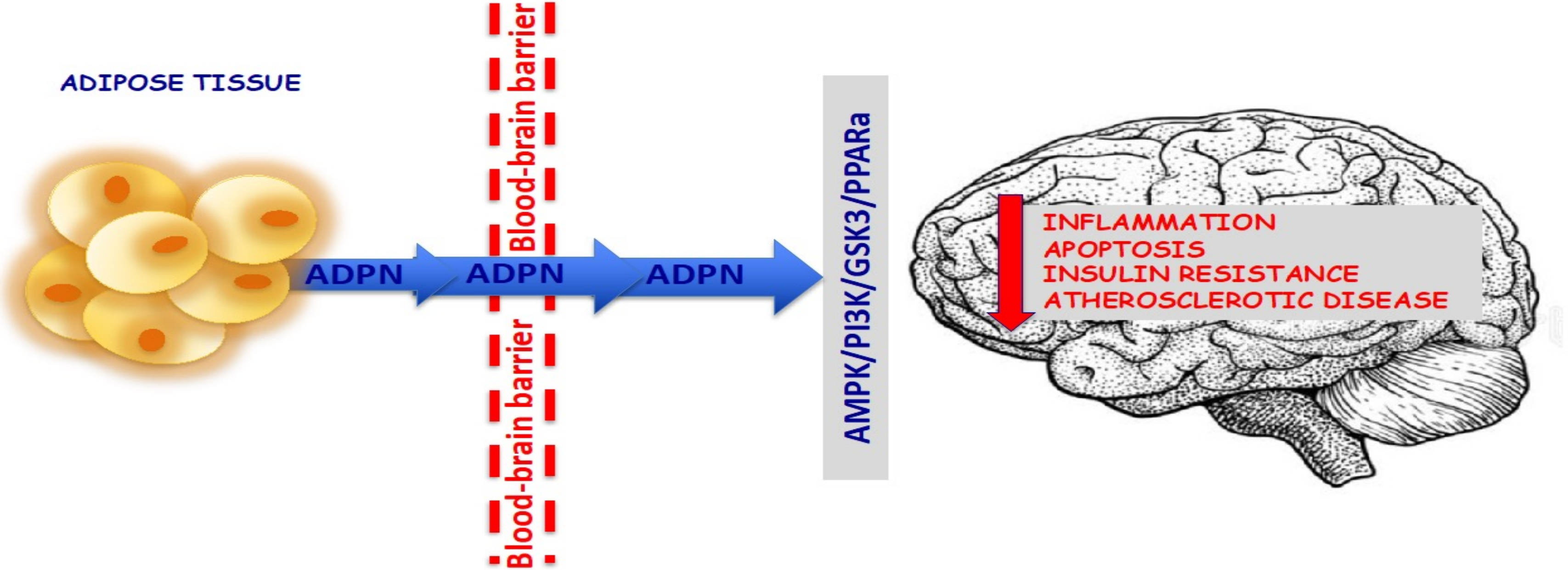
Fait T. Menopause hormone therapy: latest developments and clinical practice. *Drugs Context*. 2019;8:212551. Published 2019 Jan 2. doi:10.7573/dic.212551

What else can you do? Increase adiponectin!

Adiponectin and Cognitive Decline

- Adiponectin is a protein that is secreted by adipose tissue that is anti-diabetic, increases insulin sensitivity, anti-inflammatory, and anti-atherogenic.
- Adipose tissue that is too full of fat makes less adiponectin.
- It crosses the BBB.
- Many studies described associations between ADPN and all-cause dementia, MCI, AD, VD and their **clinical progression**.

Rizzo MR, Fasano R, Paolisso G. Adiponectin and Cognitive Decline. *Int J Mol Sci*. 2020;21(6):2010. Published 2020 Mar 16. doi:10.3390/ijms21062010



Rizzo, M. R., Fasano, R., & Paolisso, G. (2020). Adiponectin and Cognitive Decline. *International journal of molecular sciences*, *21*(6), 2010.

HRT & Cognition

CLINICAL TAKEAWAYS

- Guidelines say **NO**!
- **Biological plausibility and literature support the use of both E2 and bio-identical P early in menopause.**
  - Remember this even in patients **without a uterus** that have cognitive decline as their priority.
- I always use both E2 and P
- Reduce VAT to increase adiponectin and decrease inflammation.

HRT Decision Tree

- **Menopausal Sx Present:**
  - Treat with or without HRT (or use both)
- **At Risk for, or concerned about, CVD, CD, Osteoporosis**
  - Reduce risk with or without HRT (or both)
- **Diagnosis of CVD, CD, Osteoporosis**
  - Treat with or without HRT (or both)
- **Desire for Optimal Health/Aging**
  - Make the FM Matrix “hum” and possibly add HRT

USPSTF on Timing of HRT:

- A major point of discussion in recent years has been whether the overall net benefit of hormone therapy use may be increased if it is started early during menopause (ie, the “timing hypothesis”).
- This hypothesis proposes that hormone therapy given at or soon after menopause reduces the risks of cardiovascular disease, mortality, and dementia but that the potential beneficial effects will be attenuated or not experienced when hormone therapy is initiated several years after menopause.

Gartlehner G, Patel SV, Reddy S, Rains C, Schwimmer M, Kahwati L. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force [published correction appears in JAMA. 2023 Mar 21;329(11):943]. *JAMA*. 2022;328(17):1747-1765. doi:10.1001/jama.2022.18324

USPSTF on Timing of HRT:

Current evidence, however, does not confirm beneficial effects of timing of initiation.

Gartlehner G, Patel SV, Reddy S, Rains C, Schwimmer M, Kahwati L. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force [published correction appears in JAMA. 2023 Mar 21;329(11):943]. *JAMA*. 2022;328(17):1747-1765. doi:10.1001/jama.2022.18324

All of the professional societies recommend using HRT for treatment of menopausal symptoms at the lowest possible dose and for the shortest period of time.

I have shown you the benefits of HRT for the heart, bones and brain.

There is universal agreement that it successfully treats menopausal symptoms.

You must decide about pursuing HRT.

NAMS 2022 SUMMARY STATEMENT

- The critical window or timing hypothesis holds that estrogen can confer cognitive benefits if given early in the menopause transition, but that later use is neutral or detrimental.
- The healthy-cell bias hypothesis holds that estrogen confers cognitive benefits when the neural substrate is “healthy” but not diseased, for example in a woman with DM.

The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

NAMS 2022 SUMMARY STATEMENT

- The risk of breast cancer related to hormone therapy use is low, (less than one additional case per 1,000 women per year of hormone therapy use or three additional cases per 1,000 women when used for 5 years with CEE plus MPA).

The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

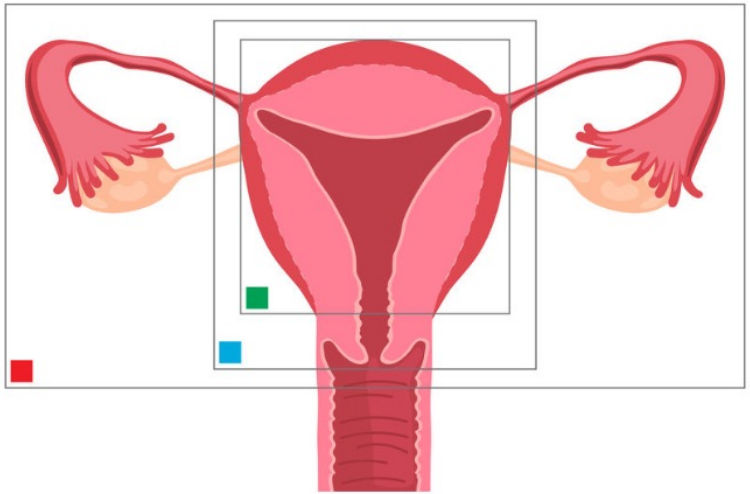
Hysterectomy

FxMed consideration:
Are ovaries left behind functioning normally?

Does hysterectomy with ovarian preservation affect ovarian function?

- Hysterectomy may impair ovarian blood supply and function

Menopause occurs on average
years earlier after hysterectomy



Xiangying H, Lili H, Yifu S. The effect of hysterectomy on ovarian blood supply and endocrine function. Climacteric. 2006 Aug;9(4):283-9.

Surgery Summary

- Wwomen that have had their ovaries removed before menopause are candidates for HRT until at least age 52.
- Women that had a hysterectomy with ovarian preservation are at risk for early menopause and should be monitored.

Normalize Blood Sugar

Dysglycemia in Postmenopause

- Cognitive impairment in postmenopausal women may also be related to elevated blood sugar
    - Recent study of over 2,000 post-menopausal women in Denmark found that **risk for developing cognitive dysfunction was 44% greater** in those with impaired fasting glucose
    - In women diagnosed with IR there was a **47% increased risk for cognitive dysfunction.**
- These associations could indicate that a significant proportion of dementia cases in women is likely to be preventable by effective prevention and control of insulin homeostasis.

Neergaard JS et al. Metabolic Syndrome, Insulin Resistance and Cognitive Dysfunction: Does your metabolic profile affect your brain? Diabetes. 2017 Apr 7. doi: 10.2337/db16-1444.

Reduce Stress

Yoga and medication can modulate cellular aging

After 12 weeks of a yoga and meditation based lifestyle intervention:

- mean levels of 8-OH2dG, ROS, cortisol, and IL-6 were significantly decreased
- mean levels of telomerase activity, β-endorphin, BDNF, and sirtuin-1 were significantly increased

Tolahunase M, Sagar R, Dada R. Erratum to "Impact of Yoga and Meditation on Cellular Aging in Apparently Healthy Individuals: A Prospective, Open-Label Single-Arm Exploratory Study". Oxid Med Cell Longev. 2017;2017:2784153. doi: 10.1155/2017/2784153.

Several previous animal and clinical studies showed an association between elevated cortisol and poor cognitive performance

Hypercortisolism is associated with poorer memory performance, independently of life events.

Ouanes S, Castelao E, Gebreab S, von Gunten A, Preisig M, Popp J. Life events, salivary cortisol, and cognitive performance in nondemented subjects: a population-based study. Neurobiol Aging. 2017 Mar;51:1-8. doi: 10.1016/j.neurobiolaging.2016.11.014.

Mindfulness-Based Stress Reduction

- In a randomized controlled clinical trail, participants (n=197) were asked to participate in 40-minute daily MBSR techniques such as **sitting and walking meditations, yoga, and guided body scans** for 8 weeks.
- Significant reduction in menopausal symptom scores even 6 months post intervention was observed verses active controls.
    - Specifically, a reduction in **anxiety** and **depression** symptoms.

Wong C, Yip BH, Gao T, et al. Mindfulness-Based Stress Reduction (MBSR) or Psychoeducation for the Reduction of Menopausal Symptoms: A Randomized, Controlled Clinical Trial. *Sci Rep*. 2018;8(1):6609. Published 2018 Apr 26. doi:10.1038/s41598-018-24945-4

Be aware of dairy

Dairy consumption at age 20 was associated with an increased risk of hip fracture in old age.

Further, metabolism of dietary protein in dairy products causes increased urinary excretion of calcium.

Cumming RG, Klineberg RJ. Case-control study of risk factors for hip fractures in the elderly. Am J Epidemiol. 1994 Mar 1;139(5):493-503.

Menopausal/Postmenopausal Stage:

The Major Physiologic Considerations

- Cardiovascular disease implications
- Osteoporosis / osteopenia
- Cognitive decline
- **Skin Hair and Beyond**

Skin, hair and beyond: the impact of menopause

- Skin is an endocrine organ and produces estrogens, androgens, and cortisol.
- Skin collagen levels rapidly decrease by about 30% within the first 5 years of menopause and continue to decline by 2.1% each year after. Skin thickness continues to reduce on average by 1.1% each year post-menopause.
- 64% of women from a menopause clinic reported skin problems with at least half reporting that menopause initiated changes in skin. (n=87)
- Skin and mucosal menopausal symptoms
    - dryness & pruritus
    - thinning & atrophy
    - wrinkles & sagging
    - poor wound healing
    - reduced vascularity

Zoubouli CC, Stamatiadis AD, Kosmadaki M, Roö E, Vexiau-Robert D, Kerob D, Goldstein SR. Skin, hair and beyond: the impact of menopause. Climacteric. 2022 Apr 4:1-9

Skin, hair and beyond: the impact of menopause

- Hair related menopausal symptoms include
  - reduced hair growth and density on the scalp
    - (diffuse effluvium and/or androgenetic alopecia of female pattern)
  - altered hair quality and structure
  - increased unwanted hair growth on facial areas

Zouboulis CC, Chen W, Thornton MJ, Kosmadaki M, Roö E, Vexiau-Robert D, Kerob D, Goldstein SR. Skin, hair and beyond: the impact of menopause. Climacteric. 2022 Apr 4:1-9

Skin, hair and beyond: the impact of menopause

- HRT is not recommended for skin and hair symptoms alone.
- Bringing awareness to the dramatic effects of hormonal changes within the skin and hair may help improve quality of life.

- The skin aging process might be accelerated by menopause. Teaching holistic skin care practices including nutrition, stress reduction and healthy cosmetic practices may also help.

Zouboulis CC, Blume-Peytavi U, Kosmadaki M, et al. Skin, hair and beyond: the impact of menopause. Climacteric. 2022;25(5):434-442. doi:10.1080/13697137.2022.2050206

DR. HYMAN+

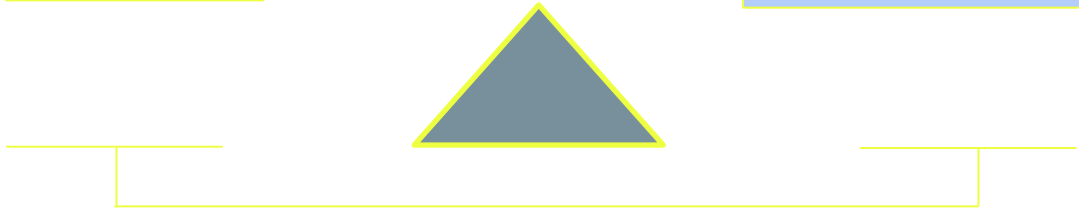
Menopause and the HRT Decision Tree: The Decision

Before starting HRT you must decide if it is appropriate for you!

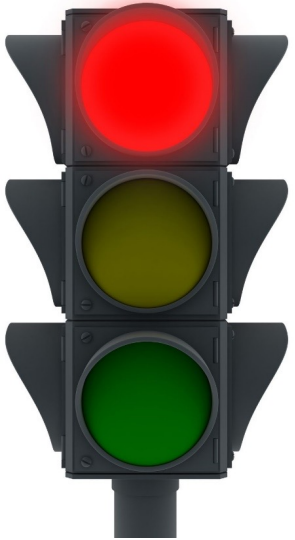
HRT Risks and Benefits

Risks
Endometrial Cancer?
Breast Cancer?

Benefits
Bone Mineral Density
Relief of Menopause Symptoms
CV Health?
Cognition?



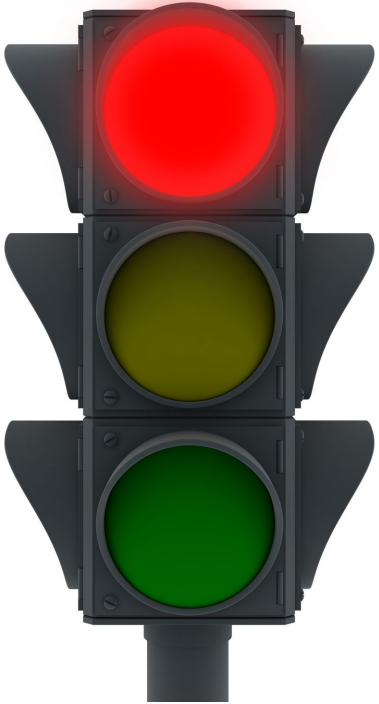
- **Women at high risk and/or have classic contraindications:**
  - **“Red light”**
- **Women where there are questions:**
  - **“Yellow light”**
- **Candidates with minimal risk**
  - **“Green light”** to prescribe HRT



The Red Light:

HRT not advisable

Classic Contraindications



Treatment of Symptoms of Menopause: An Endocrine Society Clinical Practice Guideline

According to the Endocrine Society, estrogen replacement therapy should not be used in women with any of the following conditions:

- Abnormal genital bleeding
- Known, suspected, or history of cancer of the breast
- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism, or history of these conditions
- Active arterial thromboembolic disease
- Known anaphylactic reaction or angioedema in response to any ingredient in the medication
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency
- other known thrombophilia
- Known or suspected pregnancy

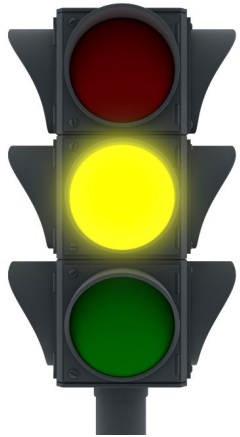
Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(11):3975-4011. doi:10.1210/jc.2015-2236

The Yellow Light

- **There are degrees of yellow!**
  - My interpretation doesn't have to be everyone's interpretation.
- **This is exciting!**
- **This is where individualization and understanding is critical.**

The Yellow Light

- **Women with increased risk of breast cancer:**
  - FM and Lifestyle
    - BMI, Abn Blood Sugar, Abn E Metabolism or Methylation
  - Elevated baseline estradiol
  - Dense breasts on mammography
- **Genetics:**
  - Strong family history of breast cancer
  - Genetics of estrogen metabolism and detoxification
  - Genetics of breast cancer risk
  - **WE ALL HAVE TO ASSESS RISK!**



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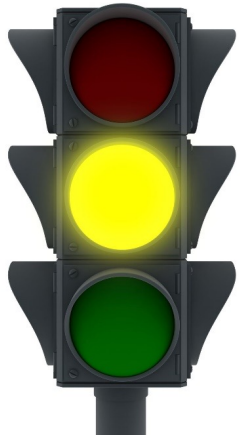

Lifestyle risk: Individualize!

- Do you start HRT and then work to lower risk?
- Do you normalize risk factors as much as possible and then start HRT?
- **You decide.**

The Yellow Light

- **Women with increased risk of breast cancer:**
  - FM and Lifestyle
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  - Dense breasts on mammography
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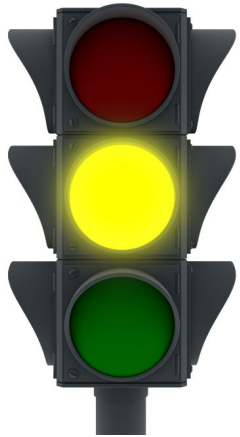
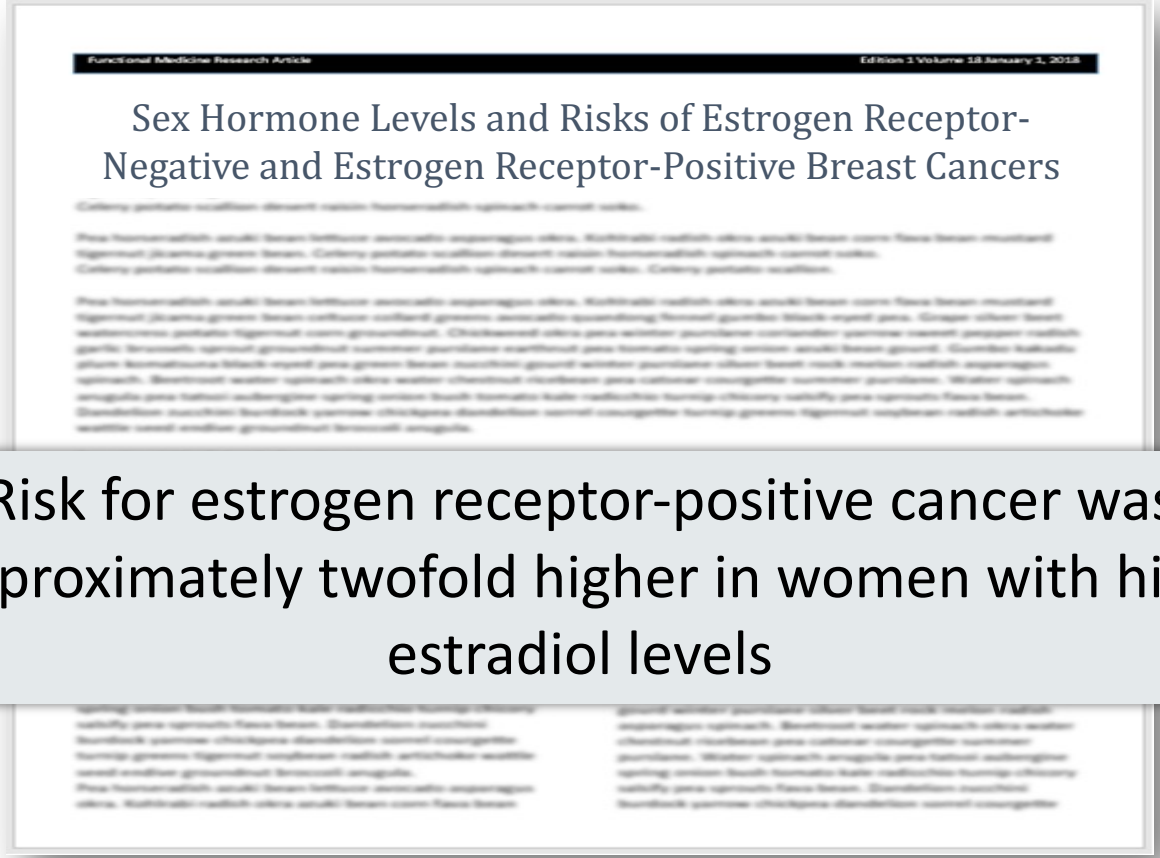




Risk for estrogen receptor-positive cancer was approximately twofold higher in women with high estradiol levels

Farhat GN, Cummings SR, Chlebowski RT, et al. Sex hormone levels and risks of estrogen receptor-negative and estrogen receptor-positive breast cancers. J Natl Cancer Inst. 2011 Apr 6;103(7):562-70. doi: 10.1093/jnci/djr031

Sex Hormone Levels and Risk of Breast Cancer with Estrogen Plus Progestin

Measurement of sex hormone levels to characterize breast cancer risk associated with E+P could inform risk–benefit ratio discussions, potentially providing a ***personalized approach to clinical decision making.***

Farhat GN, Parimi N, Chlebowski RT, et al. Sex hormone levels and risk of breast cancer with estrogen plus progestin. *J Natl Cancer Inst*. 2013;105(19):1496–1503. doi:10.1093/jnci/djt243

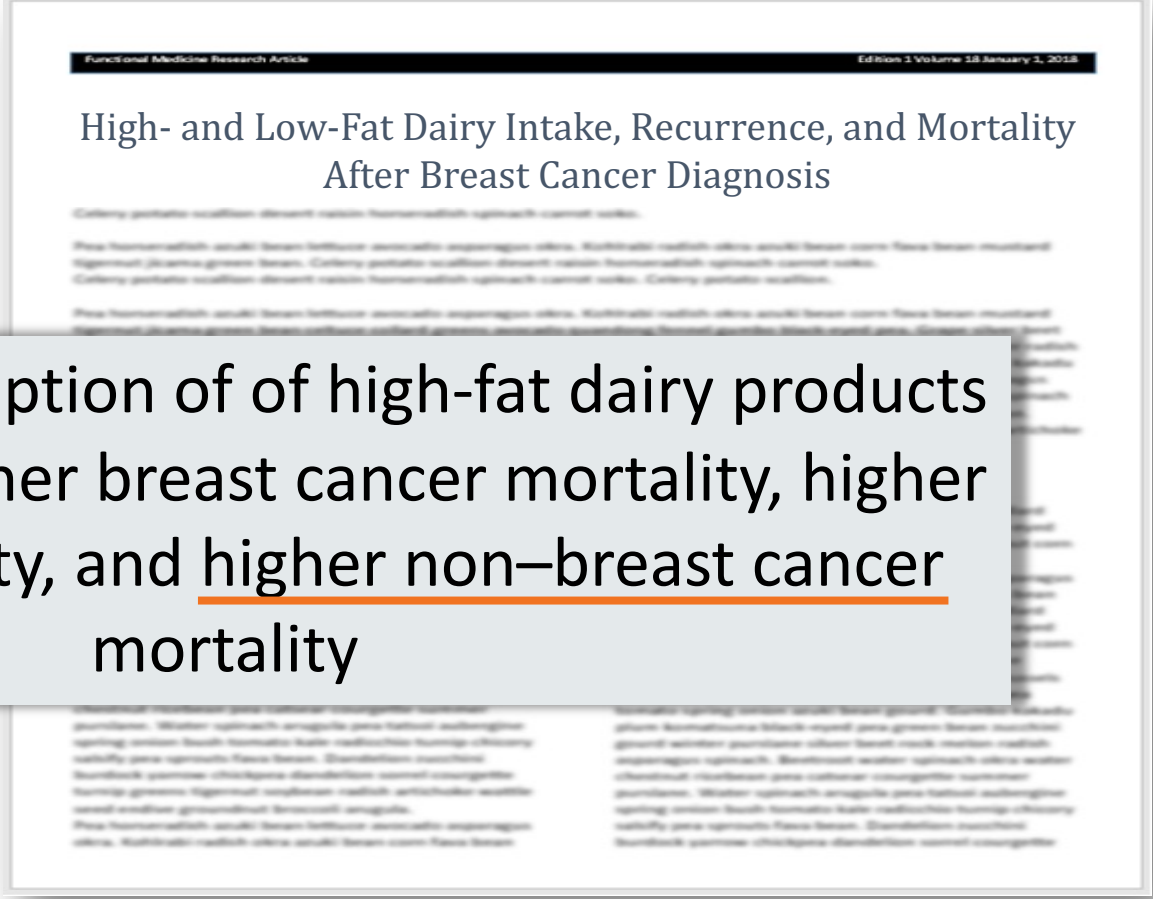
How do we reduce E2 Levels?

- Decrease VAT
- Decrease Inflammation
- Decrease Insulin
- Decrease Stress
- Improve Detoxification
- Increase SHBG
- Decrease Dairy (Whole Milk)

Modern Milk

Since the 1920's, commercial dairies have lactating cows through most of their subsequent pregnancies. Milk from these cows contain high levels of estrogen and other hormones.

Shaw J. Modern Milk. Harvard Magazine. https://harvardmagazine.com/2007/05/modern-milk.html. Published November 14, 2017.v



Increasing consumption of of high-fat dairy products was related to higher breast cancer mortality, higher all-cause mortality, and higher non–breast cancer mortality

Kroenke CH, Kwan ML, Sweeney C, Castillo A, Caan BJ. High- and low-fat dairy intake, recurrence, and mortality after breast cancer diagnosis. *J Natl Cancer Inst*. 2013;105(9):616-623. doi:10.1093/jnci/djt027

Dietary Fat Intake: Associations with Dietary Patterns and Postmenopausal Breast Cancer

A Case-Control Study (March 2022)

- This paper validates the previous association between higher dietary fat intake and increased incidence of breast cancer in peri- and postmenopausal women.
- In the percentage energy from fat > 32% sub-group, breast cancer occurrence was 3 times higher.

Conclusion:

- Frequent consumption of minimally processed plant foods and fish and moderate consumption of **low-fat dairy should be recommended.**

Stasiewicz B, Wadolowska L, Biernacki M, Slowinska MA, Stachowska E. Dietary Fat Intake: Associations with Dietary Patterns and Postmenopausal Breast Cancer-A Case-Control Study. *Cancers (Basel)*. 2022;14(7):1724. Published 2022 Mar 28.

The Yellow Light

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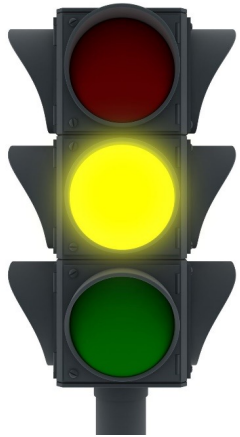


Mammographic breast density is a well-established and a strong predictor of breast cancer risk

Women with 75% or greater percent density (proportion of the breast that appears dense on the mammogram out of the total breast area) are at 4-6 times greater risk of breast cancer.

Yaghjyan L, Colditz GA, Rosner B, Tamimi RM. Mammographic breast density and breast cancer risk by menopausal status, postmenopausal hormone use and a family history of breast cancer. Cancer Causes Control. 2012 May;23(5):785-90. doi: 10.1007/s10552-012-9936-7.

The risk of breast cancer increased significantly as breast density increased (>50 % vs.< 10 %: OR=3.74)

Breast cancer risk increased with increasing breast density regardless of family history (OR = 4.00 in women with a family history vs. 3.71 in women without a family history).

Yaghjyan L, Colditz GA, Rosner B, Tamimi RM. Mammographic breast density and breast cancer risk by menopausal status, postmenopausal hormone use and a family history of breast cancer. Cancer Causes Control. 2012 May;23(5):785-90. doi: 10.1007/s10552-012-9936-7.

A
Functional Medicine
Explanation...
Density REFLECTS
Function

COMT Status Affects Steroid Hormone Levels

A product of COMT, 2-methoxyestradiol, may exert anti-tumorigenic activity.

It is **plausible that COMT activity could be associated with steroid hormone levels, thereby affecting mammographic density**

COMT Val158Met polymorphism reduces COMT activity and may be associated with mammographic density at least in healthy women.

Menopausal status and hormone replacement therapy should be considered in future studies to avoid masking of the underlying effects.

Kallionpää RA, Uusitalo E, Peltonen J. Association of Catechol-O-methyltransferase polymorphism Val158Met and mammographic density: A meta-analysis. *Gene*. 2017;624:34-42. doi:10.1016/j.gene.2017.04.049

Breast Density and Breast Cancer Link

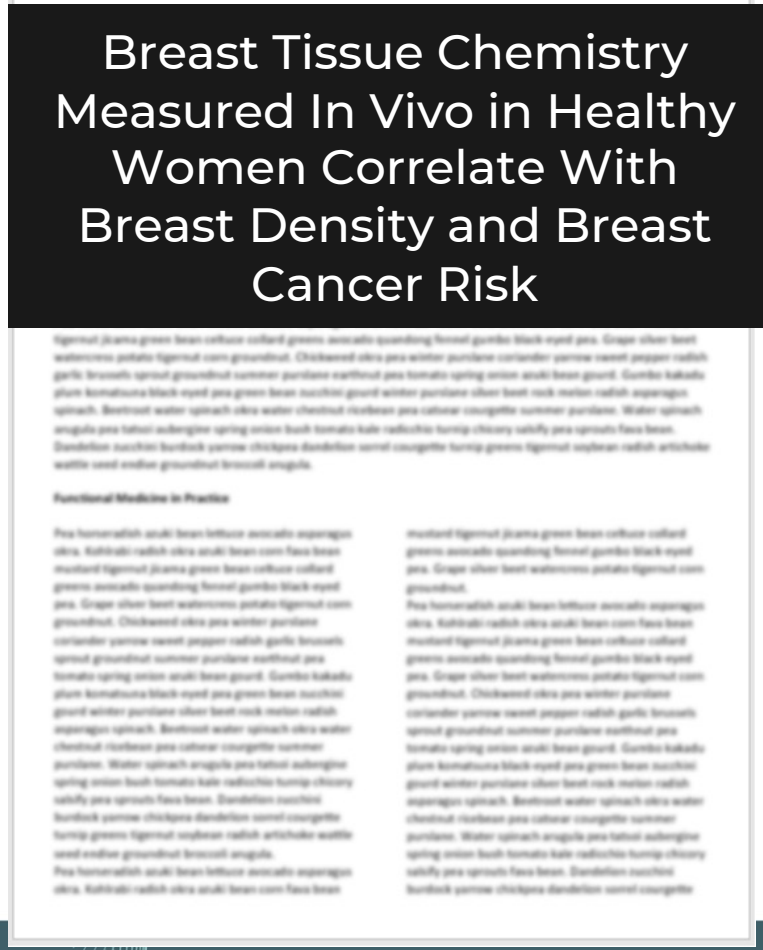
- There is evidence showing breast density in post-menopausal women is associated with a pro-inflammatory microenvironment.
- **High density (HD) breasts** showed the most active metabolic and lipid profile.
- High mammographic density is associated with protumor inflammation.

In summary, high breast density is associated with a significantly more active tissue chemistry.
This might offer an explanation as to why women with dense breasts are more likely to develop cancer.

Santamaría G, Naude N, Watson J, et al. Breast tissue chemistry measured in vivo in healthy women correlate with breast density and breast cancer risk. *J Magn Reson Imaging*. 2022;56(5):1355-1369. doi:10.1002/jmri.28168

This really speaks to *Functional* Medicine...

Breast Tissue Chemistry Measured In Vivo in Healthy Women Correlate With Breast Density and Breast Cancer Risk



Editorial from MSKCC

In both low-risk postmenopausal women and high-risk premenopausal women there is an increased risk of breast cancer if the woman has high density breast tissue.

Explanation to discuss: High breast density is associated with more active breast tissue chemistry

Katja P, Sunitha T. Editorial for "Breast Tissue Chemistry Measured In Vivo in Healthy Women Correlate With Breast Density and Breast Cancer Risk" [published online ahead of print, 2022 Apr 13]. *J Magn Reson Imaging*. 2022;10.1002/jmri.28201. doi:10.1002/jmri.28201

What I do for dense breasts:

- Check E2 levels and normalize them as previously stated.
- Improve E2 and other detoxification pathways
- Borage Oil and EPO
- Reduce Inflammation
- Iodine

Iodine and Breast Inflammation

There is a growing body of evidence that **iodine** can be used to treat and prevent bacterial and viral invasion of the ductal system

Iodine and the Breast

- Is an antioxidant and anti-proliferative agent.
- Is another dietary factor that lowers Asian breast cancer risk. A combination of soy and **iodine as seaweed** was shown to lower estrogen levels and increase 2/16OH estrogens.
- I^2 decreases size and number of benign and malignant breast tumors in animals.
- Is incorporated into anti-proliferative iodolactones in thyroid and breast.
- Is a contact antiseptic, avoiding oxidative mechanisms of the immune system.
- Iodine increases stem cell differentiation via NOTCH (a stem cell regulator) upregulation.

See References: Iodine and the Breast

References: Iodine and the Breast

1. Aceves C, Anguiano B, Delgado G. Is iodine a gatekeeper of the integrity of the mammary gland? J Mammary Gland Biol Neoplasia. 2005 Apr;10(2):189-96.
2. Teas J, Hurley TG, Hebert JR, Franke AA, Sepkovic DW, Kurzer MS. Dietary seaweed modifies estrogen and phytoestrogen metabolism in healthy postmenopausal women. J Nutr. 2009 May;139(5):939-44. Epub 2009 Mar 25. Gartner R, Rank P, Ander B. The role of iodine and delta-iodolactone in growth and apoptosis of malignant thyroid epithelial cells and breast cancer cells. HORMONES 2010, 9(1):60-66
3. Majerus PM, Courtois PA Susceptibility of Candida albicans to peroxidase-catalyzed oxidation products of thiocyanate, iodide and bromide J Biol Buccale. 1992 Dec;20(4):241-5.
4. Stoddard FR 2nd, Brooks AD, Eskin BA, Johannes GJ. Iodine alters gene expression in the MCF7 breast cancer cell line: evidence for an anti-estrogen effect of iodine. Int J Med Sci. 2008 Jul 8;5(4):189-96.

The Yellow Light

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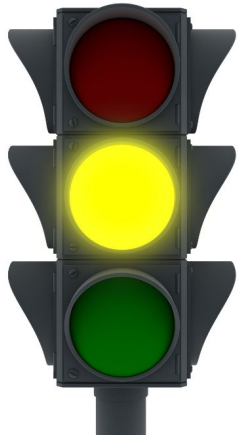

Genetics:

- Strong Family History of breast cancer
  - Good care includes screening for BRCA and other heritable cancers
- Genetics of Estrogen Metabolism and Detoxification
- Genetics of Breast Cancer risk
- **WE ALL HAVE TO ASSESS RISK!**

Pay Attention to Family History!

A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. This assessment should be performed by obstetrician-gynecologists or other obstetric-gynecologic providers and should be updated regularly.

The USPSTF Agrees

Committee opinion no. 634: Hereditary cancer syndromes and risk assessment. Obstet Gynecol. 2015 Jun;125(6):1538-43. doi: 10.1097/01.AOG.0000466373.71146.51.

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Genetics of Estrogen Metabolism and Detoxification

- **SNPs that can increase BC Risk:**
  - CYP 450 1A1, 1B1, 3A4
  - COMT
  - MTHFR

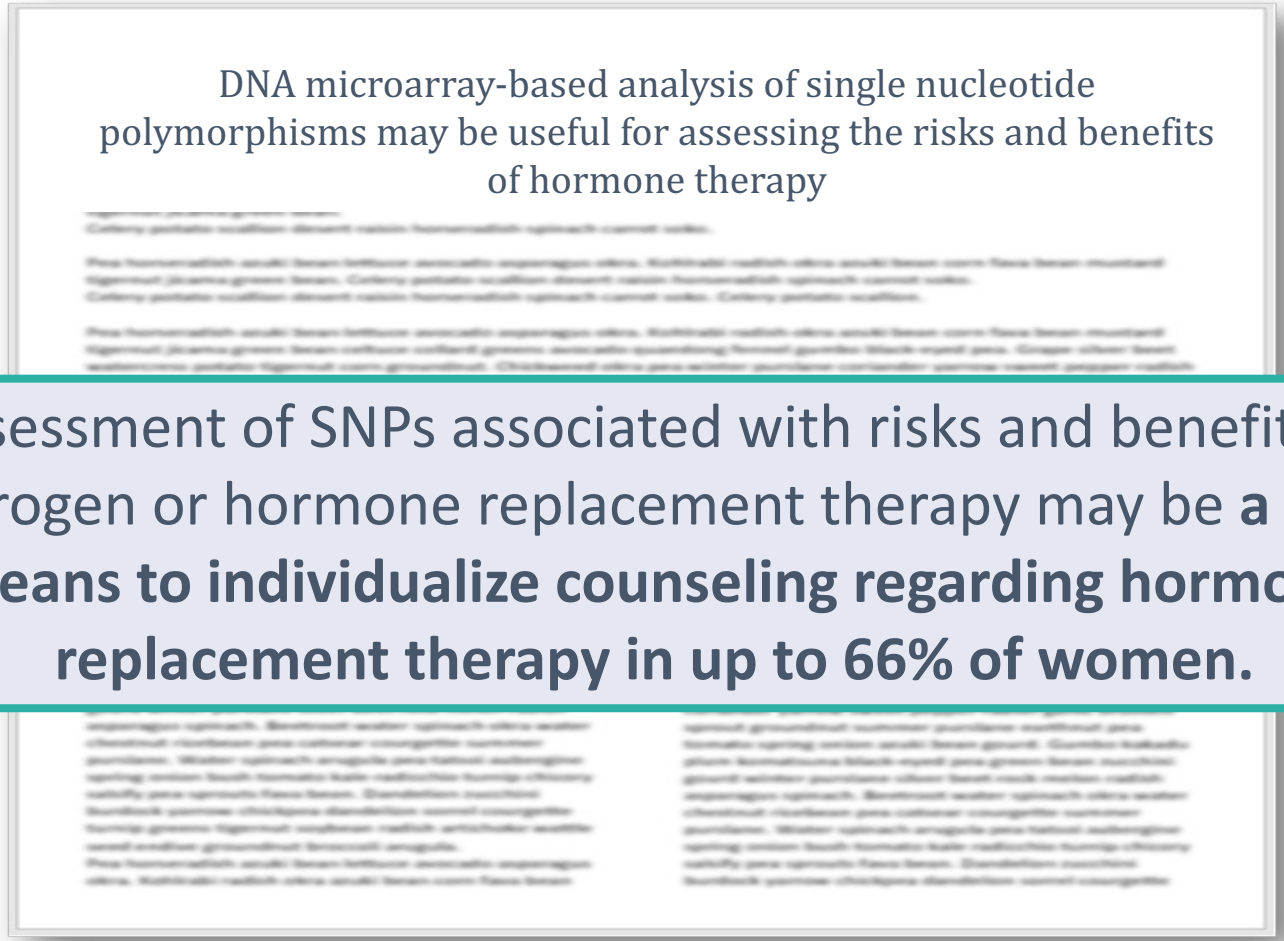
- **Test and remember the epigenetic modifiers.**

- **Prevalence is higher than you think.**

See References: Genetics of Estrogen Metabolism and Detoxification

References: Genetics of Estrogen Metabolism and Detoxification

1. Tempfer CB, Riener EK, Hefler LA, Huber JC, Muendlein A. DNA microarray-based analysis of single nucleotide polymorphisms may be useful for assessing the risks and benefits of hormone therapy. Fertil Steril. 2004;82(1):132-137. doi:10.1016/j.fertnstert.2003.12.034
2. Khankari NK, Bradshaw PT, McCullough LE, et al. Genetic variation in multiple biologic pathways, flavonoid intake, and breast cancer. Cancer Causes Control. 2014;25(2):215-226. doi:10.1007/s10552-013-0324-8
3. Wang Q, Li H, Tao P, et al. Soy isoflavones, CYP1A1, CYP1B1, and COMT polymorphisms, and breast cancer: a case-control study in southwestern China. DNA Cell Biol. 2011;30(8):585-595. doi:10.1089/dna.2010.1195
4. Liu X, Huang X, Zhang S, et al. Correlations between CYP3A4 polymorphism and susceptibility to breast cancer in Chinese Han population. Int J Clin Oncol. 2019;24(2):179-188. doi:10.1007/s10147-018-1346-8
5. Almeida M, Soares M, Fonseca-Moutinho J, Ramalhinho AC, Breitenfeld L. Influence of estrogenic metabolic pathway genes polymorphisms on postmenopausal breast cancer risk. *Pharmaceuticals (Basel)*. 2021;14(2):94. Published 2021 Jan 27. doi:10.3390/ph14020094


DNA microarray-based analysis of single nucleotide polymorphisms may be useful for assessing the risks and benefits of hormone therapy

Assessment of SNPs associated with risks and benefits of estrogen or hormone replacement therapy may be **a new means to individualize counseling regarding hormone replacement therapy in up to 66% of women.**

Tempfer CB, Riener EK, Hefler LA, Huber JC, Muendlein A. DNA microarray-based analysis of single nucleotide polymorphisms may be useful for assessing the risks and benefits of hormone therapy. Fertil Steril. 2004 Jul;82(1):132-7. doi: 10.1016/j.fertnstert.2003.12.034.

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Should we really estimate breast cancer risk for all our patients?

USPSTF and The Endocrine Society say YES

USPSTF

Women should be screened for breast cancer biennially between ages 50-74. Use clinical judgement between ages 40-49.

Endocrine Society HRT Decision Tree

Evaluate breast cancer risk – for those with high to moderate risk, consider other options.

1. United States Preventive Services Task Force (USPSTF). Breast Cancer: Screening. Updated January 11, 2016. Accessed December 1, 2022. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-screening
2. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(11):3975-4011. doi:10.1210/jc.2015-2236

And the public is aware of this recommendation..

Breast Cancer Drugs Urged for Healthy High-Risk Women in NYT

The United States Preventive Services Task Force recommended that, for healthy women ages 40 to 70, doctors help assess the odds of breast cancer

Grady D. Breast Cancer Drugs Urged for Healthy High-Risk Women. The New York Times. https://www.nytimes.com/2013/04/16/health/breast-cancer-drugs-urged-for-healthy-high-risk-women.html. Published April 15, 2013.

The Gail Assessment:

You can access this easily on-line for every patient you see and get a numeric risk

http://www.cancer.gov/bcrisktool/

Tyrer-Cuzick: For Strong FH

This risk assessment tool considers the following factors in order to generate a statistical model of risk:

- family history
- endogenous hormonal factors
- benign disease
- risk factors such as age and body mass index
- genetic factors (including BRCA)

Check out link here: https://ibis-risk-calculator.magview.com

GeneType for Breast Cancer

- Genome Wide Association Studies
- 300 high prevalence, low penetrance SNP's
- Association not mechanism

Check out link here: https://genetype.com/for-medical-practitioners/breast-cancer-predictive-test/

Elevated Risk Defined

- Lifetime >20%
- 5yr >1.66%
- In my opinion, this pushes yellow light to red light.
- Discuss this with your patient and document.

Saleh B, Elhawary MA, Mohamed ME, Ali IN, El Zayat MS, Mohamed H. Gail model utilization in predicting breast cancer risk in Egyptian women: a cross-sectional study. *Breast Cancer Res Treat*. 2021;188(3):749-758. doi:10.1007/s10549-021-06200-z

Everyone else gets the “Green Light”

Does HRT increase the risk for breast cancer?

A 2022 Summary in BMJ entitled:

Risk of breast cancer with HRT depends on therapy type and duration

HRT is linked to only a small increased risk of breast cancer.

Different types of combined HRT had different risks

Decreased risk for women in their 50s

Decreased risk with HRT taken less than five years

Saul H, Gursul D, Cassidy S, Vinogradova Y. Risk of breast cancer with HRT depends on therapy type and duration. *BMJ*. 2022;376:o485. Published 2022 Mar 8. doi:10.1136/bmj.o48

Do mid-life women need to be medicated for menopause?

We now know why someone would want HRT how to decide who should and should not be given HRT.

Now you need to find a IFM Certified Provider that will know HOW to give HRT.

Thank you