Bioidentical Hormones 101 Second Edition (2025)

Chapter 7

The Fear of Estrogen

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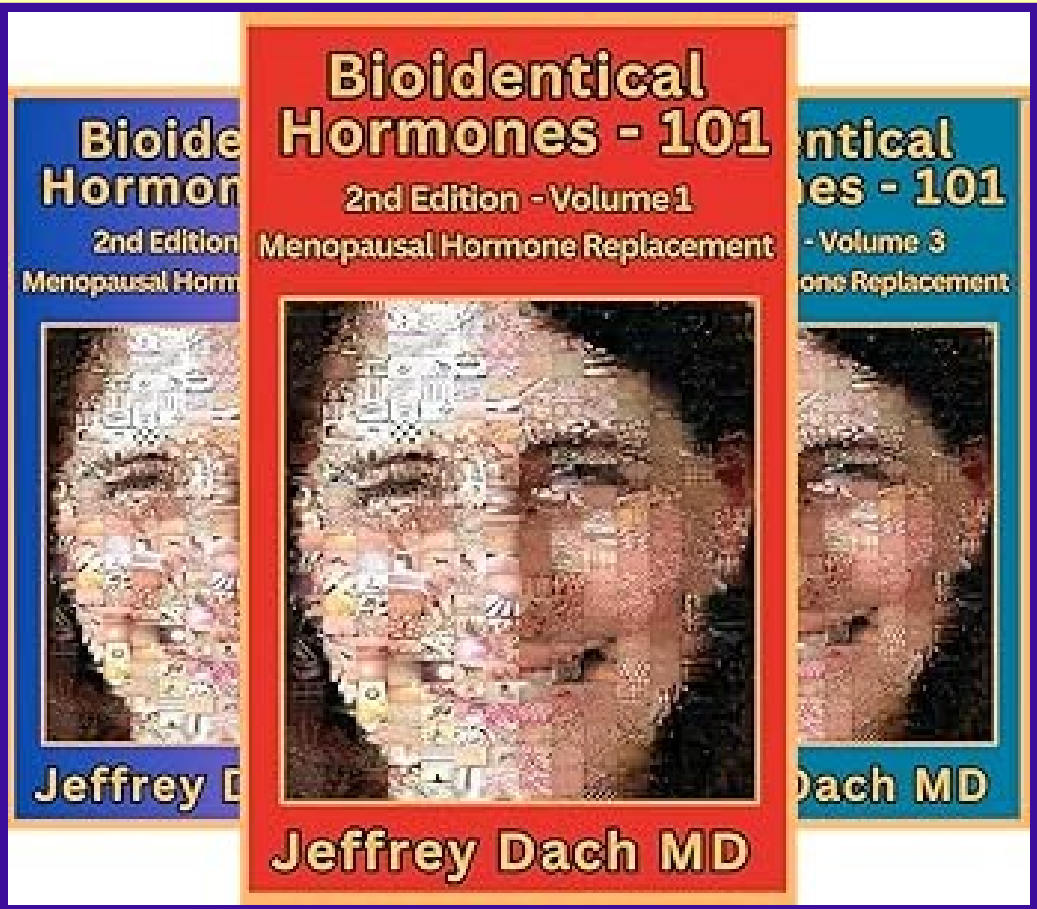
Bioidentical Hormones 101 Second Edition (2025) Chapters 7



The Fear of Estrogen

- 2002, WHI First Arm, using oral Premarin and MPA.
- Estrogen is Feared because it causes Breast Cancer and Blood Clots.

Stute, Petra, et al. "Reappraising 21 years of the WHI study: Putting the findings in context for clinical practice." Maturitas 174 (2023): 8-13.
Rossouw, Jacques E., et al. "Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial." Jama 288.3 (2002): 321-333.

2004, WHI Second Arm

- 10,739 post-menopausal women after hysterectomy randomized to estrogen-alone (Premarin, CEE) or to placebo.
- This data included 6.8 years of follow-up.
- **23% less invasive breast cancer** in the Premarin treated group compared to the placebo group.
- 94 breast cancer cases in the estrogen-treated group (Premarin, CEE).
- 124 cases of breast cancer in the placebo group

Anderson, Garnet L., et al. "Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy: The Women's Health Initiative Randomized Controlled Trial." JAMA 291.14 (2004): 1701-1712.

WHI Second arm 2004

- 10,739 post-menopausal women using Premarin CEE alone.

Table. Hazard Ratios From 3 Hormone Therapy Trials

Clinical Event	Hazard Ratio (95% Confidence Interval) HERS (Estrogen + Progestin)[5,7]	WHI (Estrogen + Progestin)[6]	WHI Estrogen Alone[14]
CHD events	0.99 (0.80-1.22)	1.29 (1.02-1.63)	0.91 (0.75-1.12)
Stroke	1.23 (0.89-1.70)	1.41 (1.07-1.85)	1.39 (1.10-1.77)
Pulmonary embolism	2.79 (0.89-8.75)	2.13 (1.39-3.25)	1.34 (0.87-2.06)
Breast cancer	1.30 (0.77-2.19)	1.26 (1.00-1.59)	0.77 (0.59-1.01)
Colon cancer	0.69 (0.32-1.49)	0.63 (0.43-0.92)	1.08 (0.75-1.55)
Hip fracture	1.10 (0.49-2.50)	0.66 (0.45-0.98)	0.61 (0.41-0.91)
Death	1.08 (0.84-1.38)	0.98 (0.82-1.18)	1.04 (0.88-1.22)
Global index†	. . .	1.15 (1.03-1.28)	1.01 (0.91-1.12)

Abbreviations: CHD, coronary heart disease; HERS, Heart and Estrogen/progestin Replacement Study; WHI, Women's Health Initiative; ellipses, not calculated.
*Data are based on the intent-to-treat analyses. For the primary CHD events outcome (myocardial infarction plus CHD death), the 3 trials had similar numbers of events and thus similar power. For other outcomes the smaller HERS trial had fewer events and less precise hazard ratios.
†The global index was composed of the first occurrence of any of the events listed in the table.

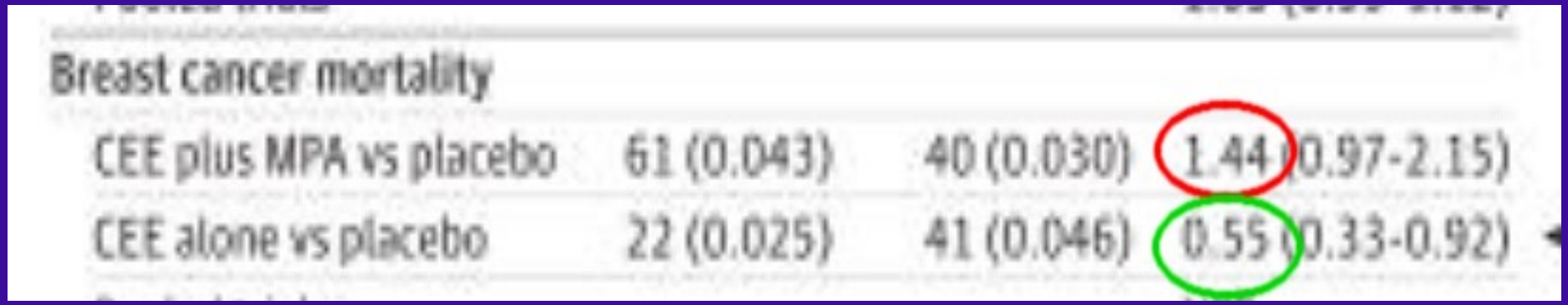
Hulley, Stephen B., and Deborah Grady. "The WHI estrogen-alone trial—do things look any better?." Jama 291.14 (2004): 1769-1771. (c) Amercan Medical Association.(53)

2004 WHI - 18 Year Follow Up

- In 2018, Dr. Howard Hodis reviewed the 18-year follow-up of the **2004, second arm** of the WHI (Premarin-alone, CEE)
- This group took estrogen for 7.2 years, and then stopped and followed for an additional 11 years.
- Dr. Howard Hodis writes: After 18 years of cumulative follow-up of the WHI-CEE cohort, **breast cancer mortality was statistically significantly reduced by 45%** (**HR, 0.55**; 95% CI, 0.33–0.92).

3) Hodis, Howard N., and P. M. Sarrel. “Menopausal Hormone Therapy And Breast Cancer: What Is The Evidence From Randomized Trials?” Climacteric 21.6 (2018):

Breast Cancer Mortality for First and Second Arms of WHI 18-year follow-up.



Breast cancer mortality			
CEE plus MPA vs placebo	61 (0.043)	40 (0.030)	1.44 (0.97-2.15)
CEE alone vs placebo	22 (0.025)	41 (0.046)	0.55 (0.33-0.92)

Manson, JoAnn E., et al. “Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women’s Health Initiative randomized trials.” JAMA 318.10 (2017): 927-938. (1)

2002 1st Arm 18 - Year Follow Up

- 2002 First Arm Breast Cancer Mortality

- CEE+MPA = 61
- Placebo = 40

- Hazard Ratio (HR)=1.44
- 44% increase in breast cancer mortality in CEE+MPA group.

3) Hodis, Howard N., and P. M. Sarrel. “Menopausal Hormone Therapy And Breast Cancer: What Is The Evidence From Randomized Trials?” Climacteric 21.6 (2018): 521-528.

2004 2nd ARM - 18 Year Follow Up

- 2004 - 2nd Arm Breast Cancer Mortality

- CEE = 22
- Placebo = 41

- Hazard Ratio (HR)= 0.55
- 45% reduction in breast cancer mortality for CEE Group.

3) Hodis, Howard N., and P. M. Sarrel. “Menopausal Hormone Therapy And Breast Cancer: What Is The Evidence From Randomized Trials?” Climacteric 21.6 (2018): 521-528.

1st Arm 2002 -18 Year F/U

- First Arm of WHI, 2002 CEE+MPA
- 16,608 post-menopausal women randomized to either Prempro (CEE +MPA) or placebo.
- After 5.2 years of follow-up, there were 290 cases of breast cancer in the Prempro group which is 26% greater than the placebo group.

4) Rossouw, Jacques E., et al. "Risks and Benefits of Estrogen Plus Progestin In Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative randomized controlled trial." Jama 288.3 (2002): 321-333.

1st Arm 2002 -18 Year F/U

- The 26% increase in Breast cancer in the **CEE plus MPA group** almost reached nominal statistical significance.
- CHD [coronary heart disease], **1.29** (1.02-1.63) with 286 cases;
- Breast cancer, **1.26** (1.00-1.59) with 290 cases;
- Stroke, **1.41** (1.07-1.85) with 212 cases;
- PE [pulm embolus], **2.13** (1.39-3.25) with 101 cases;
- Colorectal cancer, **0.63** (0.43-0.92) with 112 cases;
- Endometrial cancer, **0.83** (0.47-1.47) with 47 cases;
- Hip fracture**, 0.66** (0.45-0.98) with 106 cases
- Death other causes, 0.92 (0.74-1.14) with 331 cases.

4) Rossouw, Jacques E., et al. "Risks and Benefits of Estrogen Plus Progestin In Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative randomized controlled trial." Jama 288.3 (2002): 321-333.

90 % Decline in HRT Use

- The press release of the 2002 WHI trial created Fear of Estrogen and caused a precipitous decline in HRT use.
- Following the 2002 WHI publication in JAMA, the entire medical system of menopausal hormone replacement was dismantled. Training programs disappeared. New doctors entering practice lacked the expertise to prescribe hormone replacement. This is still the current situation in the U.S.
- HRT use has declined by **90 percent from 26.9 to 2.8 percent** of menopausal women, (Dr. Lin Yang, 2024)

8) Yang, Lin, and Adetunji T. Toriola. "Menopausal Hormone Therapy Use Among Postmenopausal Women." JAMA Health Forum. Vol. 5. No. 9. American Medical Association, 2024.,

Synthetic Progestins Are Carcinogenic

- The synthetic progestin, medroxyprogesterone (MPA) is a known breast cancer carcinogen and is commonly used to induce breast cancer in animal models.
- On the other hand, natural progesterone is non-carcinogenic and breast cancer-protective.
- if MPA is carcinogenic, why didn't the 2002 study show a statistically significant increase in breast cancer in the Premarin/MPA group.
- The HR=1.26 was not statistically significant. The answer is the anti-cancer effects of Premarin.
- Premarin contains unsaturated B-ring steroids which preferentially target ER-beta, opposing the proliferative effects of MPA.

Natural Progesterone Incapable of Causing Breast Cancer

- There is considerable experimental and clinical evidence that, alone and at physiological levels, **progesterone is incapable of causing breast cancers** so that its reputation as a 'tumorigenic' or 'carcinogenic' hormone is undeserved. (Horwitz, 2020)

15) Horwitz, Kathryn B., and Carol A. Sartorius. "90 Years of Progesterone: Progesterone And Progesterone Receptors In Breast Cancer: Past, Present, Future." Journal of Molecular Endocrinology 65.1 (2020): T49-T63.

Natural Progesterone Incapable of Causing Breast Cancer

- it is important to distinguish between progestins and natural progesterone.
- Currently, these tend to be lumped together leading to the view that progesterone is 'carcinogenic' (i.e. cancer causer).
- It is our opinion that **natural progesterone does not 'cause' breast cancer**…(Horwitz, 2020)

15) Horwitz, Kathryn B., and Carol A. Sartorius. "90 Years of Progesterone: Progesterone And Progesterone Receptors In Breast Cancer: Past, Present, Future." Journal of Molecular Endocrinology 65.1 (2020): T49-T63.

The WHI Trial Did Not Study Women's Hormones at All!!

- While the WHI trial [2002, first arm] made a valuable contribution in revealing the risks associated with conjugated equine estrogens [Premarin, CEE] plus MPA [medroxyprogesterone] treatment in postmenopausal women, it unfortunately generated considerable controversy in the field because it was interpreted as an indictment of postmenopausal hormone replacement, when in fact, **it did not study hormone replacement at all: that would have required use of the natural hormones, estradiol and progesterone.** The actions of the natural hormones are significantly different from those of Premarin and MPA. (Bethea, 2011)

16) Bethea, Cynthia L. "MPA: Medroxy-Progesterone Acetate Contributes to Much Poor Advice for Women." Endocrinology. (2011): 343-345.

2019, Rowan Chlebowski MD, PhD, Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center

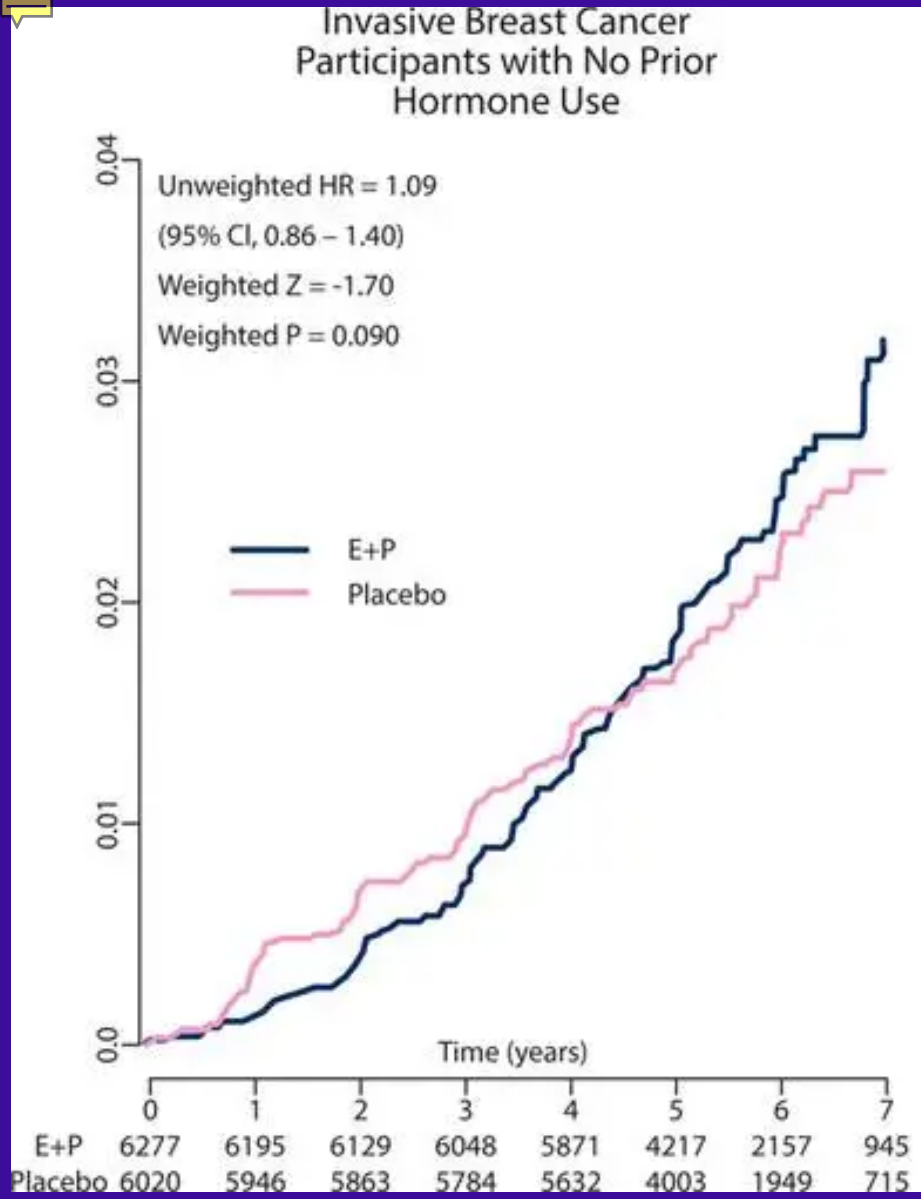
- all postmenopausal women with prior hysterectomy using CEE-alone have the potential benefit of experiencing a **reduction in breast cancer incidence** while all postmenopausal women using CEE plus MPA have the potential **risk of experiencing an increase in breast cancer incidence.**

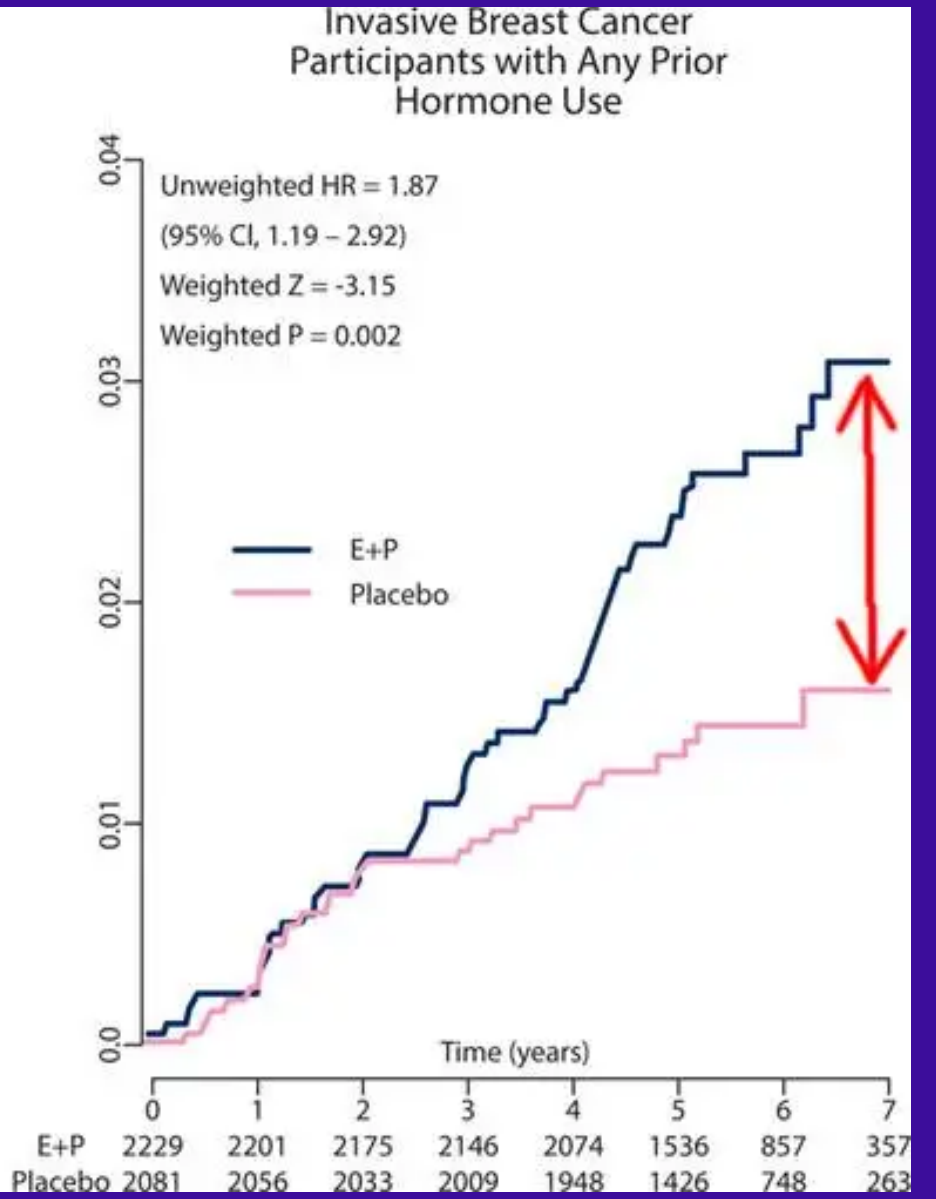
17) Chlebowski RT. Abstract GS5-00. Presented at: San Antonio Breast Cancer Symposium; Dec. 10-14, 2019; San Antonio.

Re-Analysis of First Arm WHI Data Shows Error

- 2018, Drs. Howard Hodis and Phillip Sarrel re-analyzed the data from the WHI 2002, first arm
- Some of the women in the placebo group had a history of prior HRT use.
- These women should have been removed from the placebo group, yet they were not.
- The prior use of estrogen confers protection from breast cancer and falsely reduces the incidence of breast cancer in the placebo group.
- If the women with prior HRT use are removed from the placebo group, the data chart is entirely different. There is a null effect, meaning no difference between the Prempro group (CEE/MPA) and the placebo group in breast cancer incidence.

3) Hodis, Howard N., and P. M. Sarrel. “Menopausal Hormone Therapy And Breast Cancer: What Is The Evidence From Randomized Trials?” Climacteric 21.6 (2018): 521





2) Hodis, Howard N., and P. M. Sarrel. “Menopausal hormone therapy and breast cancer: what is the evidence from randomized trials?.” Climacteric 21.6 (2018): 521-528.

2023 Lindsey Berkson: Estrogen is Breast Protective

- Estrogen “protects” healthy breast tissue from getting breast cancer in the first place.
- And, if a women has been on estrogen therapies for an average of 5 years and then gets breast cancer, the estrogen therapies “reduce” her risk of dying from breast cancer by 44%.
- Nothing else like estrogen therapies has ever been shown to be so breast protective. (18)

18) Mercola and Guest's Analysis - WRONG on Estrogen by Devaki Berkson, Oct. 24, 2023. https://drlindseyberkson.substack.com/p/mercola-and-guests-analysis-wrong

Natural Progesterone is Breast Cancer Preventive 2017 Dr. Allan Lieberman

- Much of the medical literature on progesterone or progesterone-like compounds is contradictory, with progesterone sometimes implicated as a cause of breast cancer. These contradictory results are the result of researchers confusing the effects of synthetic progestins with those of natural progesterone…
- To avoid confusion surrounding the long-term health benefits and consequences of using progestogenic drugs, we recommend that the term progesterone be used only for the naturally occurring progestogen, P4, whereas the term progestin be used for any of the synthetic versions.

19) Lieberman, Allan, and Luke Curtis. “In Defense of Progesterone: A Review of The Literature.” Alternative Therapies in Health & Medicine 23.7 (2017).

Natural Progesterone is Breast Cancer Preventive 2017 Dr. Allan Lieberman

- The evidence strongly suggests that **natural progesterone is protective and preventive of breast cancer**…
- The authors wish to emphasize that natural progesterone is preventive of breast and endometrial cancer, and physicians should have no hesitation prescribing it. (Lieberman, 2017)

19) Lieberman, Allan, and Luke Curtis. “In Defense of Progesterone: A Review of The Literature.” Alternative Therapies in Health & Medicine 23.7 (2017).

2007, Dr. Stephen Birrell

- In two French studies- the E3N-EPIC cohort of 54,548 women and a smaller study of 3175 women,
- no significant increase in breast cancer risk due to HRT [Estradiol] use with micronized progesterone was observed compared with untreated women. (Birrell, 2007)

20) Birrell, Stephen N., et al. "Disruption of androgen receptor signaling by synthetic progestins may increase risk of developing breast cancer." The FASEB Journal 21.10 (2007): 2285-2293.

21) de Lignieres, B., de Vathaire, F., Fournier, S., Urbinelli, R., Allaert, F., Le, M. G., and Kuttenn, F. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. Climacteric. 5, (2002): 332–340

22) Fournier, A., Berrino, F., Riboli, E., Avenel, V., and Clavel-Chapelon, F. (2005) Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int. J. Cancer. 114.3, (2005): 448–454

The Estrogen Paradox
V. Craig Jordan

- Notice the above WHI second arm study showed a reduced incidence of breast cancer with the use of estrogen. However, this estrogen was not human 17-beta-estradiol.
- The WHI 2nd arm used Premarin, pregnant horse estrogen called CEE (conjugated equine estrogen).
- In addition, the average age of the women was 63 years, meaning they were started on HRT **after long term estrogen deprivation (LTED).**
- **After LTED,** estrogen changes from a cancer growth factor to a cancer death factor. This is called the estrogen paradox described by V. Craig Jordan, 2011.

25) Jordan, V. Craig, and Leslie G. Ford. "Paradoxical Clinical Effect Of Estrogen On Breast Cancer Risk: A "New" Biology Of Estrogen-Induced Apoptosis." Cancer prevention research 4.5 (2011): 633-637.,

Estradiol-alone Without LTED

- We have three large observational studies.
- 2008 French E3N Cohort study by Dr. Agnes Fournier,
- 2006 Finland study by Dr. Heli Lyytinen,
- 2011 EPIC study by Dr. Kjersti Bakken.
- All three observational studies are in close agreement that estradiol alone without LTED, and without natural progesterone **increases breast cancer risk by about 25-30 percent.** (26-28)

26) Fournier, Agnès, et al "Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study." Breast cancer research and treatment 107 (2008): 103-111.

27) Lyytinen, Heli, et al. "Breast cancer risk in postmenopausal women using estrogen-only therapy." Obstetrics & Gynecology 108.6 (2006): 1354-1360.

28) Bakken, Kjersti, et al. "Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition." International journal of cancer 128.1 (2011): 144-156.

Estradiol Without LTED

- Increased breast proliferation with estradiol was also found by Dr. Charles Wood's primate studies comparing proliferative effects of estradiol (E2) to that of CEE (Premarin).
- When natural progesterone is added to the estradiol, breast cancer risk is eliminated. (26-28)

Wood, Charles E., et al. "Comparative Effects of Oral Conjugated Equine Estrogens and Micronized 17β-Estradiol on Breast Proliferation: A Retrospective Analysis." Menopause 15.5 (2008): 978-983.
Wood, Charles E., et al. "Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys." Breast cancer research and treatment 101 (2007): 125-134.

ER-alpha and ER-beta

- Much of the early work on estrogen receptors was done by Elwood Jensen and Jan-Åke Gustafsson.
- ER-alpha was cloned in 1986 from human breast cancer (MCF-7) cells and ER-beta was cloned in 1996 from rat prostate cells. Estrogen receptors alpha (ER-alpha) and beta (ER-beta) have opposing roles.
- ER-alpha is proliferative and activates the oncogenes, Cyclin D1 and C-Myc.
- ER-beta opposes the ER-alpha activation of Cyclin D1, thus serving as a tumor suppressor, downregulating the proliferative effects of ER-alpha. (29-36)

29) Lee, Hye-Rim, Tae-Hee Kim, and Kyung-Chul Choi. "Functions and physiological roles of two types of estrogen receptors, ER-alpha and ER-beta, identified by estrogen receptor knockout mouse." Laboratory animal research 28.2 (2012): 71-76.

Premarin (CEE) is Less Proliferative than Estradiol

- In 2008, Dr. Charles E. Wood in Winston Salem studied a post-menopausal primate model to compare the proliferative effects of CEE (Premarin, horse estrogen) to that of 17-beta estradiol (human estrogen). Proliferation was measured with the KI-67 marker, a commonly used proliferative marker in clinical pathology.
- Dr. Wood found a highly significant 259-330% increase in breast cell proliferation in estradiol-treated monkeys compared to controls. However, in the Premarin (CEE) treated monkeys there was far less breast cell proliferation, only 75% compared to controls.

37) Wood, Charles E., et al. "Comparative effects of oral conjugated equine estrogens and micronized 17β-estradiol on breast proliferation: a retrospective analysis." Menopause 15.5 (2008): 978-983.

Premarin (CEE) is Less Proliferative than Estradiol

- This difference in proliferative effect was explained in 2024 by Dr. Barbara Levy writing that horse estrogen, **CEE, contains unsaturated B ring steroids which preferentially bind to and activate ER-beta,** thus explaining less proliferative effects compared to estradiol. There are no unsaturated B-ring steroids in human estrogen. However, human hormones with ER-beta binding preference are estriol (E3) and testosterone metabolite 3Beta-diol, thus explaining their cancer-protective properties. (Levy, 2024)

38) Levy, Barbara, and James A. Simon. “A Contemporary View of Menopausal Hormone Therapy.” Obstetrics & Gynecology 144.1 (2024): 12-23.

B-Ring Steroids in CEE Breast Cancer Preventive

- **The choice of CEE [horse estrogen] in the ET arm [estrogen only second arm] of the WHI may explain the favorable effects seen on the breast.** CEE contains a mixture of multiple estrogens, and each estrogen-type not only preferentially binds the two estrogen receptors, but may also exert differential actions depending on the target tissue. While E2 [human estradiol] is the well characterized estrogen, less is known about the many estrogenic components of CEE. Unlike E2, these other estrogens differ in **their B-ring saturation** and in their chemical moieties at the 17-position…(Flores, 2015)

41) Flores, Valerie A "The Effect Of Menopausal Hormone Therapies On Breast Cancer: Avoiding The Risk." Endocrinology and Metabolism Clinics 44.3 (2015): 587-602.

B-Ring Steroids in CEE Bind to ER Beta Breast Cancer Preventive

- Bhavnani et al analyzed the effects of 11 equine estrogens (in CEE preparations) on the transcriptional activity of ER alpha and beta, and found that **many of the equine estrogens preferentially bind ER beta**. **ER beta activation can inhibit ER alpha activity on cell proliferation. This inhibition induced by equine estrogens may in part explain the decreased risk of breast cancer observed in the WHI ET study** [2004 second arm Womens Health Initiative Estrogen Therapy-only]. (41)

39) Bhavnani, Bhagu R., and Frank Z. Stanczyk. "Pharmacology of conjugated equine estrogens: efficacy, safety and mechanism of action." The Journal of steroid biochemistry and molecular biology 142 (2014): 16-29.
40) Bhavnani, Bhagu R., Shui-Pang Tam, and XiaoFeng Lu. "Structure Activity Relationships And Differential Interactions And Functional Activity Of Various Equine Estrogens Mediated Via Estrogen Receptors (Ers) ER-Alpha And ER-Beta." Endocrinology 149.10 (2008): 4857-4870.

Progesterone Acts as Proliferative Brake

- In 2015, Dr. Hisham Mohammed, Assistant Professor of Molecular and Medical Genetics CEDAR, OHSU Knight Cancer Institute, School of Medicine, states that:
- Natural progesterone functions as a proliferative brake on ER-alpha and downregulates estradiol-stimulated ER-alpha proliferative effects

42) Mohammed, Hisham, et al. “Progesterone Receptor Modulates ER-Alpha Action In Breast Cancer.” Nature 523.7560 (2015): 313-317.

Progesterone Acts as Proliferative Brake

- We conclude that activation of PR [progesterone receptor] results in **a robust association between PR and the ER-alpha complex**…
- PR is a critical determinant of ER-alpha function due to crosstalk between PR and ER-alpha.
- In this scenario, under estrogenic conditions, **an activated PR functions as a proliferative brake** in ER-alpha+ breast tumors by re-directing ER-alpha chromatin binding and altering the expression of target genes that induce a switch from a proliferative to a more differentiated state. (42)

42) Mohammed, Hisham, et al. "Progesterone Receptor Modulates ER-Alpha Action In Breast Cancer." Nature 523.7560 (2015): 313-317.

Progesterone Acts as Proliferative Brake

- We know from the 2008 French Cohort study by Dr. Agnes Fournier that the addition of natural progesterone to estradiol (E2) reduces the HR 1.25 for breast cancer down to 1.00.

26) Fournier, Agnès, et al "Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study." Breast cancer research and treatment 107 (2008): 103-111.

2020, Dr. Rahul Mal

- ER-beta as a tumor suppressor, downregulating the proliferative effects of estrogen via downregulation of the expression of the **oncogene, cyclin D1**. Dr. Rahul Mal suggested hormones, drugs or plant extracts that activate ER-beta could serve as a targeted therapy for breast cancer, **thus replacing chemotherapy,**

27) Mal, Rahul, et al. “Estrogen Receptor Beta (ER-beta): A Ligand Activated Tumor Suppressor.” Frontiers In Oncology 10 (2020): 587386.

2020, Dr. Rahul Mal

- High ER-beta expression is associated with improved overall survival in women with breast cancer…
- **ER-beta is a nuclear receptor with broad-spectrum tumor suppressor activity**, which could serve as a potential treatment target in a variety of human cancers including breast cancer…
- Relative to ER alpha**, ER beta binds estriol and ring B unsaturated estrogens [Premarin, CEE] with higher affinity, while the reverse is true of 17β-estradiol and estrone. (Mal, 2020)**

27) Mal, Rahul, et al. “Estrogen Receptor Beta (ER-beta): A Ligand Activated Tumor Suppressor.” Frontiers In Oncology 10 (2020): 587386.

2020, Dr. Rahul Mal

- Dihydrotestosterone metabolites 5-androstenediol and 3beta androstanediol [3Beta-Diol] are relatively selective **(3-fold) for ER-beta** over ER-alpha…
- The cell division protein **cyclin D1** (CCND1), one target of AP-1 and SP1 mediated transcription, is **upregulated by ER alpha and induces estrogen-mediated proliferation…**
- Opposing actions and dominance of ER-beta over ER-alpha with respect to activation of **cyclin D1 gene** expression may explain why **ER-beta is a negative regulator of the proliferative effects of estrogen**…

27) Mal, Rahul, et al. “Estrogen Receptor Beta (ER-beta): A Ligand Activated Tumor Suppressor.” Frontiers In Oncology 10 (2020): 587386.

2020, Dr. Rahul Mal

- Thus, ER-beta and ER-alpha have shown opposing effects on proliferation and the expression of various oncogenes and tumor suppressors in breast cancer cell lines in the presence of estradiol…
- ER-beta is unique in that it functions as a tumor suppressor in diverse biologic contexts. ER-beta has been implicated in various cancer types, including **breast, prostate, lung, glioblastoma, thyroid, and ovarian cancer**… (Mal, 2020)

27) Mal, Rahul, et al. “Estrogen Receptor Beta (ER-beta): A Ligand Activated Tumor Suppressor.” Frontiers In Oncology 10 (2020): 587386.

Estriol (E3), the "Forgotten Hormone".

- Dr. Henry Lemon's work showing estriol prevented breast cancer in animal models of chemically induced breast cancer.
- Another study by Dr. Lemon showed decreased urinary excretion of estriol (E3) in breast cancer patients compared to normal controls.
- As mentioned above, estriol (E3) preferentially binds to ER-beta thus serving as a breast cancer preventive.

61) Lemon HM, Wotiz HH, Parsons L, Mozden PJ. Reduced estriol excretion in patients with breast cancer prior to endocrine therapy. JAMA. 1966;196(13):1128-1136.
62) Lemon, Henry M. "Estriol prevention of mammary carcinoma induced by 7, 12-dimethylbenzanthracene and procarbazine." Cancer Research 35.5 (1975): 1341-1353.
63) Lemon, Henry M. "Antimammary carcinogenic activity of 17-alpha-ethinyl estriol." Cancer 60.12 (1987): 2873-2881.
64) Lemon, Henry M., et al. "Inhibition of Radiogenic Mammary Carcinoma In Rats By Estriol Or Tamoxifen." Cancer 63.9 (1989): 1685-1692.

Our Breast Cancer Prevention Program

- Natural Progesterone:
- Bi-Est which is 80% estriol (E3) and 20% estradiol (E2). Estriol (E3) is breast cancer preventive.
- Both estriol (E3) and metabolites of testosterone predominantly target the ER-beta receptor
- Iodine:
- Testosterone
- DIM (Di-Indole-Methane)
- Methyl-Folate, Selenium, Vitamin D

Dr. Ercole Cavalieri Breast Cancer Caused by Catechol Estrogen 3,4, Quinones

- Dr. Cavalieri writes:
- Cancer can be initiated by increased formation of reactive estrogen metabolites called catechol estrogen-3,4-quinones. If estrogen metabolism becomes unbalanced and significant amounts of these quinones arise, depurinating estrogen-DNA adducts are primarily formed, leading to cancer-causing mutations. (Cavalieri, 2021)

82) Cavalieri, Ercole, and Eleanor Rogan. “The 3, 4-Quinones Of Estrone And Estradiol Are The Initiators Of Cancer Whereas Resveratrol And N-Acetylcysteine Are The Preventers.” International Journal Of Molecular Sciences 22.15 (2021): 8238.

Exposure to Exogenous Estrogen Prevents Breast Cancer.

- The WHI [Women's Health Initiative] study of ERT [CEE estrogen replacement, second arm, 2004] versus placebo in women with a prior hysterectomy is a most robust piece of research:
- Prospective, randomized, placebo-controlled and with a 20-year follow-up, which now compels a direct interpretation of its finding, **namely that exposure to exogenous estrogen (ERT) prevents breast cancer**. This is of profound importance, not only in relation to the prevention of the most common cancer in women in the Western world but also because estrogen, whilst being cost-effective and well-tolerated also has other **preventative properties against osteoporosis and cardiovascular disease**, to name but two.

99) Manyonda, Isaac, et al. "Could Perimenopausal Estrogen Prevent Breast Cancer? Exploring The Differential Effects Of Estrogen-Only Versus Combined Hormone Replacement Therapy." Journal of Clinical Medicine Research 14.1 (2022): 1-7.,

“Estrogen Paradox”

- 2008 by Dr. V. Craig Jordan, PhD, the Father of Tamoxifen
- LTED switches Estrogen from a survival signal to a death signal.

101) Jordan, V. Craig. “Molecular Mechanism For Breast Cancer Incidence In The Women’s Health Initiative.” Cancer Prevention Research 13.10 (2020): 807-816.

“Estrogen Paradox”

- An estrogen deprivation gap of 5 years after menopause is required for high-dose estrogen to be an effective treatment for breast cancer.
- The same applies to 5 years of adjuvant tamoxifen therapy when recurrence and mortality continue to decrease after adjuvant tamoxifen treatment is stopped …

101) Jordan, V. Craig. “Molecular Mechanism For Breast Cancer Incidence In The Women’s Health Initiative.” Cancer Prevention Research 13.10 (2020): 807-816.

“Estrogen Paradox”

- the paradox, which is maintained throughout the WHI [Women’s Health Initiative] evaluation of more than 12 years, **is estrogen causes a decrease in mortality and a decrease in the incidence of new breast cancers**.
- This is **counterintuitive** to the scientific and medical community unless one embraces and understands the known clinical evidence that governs safe estrogen use for the treatment of breast cancer after menopause. These were established 70 years ago. (Jordan, 2020)

34) Jordan, V. Craig. “Molecular mechanism for breast cancer incidence in the Women’s Health Initiative.” Cancer Prevention Research 13.10 (2020): 807-816.

“Estrogen Paradox”

- 34) Jordan, V. Craig. “Molecular mechanism for breast cancer incidence in the Women’s Health Initiative.” Cancer Prevention Research 13.10 (2020): 807-816.
- 35) Jordan, V. Craig. “The 38th Karnofsky lecture: the paradoxical actions of estrogen in breast cancer—survival or death?” Journal of Clinical Oncology 26.18 (2008): 3073-3082.
- 36) Jordan, V. Craig. “The new biology of estrogen-induced apoptosis applied to treat and prevent breast cancer.” Endocrine-related cancer 22.1 (2015): R1-R31.

Estrogen Paradox Reversed by MPA

- The clinical description and discovery of estrogen-induced apoptosis [programmed cell death]…has now provided a mechanistic insight into the adjuvant treatment of breast cancer, an insight into the "unexpected" results of the Women's Health Initiative investigation of estrogen and estrogen/progestin given to women as hormone replacement at the age of 60 vs the Million Women Study…
- The results of the two epidemiological interventional studies were not comparable but instructive about mechanisms of hormone action in the real world **if long-term estrogen deprivation occurs at menopause prior to HRT administration of estrogen alone produces a sustained decrease in breast cancer and the addition of medroxyprogesterone acetate [MPA] not only reverses but increases breast carcinogenesis.**

102) Abderrahman, Balkees, and V. Craig Jordan. "Estrogen for the Treatment And Prevention Of Breast Cancer: A Tale Of 2 Karnofsky Lectures." The Cancer Journal 28.3

Hormones of Pregnancy Confer Long-Term Protection from Breast Cancer

- Dr. Lakshmanaswamy writes:
- These studies demonstrate that short doses of the hormones estrogen and progesterone **induce a long-lasting protective** effect on mammary tumorigenesis in two genetically engineered mouse models. (115-122)

121) Lakshmanaswamy, Rajkumar, et al. “Short-term exposure to pregnancy levels of estrogen prevents mammary carcinogenesis.” Proceedings of the National Academy of Sciences 98.20 (2001): 11755-11759.

The Role Of Hormones And Aromatase Inhibitors On Breast Tumor Growth And General Health In A Postmenopausal Mouse Model

- Because estrogen-blocking aromatase inhibitors are the current adjuvant treatment after hormone-sensitive breast cancer, common sense leads to the assumption that any treatment containing estrogen itself would lead to opposite, highly negative impact on tumor growth. **However, this turned out not to be the case.**
- **Maximal reduction in tumor growth was achieved by E [estrogen] plus P [progesterone] plus T [testosterone] treatment….**

123) Rajkumar Lakshmanaswamy. “Role Of Hormones And Aromatase Inhibitors On Breast Tumor Growth Postmenopausal Mouse.” Repro Biol and Endo 12 (2014): 1-13.

Better Than Aromatase Inhibitors

- Current standard of practice considers hormones of any type absolutely contraindicated after hormone-receptor-positive breast cancer, with the assumption being that hormones "throw fuel on the fire" of cancer.
- This assumption makes intuitive sense, since **current treatment is to block remaining estrogens with aromatase inhibitors**, **the exact opposite**…
- Our results thus did not confirm the "throwing fuel on the fire" conception prevalent among clinicians….
- In summary, our results indicate that the use of appropriate combinations of natural hormones along with, or **instead of, classical breast cancer treatments [aromatase inhibitors]** is beneficial against postmenopausal symptoms and improves cardiac and osteoporotic health in the mouse model.

123) Rajkumar Lakshmanaswamy. "Role Of Hormones And Aromatase Inhibitors On Breast Tumor Growth Postmenopausal Mouse." Repro Biol and Endo 12 (2014): 1-13.

Better Than Aromatase Inhibitors

- The natural hormone combinations tested in this study provide evidence for a better alternative to standard aromatase inhibitor treatment following breast cancer in women. (123)

123) Rajkumar Lakshmanaswamy. “Role Of Hormones And Aromatase Inhibitors On Breast Tumor Growth Postmenopausal Mouse.” Repro Biol and Endo 12 (2014): 1-13.

Adding Aromatase Inhibitor Increases Recurrence

- 2022 Dr. Søren Cold MD, PhD, senior oncologist Department of Oncology, Odense University Hospital, Denmark.
- Observational cohort study.
- 8461 women **following a breast cancer diagnosis.**
- 1,957 women used vaginal estrogen therapy (VET) and
- 133 used menopausal hormone therapy (MHT).
- The cohort was followed 9.8 years for recurrence and 15.2 years for mortality.

124) Cold, Søren, et al. “Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study.” J of the Nat Cancer Institute 114.10 (2022): 1347

Adding Aromatase Inhibitor Increases Recurrence

- The overall mortality was **decreased by 22 percent for VET and 6 percent for MHT.**
- No increased recurrence of breast cancer for either of the VET or MRT groups.
- However, in women receiving VET or MRT and receiving **adjuvant AI drug, breast cancer recurrence was increased by 39% compared to non-users.**
- These findings suggest a **better outcome is achieved without adding adjuvant AI drugs to HRT for breast cancer survivors.**

124) Cold, Søren, et al. “Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study.” J of the Nat Cancer Institute 114.10 (2022): 1347.

Mechanism for breast cancer?

- Estrogens are converted to quinone metabolites, which directly bind to DNA and form adducts…
- Error prone DNA repair then results in the formation of mutations at the depurinated sites. Accumulation of these mutations would then contribute to the development of breast cancer. (Yue, 2019)

125) Yue, Wei, et al. “Pro-Apoptotic Effects Of Estetrol On Long-Term Estrogen-Deprived Breast Cancer Cells And At Low Doses On Hormone-Sensitive Cells.” Breast cancer: basic and clinical research 13 (2019): 1178223419844198.

Mechanism for breast cancer?

- As predicted from the "estrogen genotoxic metabolite" hypothesis, a predisposition to breast cancer would be expected in **women with combinations of mutations of estrogen metabolizing enzymes**, a finding reported by Park et al. and Ritchie et al…
- Finally, a speculative consideration for the future is that blockade of estradiol metabolism with CYP1B1 and 1A1 inhibitors might be a means to reduce breast cancer incidence without blocking formation of E2 itself. (Yue, 2019)

125) Yue, Wei, et al. "Pro-Apoptotic Effects Of Estetrol On Long-Term Estrogen-Deprived Breast Cancer Cells." Breast cancer basic clin res 13 (2019): 1178223419844198.

WHI-Estrogen Alone (Premarin) Prevents Breast Cancer

- 11-year follow-up data of the 2004 Second Arm, Premarin-Alone (CEE) study of the Women's Health Initiative:
- The Premarin-alone arm (CEE) showed a 20-27% decrease in breast cancer compared to placebo.
- 18-year follow-up showed the estrogen-alone group (Premarin) enjoyed a 40 percent reduction in mortality from breast cancer.

20) Chlebowski, Rowan T., et al. "Association of Menopausal Hormone Therapy with Breast Cancer Incidence and Mortality During Long-Term Follow-Up of The Women's Health Initiative Randomized Clinical Trials." JAMA 324.4 (2020): 369-380.

French E3N cohort study 2008 Fournier

- Compare the association between different HRTs and breast cancer risk.
- 80,377 postmenopausal women.
- Biennial self-administered questionnaires from 1990 to 2002.
- 2,354 cases of invasive breast cancer.
- 8.1 years of follow-up.

Fournier, Agnès, et al. "Unequal Risks for Breast Cancer with Different Hormone Replacement Therapies: E3N Cohort Study." Breast Cancer Research and Treatment 107 (2008): 103-111.

French Cohort Study 2008 Fournier

Hormone Combination	RR Risk of Invasive BC
Non-User	1.0
Estradiol Alone	1.29 (non-significant)
Estradiol/Progest	1.0
Estradiol/MPA	1.48

These findings suggest that the choice of the progestagen component in combined HRT is of importance regarding breast cancer risk; it could be preferable to use progesterone.

Fournier, Agnès, et al. "Unequal Risks for Breast Cancer Associated with Different Hormone Replacement Therapies: Results from The E3N Cohort Study." Breast Cancer Research and Treatment 107 (2008): 103-111.

French Cohort Agnes Fournier

- Our finding of a **1.3-fold increased breast cancer risk** associated with the use of estrogen alone (almost exclusively estradiol compounds, and mostly administered through the skin)
- **Differs with that of the WHI estrogen-alone trial** which found **a decreased risk [23 percent] when oral conjugated equine estrogens [Premarin]** were used in a population of older and often overweight women. (Fournier, 2008)

21) Fournier, Agnès, et al. "Unequal Risks for Breast Cancer Associated with Different Hormone Replacement Therapies: Results from The E3N Cohort Study." Breast Cancer Research and Treatment 107 (2008): 103-111.,

Primate Study E2 vs Premarin

- Dr. Charles E. Wood at the primate center in Winston Salem in a 2008
- Compared Premarin (CEE) to 17-beta estradiol (E2) as hormone replacement
- E2= 250-330% increase proliferation (KI-67)
- Premarin = 75 % increased proliferation.

22) Wood, Charles E., et al. “Comparative Effects of Oral Conjugated Equine Estrogens and Micronized 17β-Estradiol on Breast Proliferation: A Retrospective Analysis.” Menopause 15.5 (2008): 978-983.

Ring B unsaturated Equine Estrogens

- Dr. Bhagu R. Bhavnani
- studied equine estrogens (CEE) finding they contain “ring B unsaturated equine estrogens” which selectively bind to and activate ER-beta, Our data indicate that some natural estrogens such as the **ring B unsaturated equine estrogens** of the type present in the drug **CEE [Premarin]** have characteristics that can be useful as selective ER-beta ligands.

24) Bhavnani, Bhagu R.“Pharmacology Of Conjugated Equine Estrogens: Efficacy, Safety and Mechanism of Action.” The J of steroid biochem and mol biol 142 (2014): 16-29.
25) Bhavnani, Bhagu R., et al. “Structure Activity Relationships and Differential Interactions And Functional Activity Of Various Equine Estrogens Mediated Via Estrogen Receptors (ERs) ERα and ERβ.” Endocrinology 149.10 (2008): 4857-4870.

Progesterone: Breast Cancer Prevention

- 2015, Dr. Hisham Mohammed
- PR associates with ER-alpha.
- PR functions as a molecular rheostat to control ER-alpha chromatin binding and transcriptional activity.

42) Mohammed, Hisham, et al. “Progesterone Receptor Modulates ER-Alpha Action In Breast Cancer.” Nature 523.7560 (2015): 313-317.

Progesterone: Breast Cancer Prevention

- 2015, Dr. Hisham Mohammed
- We conclude that activation of PR [progesterone receptor] results in a robust association between PR and the ER-alpha complex…Progesterone blocks ER-alpha+ tumour growth….
- PR is a critical determinant of ER-alpha function due to crosstalk between PR and ER-alphaogenic conditions,
- an **activated PR functions as a proliferative brake in ER-alpha+ breast tumors** by re-directing ER-alpha chromatin binding and altering the expression of target genes that induce a switch from a proliferative to a more differentiated state. (47)

42) Mohammed, Hisham, et al. “Progesterone Receptor Modulates ER-Alpha Action In Breast Cancer.” Nature 523.7560 (2015): 313-317.

Breast Cancer Prevention

- Bi-est (80 % Estriol E3, 20 % Estradiol E2),
- Testosterone (metabolized to 3-Beta-Diol)
- Topical and oral progesterone.
- Iodine testing and supplementation.
- I3C and DIM
- Methyl-folate (MTHFR mutation impairs the functioning of the COMT enzyme.)
- Vitamin D3 target above 50 ng/mL, and for
- Selenium is above 135 mcg/L. (48)

2008, Dr. Bao Ting Zhu

- It is evident that many of the equine estrogens contained in Premarin have a **strong differential binding affinity for human ER-beta** over ER-alpha, which is very similar to the human **pregnancy estrogen [estriol] E3**…
- The inclusion of methoxyestrogen sulfates in HRT may be beneficial because **of 2-methoxyestradiol's strong anti-tumorigenic activity…**

62) Zhu, Bao Ting. "Is It Necessary to Control the Level of Estrogen Receptor alpha and beta Activation In Postmenopausal Hormone Replacement Therapy To Achieve The Optimal Outcome?" Molecular Medicine Reports 1.1 (2008): 15-20.

2008, Dr. Bao Ting Zhu

- Our recent study showed that endogenous estrogens (such as E1 and 2-OH-E1) present in non-pregnant women mainly **activate the ER-alpha system**,
- whereas estrogens (such as E3 and epi-E3) present in pregnant women **predominantly activate the ER-beta system…**
- It is believed that an optimally-adjusted activation of the ER-alpha and ER-beta signaling systems would help maximize the beneficial effects of HRT, and additionally minimize its untoward effects. (62-64)

62) Zhu, Bao Ting. "Is It Necessary to Control the Level of Estrogen Receptor alpha and beta Activation In Postmenopausal Hormone Replacement Therapy To Achieve The Optimal Outcome?" Molecular Medicine Reports 1.1 (2008): 15-20.

Progestins Activate ER-Alpha

- In 2012, Dr. Sebastián Giulianelli
- We found that treatment with the progestin medroxyprogesterone acetate (MPA) induced the expression and activation of ER alpha, as well as rapid nuclear colocalization of activated ER alpha with PR [Progesterone Receptor]…

65) Giulianelli, Sebastián, et al. “Estrogen Receptor Alpha Mediates Progestin-Induced Mammary Tumor Growth by Interacting with Progesterone Receptors at The Cyclin D1/MYC Promoters.” Cancer research 72.9 (2012): 2416-2427.

Progestins Activate ER-Alpha

- Chromatin immunoprecipitation studies showed that **MPA triggered binding of ER alpha and PR to the CCND1 [Cyclin D1] and MYC promoters**…
- Nuclear colocalization of both receptors also occurred in human breast cancer samples…Together, our findings argued that ER alpha–PR association on target gene promoters is essential for progestin-induced cell proliferation.

65) Giulianelli, Sebastián, et al. “Estrogen Receptor Alpha Mediates Progestin-Induced Mammary Tumor Growth by Interacting with Progesterone Receptors at The Cyclin D1/MYC Promoters.” Cancer research 72.9 (2012): 2416-2427.

Progestins are carcinogenic

- 2024 Dr. Meghan S. Perkins in-vitro studies of MCF-7 breast cancer cells.
- all progestogens [synthetic progestins] promoted the association of the PR [progesterone receptor] and ER alpha [estrogen receptor alpha] on the promoter of the PR target gene, MYC [a proliferative oncogene], thereby increasing its expression …
- These progestins are used globally in both contraception and menopausal hormone therapy (MHT)…

68) Perkins, Meghan S., et al. “Upregulation of an estrogen receptor-regulated gene by first generation progestins requires both the progesterone receptor and estrogen receptor alpha.” Frontiers in Endocrinology 13 (2022): 959396.

Progestins are carcinogenic

- MHT]Menopausal Hormone Therapy] containing progestins such as first generation **medroxyprogesterone acetate (MPA) or norethisterone (NET), or second generation levonorgestrel (LNG) have been associated with a higher risk [of breast cancer] than estrogen-only MHT**…
- Considering that the expression of **MYC** is often upregulated in breast cancer, and that it plays a role in promoting proliferation, these results suggest that the progestogens evaluated in this study all promote breast cancer cell proliferation, albeit to different extents, via a mechanism requiring an association of the PR and ER alpha on the MYC promoter.
- Similarly, many other studies find synthetic progestins increase breast cell proliferation. (68-76)

68) Perkins, Meghan S., et al. “Upregulation of an estrogen receptor-regulated gene by first generation progestins requires both the progesterone receptor and estrogen receptor alpha.” Frontiers in Endocrinology 13 (2022): 959396.

2007, Dr. Charles E. Wood

- Breast cell proliferation in a primate model:
- Estradiol plus medroxyprogesterone (MPA) significantly increased breast cell proliferation using Ki67 markers. However, estradiol with progesterone did not increase cellular proliferation...
- Oral micronized progesterone has a more favorable effect on risk biomarkers for postmenopausal breast cancer than medroxyprogesterone acetate.

77) Wood, Charles E., et al. “Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys.” Breast cancer res treatment 101 (2007): 125-134.

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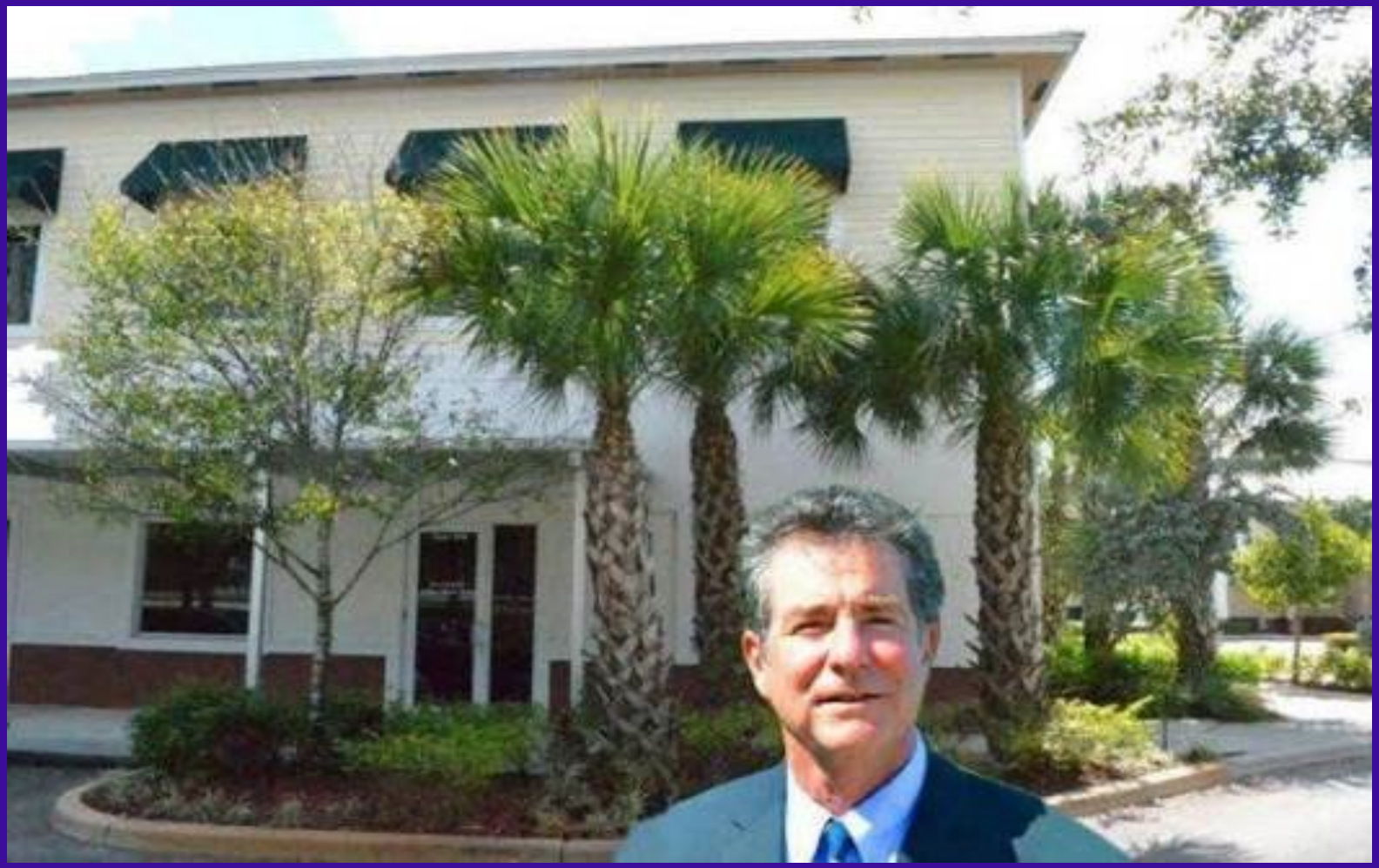

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