Bioidentical Hormones 101
Second Edition (2025)
Chapter 19
Hormone Replacement for Breast Cancer Survivors Part Two

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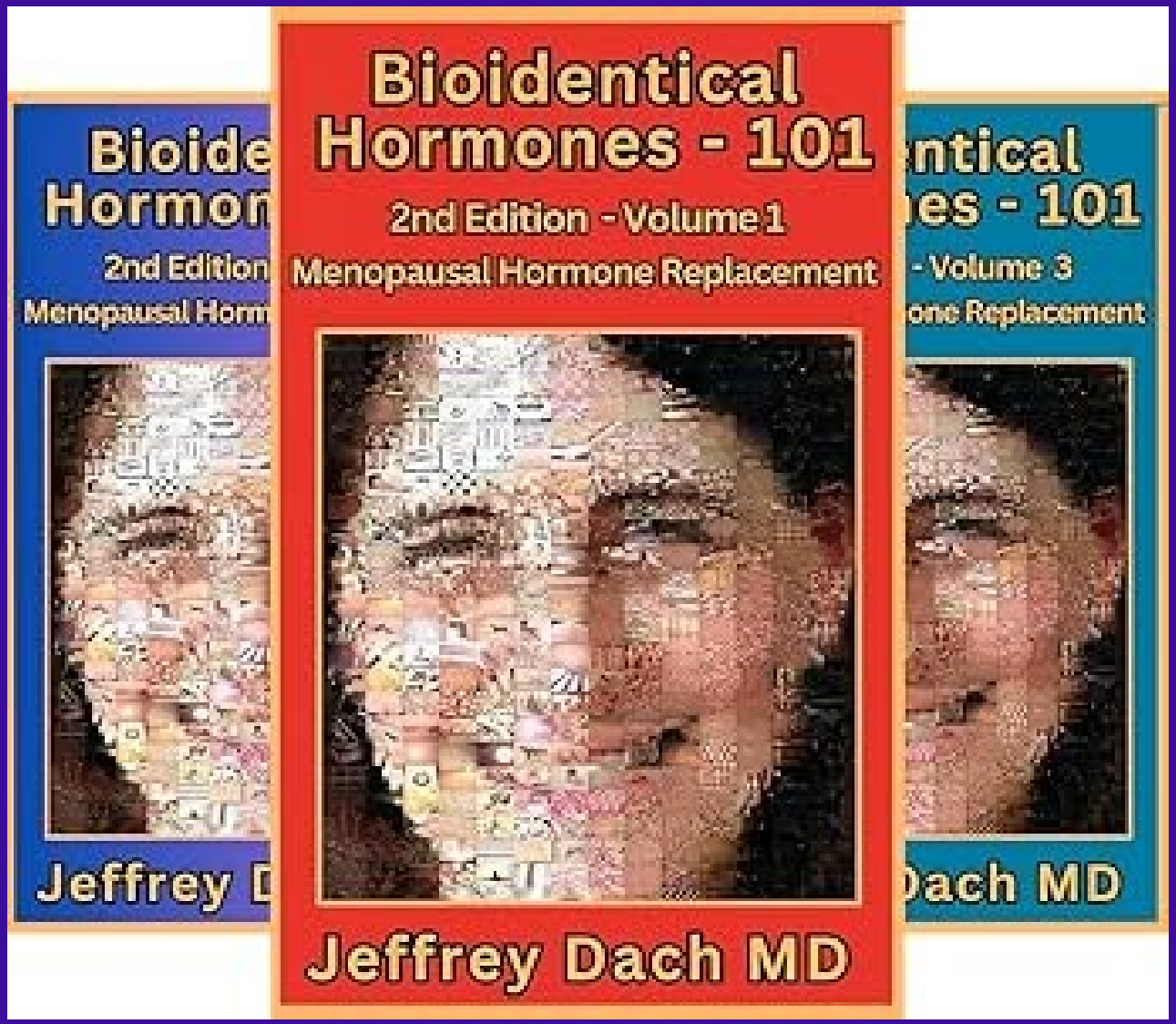
Bioidentical Hormones 101
Second Edition (2025) Chapters 19



Breast Cancer Survivors Using HRT in U.S.?

- **1993:** 2.5 million breast cancer survivors in the U.S.
- 10 percent or 250,000 used HRT.
- **2024:** 4 million breast cancer survivors.
- 10 percent or 400,000 use HRT.
- (Marchant, 1993.)

6) Marchant, Douglas J. Estrogen-Replacement Therapy After Breast Cancer. Risks Versus Benefits. Cancer 1993;71(6 Suppl):2169–76.

Avrum Bluming Compiled 26 Studies

- Of the 26 studies, **25 show no increased cancer** recurrence in the hormone-treated group.
- The only study to show increased recurrence with HRT is the HABITS study by Dr. Lars Holberg from Sweden, using **Estradiol + norethisterone, a highly carcinogenic progestin derived from a testosterone backbone.**
- All patients in the HABITS trial on hormone replacement who suffered a recurrence of breast cancer were also taking **tamoxifen,** an estrogen receptor-blocking drug, a commonly used adjunctive endocrine therapy.

1) Bluming, Avrum Zvi. "Hormone Replacement Therapy After Breast Cancer: It Is Time." The Cancer Journal 28.3 (2022): 183-190.

HABITS - 300% Increase in BC

- In 2022, Dr. Avrum Bluming on the HABITS trial, writing:
- The HABITS trial was prematurely terminated in 2003, after only 2 years of follow-up,
- Only **434** of 1300 had been enrolled.
- The reason for the sudden termination was the number of women randomized to HRT who developed another breast cancer (26 of 174 = 15%), compared with only 7 of the 171 (5%) randomized to no HRT. **(300% Increase**).

1) Bluming, Avrum Zvi. "Hormone Replacement Therapy After Breast Cancer: It Is Time." The Cancer Journal 28.3 (2022): 183-190.

Avrum Bluming on HABITS 2nd

- No increase among women randomized to estrogen alone. Why?
- No increase when Premarin [CEE] (conjugated estrogens) was used as the source of estrogen. Why?
- **300 % increase only among women who were taking Tamoxifen in conjunction with HRT (Estradiol plus Norethisterone). Why?** (1)

1) Bluming, Avrum Zvi. "Hormone Replacement Therapy After Breast Cancer: It Is Time." The Cancer Journal 28.3 (2022): 183-190.

Avrum Bluming on HABITS 2nd

- TAM blocks ER-alpha!
- TAM does NOT block ER-Beta?
- Premarin activates ER-beta signaling while Tamoxifen is blocking ER-alpha.
- This explains why HABITS Pts. on Premarin HAD NO RECURRENCE, despite taking Norethisterone.

1) Bluming, Avrum Zvi. "Hormone Replacement Therapy After Breast Cancer: It Is Time." The Cancer Journal 28.3 (2022): 183-190.

TAM and ER-Beta

- TAM targets ER-beta to kill lymphoma cells in vitro. (Lanendonk, 2022)
- 2025 Dr. Gokul M. Das: These findings add to the evidence suggesting a role of [TAM] estrogen modulator therapy in **enhancing ER-beta levels and the ensuing antiproliferative ER-beta-mutant p53 interaction**. (Das, Gokul, 2025)

Das, Gokul M. "Interaction between Estrogen Receptors and p53: A Broader Role for Tamoxifen?." Endocrinology (2025): bqaf020.
Langendonk, Myral. "Identification of estrogen receptor beta as tamoxifen-sensitive target in B-cell lymphoma." Blood cancer journal 12.3 (2022): 36.

Reviewing the 26 Studies

- Question?
- Which of the 26 studies had the best outcomes?

1) Bluming, Avrum Zvi. "Hormone Replacement Therapy After Breast Cancer: It Is Time." The Cancer Journal 28.3 (2022): 183-190.

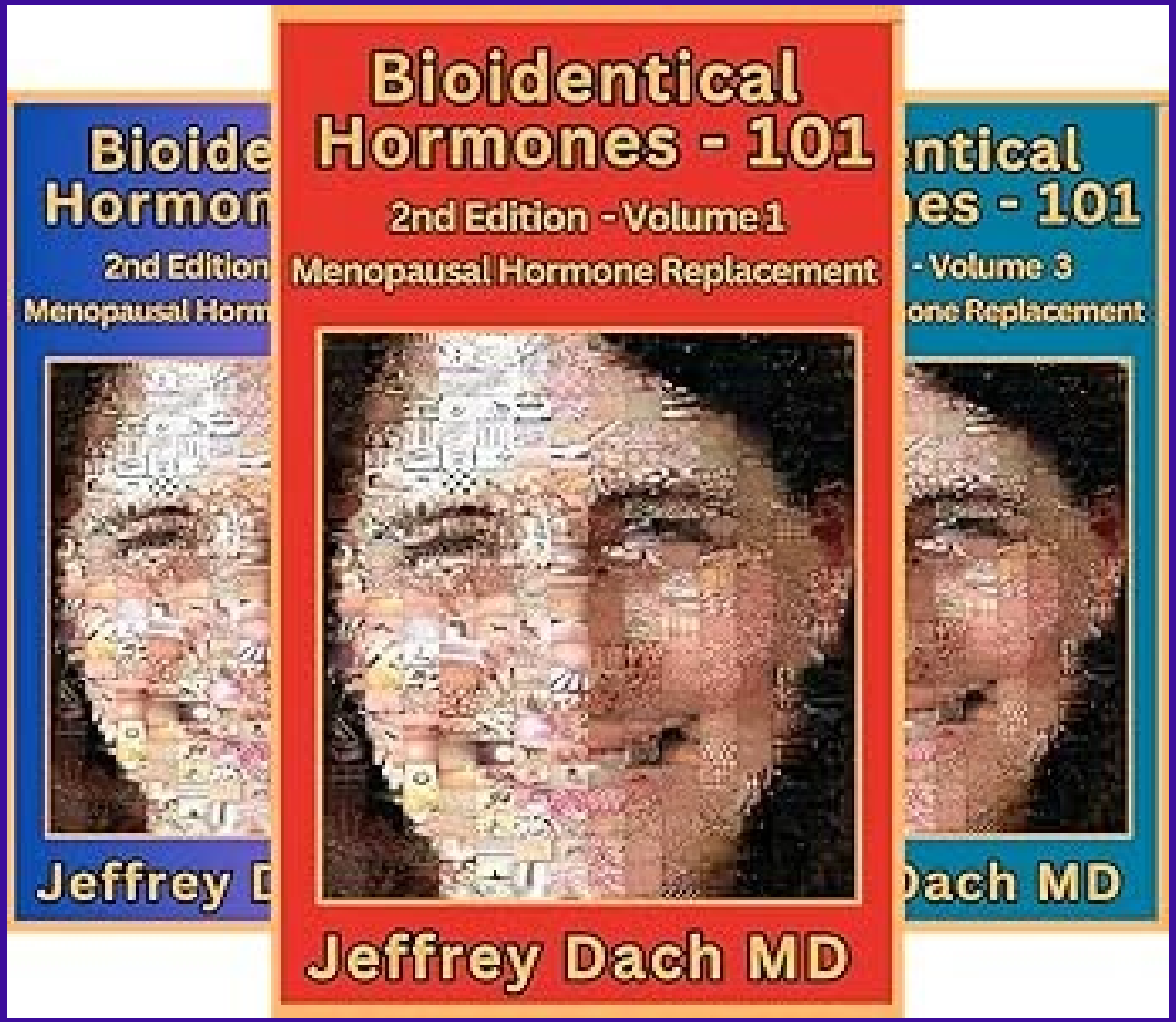
Does the HRT Contain Testosterone?

- One such study in 1999 by Dr. Puthgraman Natrajan from Augusta, Georgia included testosterone pellets in 38 of 50 patients on HRT after a diagnosis of breast cancer.
- Amazing **81% reduction in mortality in HRT users compared to non-user controls.**
- On a practical basis, all HRT formulas must include testosterone for its superb ability to prevent breast cancer. (60)

60) Natrajan, Puthgraman K., et al. "Estrogen Replacement Therapy in Women with Previous Breast Cancer." American Journal of Obstetrics and Gynecology 181.2 (1999): 288-295.


STOP

Part Two – Jeffrey Dach MD



Vaginal Estrogen Associated with Exceptionally Good Outcomes

- In 2002, Dr. Eva Durna from Australia:
- Excellent outcomes with vaginal E2/E3-alone in 32 breast cancer survivors in a retrospective observational study.
- This group of 32 patients showed the lowest relative risk (**RR for recurrence, 0.18** compared to non-users. **82 percent less recurrence than HRT non-users**,
- **70 percent reduction in all-cause mortality and 65 percent reduction in death from breast cancer.**
- This is astounding and is superior to anti-estrogen therapy!

13) Durna, Eva M., et al. "Hormone Replacement Therapy After a Diagnosis of Breast Cancer: Cancer Recurrence and Mortality." Med J of Australia 177.7 (2002): 347-351

Vaginal Estrogen - Exceptionally Good Outcomes

- Dr. Durna writes:
- Vaginal estrogens included estriol [E3] cream (0.5 g) and estradiol [E2] vaginal tablets (25 microg) used twice weekly…vaginal estrogen (n=32)…those who used vaginal estrogen alone [32 patients] had significantly lower risk of recurrence or new breast cancer **(adjusted RR, 0.18)…** we believe that the current practice of withholding HRT from women with breast cancer who suffer menopausal symptoms may need review. (13)

13) Durna, Eva M., et al. "Hormone Replacement Therapy After a Diagnosis of Breast Cancer: Cancer Recurrence and Mortality." Med J of Australia 177.7 (2002): 347-351.

Eight Vaginal Estrogen Patients

- In 2001, Dr. George N. Peters, a breast surgeon in Dallas Texas studied HRT use in breast cancer survivors, finding eight vaginal estrogen patients in his study group that had results so outstanding, they were reported separately so as not to skew the results of the main study. The exact type of vaginal estrogen cream, whether E2 or E3 was not specified.
- In these eight patients followed for 11.4 years, there were **no cancer recurrences and no deaths.**

61) Peters, George N., et al. "Estrogen Replacement Therapy After Breast Cancer: A 12-Year Follow-Up." Annals Of Surgical Oncology 8 (2001): 828-832.

Eight Vaginal Estrogen Patients

- Dr. Peters writes:
- Of the eight patients who have used only vaginal cream ERT [estrogen replacement therapy], median follow-up from diagnosis was 11.4 years, and median time on ERT since diagnosis was 4.0 years.
- There have been no contralateral breast cancers; no local, regional, or distant recurrences; and no cancer deaths in this group. it is reasonable to conclude that ERT does not appear to have an adverse effect on cancer outcome. (61)

61) Peters, George N., et al. "Estrogen Replacement Therapy After Breast Cancer: A 12-Year Follow-Up." Annals Of Surgical Oncology 8 (2001): 828-832.

More on Vaginal Estrogen

- A 2019 meta-analysis of **58** epidemiological studies from **21** countries including **143,887** postmenopausal women with invasive breast cancer and **424,972** without breast cancer serving as controls.
- **Vaginal delivery of estrogen is the only form of menopausal hormone replacement NOT associated with increased breast cancer risk.**
- Note: this 2019 Lancet study is not a breast cancer survivor study. It includes only every-day postmenopausal HRT users. This study also found greater breast cancer risk when synthetic progestins are used.

4) Collaborative Group on Hormonal Factors in Breast Cancer. "Type And Timing of Menopausal Hormone Therapy and Breast Cancer Risk: Meta-Analysis of Worldwide Epidemiological Evidence." The Lancet 394.10204 (2019): 1159-1168.

More on Vaginal Estrogen

- The authors write:
- Every MHT [menopausal hormone therapy] type, **except vaginal estrogens**, was associated with excess breast cancer risks, which increased steadily with duration of use and were greater for estrogen-progestogen [synthetic progestins] than estrogen-only preparations. (4)

4) Collaborative Group on Hormonal Factors in Breast Cancer. "Type And Timing of Menopausal Hormone Therapy and Breast Cancer Risk: Meta-Analysis of Worldwide Evidence." The Lancet 394.10204 (2019): 1159-1168.

Dr. H. Lyytinen in Finland

- In 2006, Dr. H. Lyytinen in Finland studied **110,000 post** menopausal women using HRT.
- Dr. H. Lyytinen found **vaginal use of any type of estrogen-alone (without progestin) was not associated with increased breast cancer risk,** writing:
- The use of estradiol [without progestin] was associated with an increased risk of breast cancer after 5 years of use (incidence ratio IR=1.3-1.4).
- Neither an **oral estriol [E3]** regimen nor **vaginal use of any estrogen formulations** were accompanied by a significantly increased risk of breast cancer. (62)

62) Lyytinen H, et al. Breast Cancer Risk in Postmenopausal Women Using Estrogen-Only Therapy. Obstet Gynecol. 2006;108(6):1354-1360.

Vaginal Estrogen Breast cancer survivors

- In 2024, Dr. Lauren McVicker studied breast cancer survivors using vaginal estrogen in two large cohorts of **49,237** females in Scotland and Wales.
- About 5% used vaginal estrogen, and these women had a **23% reduction in breast cancer mortality** compared to nonusers.

64) McVicker, Lauren, et al. "Vaginal Estrogen Therapy Use and Survival In Females With Breast Cancer." JAMA Oncology 10.1 (2024): 103-108.

Vaginal Estrogen Breast Cancer Survivors

- What About Vaginal Estrogen in Women Taking Aromatase Inhibitors?

64) McVicker, Lauren, et al. "Vaginal Estrogen Therapy Use and Survival In Females With Breast Cancer." JAMA Oncology 10.1 (2024): 103-108.

Vaginal Estrogen Breast Cancer Survivors

- 2024 JAMA Dr. Lauren McVicker writes:
- A recent observational Danish study [**Søren Cold,** 2022] showed no increase in recurrence in patients with breast cancer who received vaginal estrogen therapy **aside from a sub-group who received both vaginal estrogen therapy and aromatase inhibitors (39% increased recurrence)**
- the cohort comprised 49,237 females with breast cancer (between 40 and 79 years of age) and 5,795 breast cancer-specific deaths. **Five percent of patients with breast cancer used vaginal estrogen therapy after breast cancer diagnosis.**
- In vaginal estrogen therapy users compared with HRT nonusers, there was no evidence of a higher risk of breast cancer-specific mortality in the pooled fully adjusted model (**HR, 0.77**)

64) McVicker, Lauren, et al. "Vaginal Estrogen Therapy Use and Survival In Females With Breast Cancer." JAMA Oncology 10.1 (2024): 103-108.

Vaginal Estrogen Breast Cancer Survivors

- Conclusions and relevance:
- Results of this study showed no evidence of increased early breast cancer-specific mortality in patients who used vaginal estrogen therapy compared with patients who did not use HRT.
- This finding may provide some reassurance to prescribing clinicians and support the guidelines suggesting that vaginal estrogen therapy can be considered in patients with breast cancer and genitourinary symptoms. (64) (79)

64) McVicker, Lauren, et al. "Vaginal Estrogen Therapy Use and Survival In Females With Breast Cancer." JAMA Oncology 10.1 (2024): 103-108.

Adding AI to Vag HRT Increases Recurrence 39%

- **In 2022, Dr. Søren Cold from Denmark** : observational cohort study using a national prescription registry of 8,461 women not using HRT diagnosed with breast cancer. After the breast cancer diagnosis was confirmed, **1,957** of the original 8,467 women used VET [vaginal estrogen therapy] and **133** used MHT [systemic menopausal hormone therapy].
- The women were followed 9.8 years for recurrence and 15.2 years for mortality.
- No increased risk of breast cancer recurrence for VET or MHT users, compared to non-users.
- **Women using VET in the subgroup also receiving adjuvant aromatase inhibitors, the recurrence rate was increased by 39 percent.**

79) Cold, Søren, et al. "Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study." Journal of the National Cancer Institute 114.10 (2022): 1347-1354.

Aromatase Inhibitor Increases Recurrence in Breast Cancer Survivors on VAG HRT

- Dr. Søren Cold writes:
- Overall, there was no increased risk of recurrence but notably the risk of recurrence (but not mortality) was increased in women using **VET [vaginal estrogen therapy] whilst also taking an aromatase inhibitor (HR 1.39).** (79)

79) Cold, Søren, et al. "Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study." Journal of the National Cancer Institute 114.10 (2022): 1347-1354.

Aromatase Inhibitor Reduces Outcome in HRT Mice with Breast Cancer

- In 2014, Drs. A. Arumugam and Rajkumar Lakshmanaswamy studied ovarectomized mice xenografted with human breast cancer cells, after which the mice were treated with various combinations of natural hormones, estrogen, progesterone, testosterone, and DHEA.
- **Natural hormone-treated mice had a maximum reduction in tumor growth and better outcomes.**
- **Outcomes were reduced by adding an AI (aromatase inhibitor) drug to the treated mice.**

81) Lakshmanaswamy, Rajkumar,"Hormone-Induced Protection of Mammary Tumorigenesis In Genetic Engineered Mouse Models." Breast Cancer Res 9 (2007): 1-11.
82) Arumugam, Arunkumar, and Rajkumar Lakshmanaswamy. “Hormones and Aromatase Inhibitors On Breast Tumor Growth In Postmenopausal Mouse Model.” Reproductive Biology and Endocrinology 12 (2014): 1-13.

- Adding Aromatase Inhibitor to Vaginal HRT Worsens the Outcome!

Speculative Thoughts on Vag E

- Firstly, in the studies using estrogen alone via transvaginal delivery, there was no added carcinogenic progestin. This could explain improved outcomes.
- The second explanation is that many of the vaginal preparations contain estriol (E3) which preferentially binds to ER-beta, the tumor suppressor.
- Thirdly, vaginal route has a much better absorption rate compared to transdermal route, reaching higher blood levels without first pass through the liver.
- Thus, vaginal estrogen (Bi-est is 20% estradiol E2 and 80% estriol E3), used at systemic doses, **closely mimics the high hormone levels of pregnancy which is known for centuries to confer protection from breast cancer.** (65-69)

Pregnancy Reprograms the Epigenome

- 2020: Dr. Mary Feigman found that in this CAGMYC mouse model, pregnancy conferred protection from cancer by increasing the P53 protein content in the MECs (mammary epithelial cells),
- **Pregnancy modified the epigenome** of the mice, and made the MECs less responsive to cMYC oncogene overexpression, thus blocking the development of premalignant lesions.

Feigman, Mary J., et al. "Pregnancy reprograms the epigenome of mammary epithelial cells and blocks the development of premalignant lesions." Nature communications 11.1 (2020): 2649..

- 65) Mal, Rahul "ER-Beta : Ligand Activated Tumor Suppressor." Front Onc 10 (2020): 587386.
- 66) Beste, Mary E., "Vaginal Estrogen Use in Breast Cancer Survivors: A Systematic Review and Meta-Analysis of Recurrence and Mortality Risks." Am J of Obstetrics and Gynecology (2024).
- 67) Agrawal, Pranjal, "Safety of Vaginal Estrogen for Genitourinary Syndrome of Menopause with history Of Breast Cancer." Ob & Gyne (2022): 10-1097.
- 68) Moegele, M."Vaginal Estrogen Therapy for Patients with Breast Cancer." Geburt und Frauen 73.10 (2013): 1017-1022.
- 69) Dew, Jennifer. E , John A. Eden. "A Cohort Study of Vaginal Estrogen Therapy in Women Previously Treated For Breast Cancer." Climacteric 6.1 (2003): 45-52.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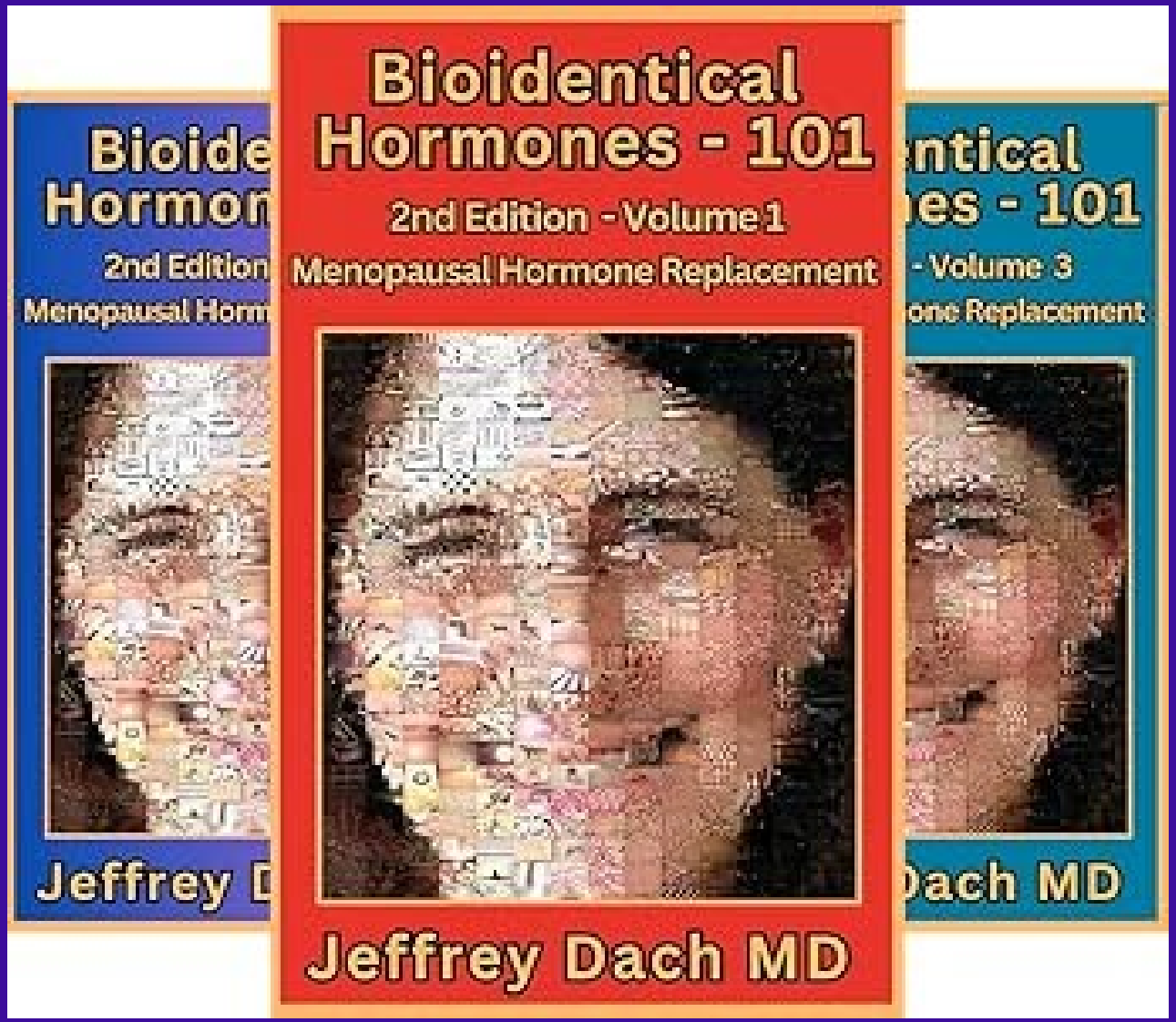
Part Three – Jeffrey Dach MD



Premarin (CEE) Cancer Preventive

- The cancer preventive properties of Premarin (CEE)
- vs. the proliferative properties of estradiol
- were recognized in 2019 by Richard J. Santen,
- What Are the Unique Properties of CEE, Premarin?

75) Santen, R. J., and W. Yue. "Cause or Prevention of Breast Cancer with Estrogens: Analysis from Tumor Biologic Data, Growth Kinetic Model and Women's Health Initiative study." Climacteric 22.1 (2019): 3-12.

Unique Properties of Premarin (CEE) Cancer Preventive

- B-ring unsaturated steroids in Premarin (CEE) are not made from cholesterol and are not present in humans.
- B-ring steroids act preferentially on ER-beta, the tumor suppressor receptor, and thus are cancer-protective, much like Estriol and Testosterone metabolites 3-beta-diol, which also preferentially target ER-beta.

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.

Premarin (CEE) Cancer Preventive

- In 2008, Dr. Bhagu Bhavnani :
- Some of these unique estrogens [ring B unsaturated estrogens] had **two to four times greater affinity for ER beta than ER alpha**...
- the effects of ring B unsaturated estrogens are **mainly mediated via ER-beta** and that the presence of both ER subtypes further enhances their activity.

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.

HABITS vs. Stockholm

- The Two Parallel Studies in Sweden.
- HABITS by Lars Holmberg (2004)
- Stockholm study by Dr. Eva von Schoultz (2005)

87) von Schoultz Eva, Menopausal Hormone Therapy After Breast Cancer: The Stockholm Randomized Trial. J Natl Cancer Inst. 2005; 97:533–535.
38) Holmberg, Lars. "HABITS (Hormonal Replacement Therapy After Breast Cancer Is It Safe?), RCT: Trial Stopped." The Lancet 363.9407 (2004): 453-455.
39) Holmberg, Lars. "Increased Risk of Recurrence After Hormone Replacement Therapy In Breast Cancer Survivors." J of the National Cancer Institute 100.7 (2008): 475-482.

2005 Stockholm Study Dr. Eva von Schoultz

- Dr. Eva von Schoultz (Stockholm study) recognized the carcinogenic effect of progestins.
- She modified the Stockholm study design to minimize the use of the progestin, medroxyprogesterone (MPA), thought to be less carcinogenic than the norethisterone used in the HABITS study.
- This modification was a reduction in exposure time to the progestin.

87) von Schoultz Eva, Rutqvist LE, Stockholm Breast Cancer Study Group. Menopausal Hormone Therapy After Breast Cancer: The Stockholm Randomized Trial. J Natl Cancer Inst. 2005; 97:533–535.

2005 Stockholm Study Dr. Eva von Schoultz

- Instead of continuous progestin use (MPA), this was changed to sequential use for 10 days per month, every third month in 73 percent of the women.
- **RR value of 0.82 for recurrence in the hormone-treated group, meaning there was 18 percent less recurrence for HRT users compared to non-users in the Stockholm Study.**

87) von Schoultz Eva, Rutqvist LE, Stockholm Breast Cancer Study Group. Menopausal Hormone Therapy After Breast Cancer: The Stockholm Randomized Trial. J Natl Cancer Inst. 2005; 97:533–535.

2005 Stockholm Study Dr. Eva von Schoultz

- 18 percent less cancer recurrence for HRT users.
- Both Total Mortality and Breast Cancer Mortality was Reduced in Half compared to non-users.

87) von Schoultz Eva, Rutqvist LE, Stockholm Breast Cancer Study Group. Menopausal Hormone Therapy After Breast Cancer: The Stockholm Randomized Trial. J Natl Cancer Inst. 2005; 97:533–535.

Ranking Hormone Formulas by Carcinogenicity

- **Most Carcinogenic - HABITS:**
- Oral estradiol combined with oral norethisterone while on tamoxifen.
- This is the HABITS trial finding 3-fold greater breast cancer recurrence in the HRT group, and all recurrent cancers were using **tamoxifen**, an estrogen blocker.

76) Holmberg L, Anderson H. HABITS (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?), A Randomised Comparison: Trial Stopped. Lancet. 2004; 363:453–455.

77) Holmberg, Lars, et al. "Increased Risk of Recurrence After Hormone Replacement Therapy in Breast Cancer Survivors." Journal of the National Cancer Institute 100.7 (2008): 475-482.

Ranking Hormone Formulas by Carcinogenicity

- **Less Carcinogenic (E2 +MPA):**
- Oral estradiol plus oral medroxyprogesterone
- Dr. Agnes Fournier French Cohort Study: increased risk of breast cancer (RR=1.69). (92)

92) 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.

Ranking Hormone Formulas by Carcinogenicity

- **Neutral: Oral Premarin plus oral medroxyprogesterone (MPA)**
- (The corrected 2002 first arm WHI study shows no increased breast cancer, once prior estrogen exposure is removed from the placebo group.
- Avrum Bluming and Howard Hodis (2023).

49) Bluming, Avrum Z., Howard N. Hodis, and Robert D. Langer. "'Tis but a Scratch: A Critical Review of The Women's Health Initiative Evidence Associating Menopausal Hormone Therapy with The Risk of Breast Cancer." Menopause (2023): 10-1097.

51) 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.

Ranking Hormone Formulas by Carcinogenicity

Preventive: Oral Premarin Alone: Better than Tamoxifen in ER-negative Breast Cancer !

- In 1999 Dr. Rena Vassilopoulou-Sellin followed 319 breast cancer survivors prospectively **four years.**
- 39 of these were treated with oral Premarin-alone (CEE) 0.625 mg on days 1–25 of each month. 75% were ER-negative and the other 25% had unknown ER status.
- Premarin reduced breast cancer recurrence to **one-half** that of non-users (1/39=2.6% vs. 14/280=5.0%).
- **No Deaths** in the Premarin (CEE) treated group.

93) Manna, Subrata, and Marina K. Holz. "Tamoxifen Action in ER-Negative Breast Cancer." Signal transduction insights 5 (2016): 1.
94) Vassilopoulou-Sellin, Rena, et al. "Estrogen Replacement Therapy After Localized Breast Cancer: Clinical Outcome Of 319 Women Followed Prospectively." Journal Of Clinical Oncology 17.5 (1999): 1482-1482.

Preventive: Oral Premarin Alone

- Among the 39 patients in this study, 75% were ER-negative and the other 25% had unknown ER status. Note: ER-negative breast cancers are usually not treated with Tamoxifen, as this drug is ineffective in ER-negative breast cancer.
- Hence, a **50% reduction in recurrence** with Premarin is a marked improvement compared to the expected eventual disease progression in all patients on Tamoxifen for ER-negative breast cancer. **This study is remarkable because it shows a good outcome using estrogen (CEE) therapy for ER-negative cell types that do not respond to estrogen-blocking drugs.**

94) Vassilopoulou-Sellin, Rena, et al. "Estrogen Replacement Therapy After Localized Breast Cancer: Clinical Outcome Of 319 Women Followed Prospectively." Journal Of Clinical Oncology 17.5 (1999): 1482-1482.

Ranking Hormone Formulas by Carcinogenicity

Tamoxifen does not work in ER-negative Breast Cancer !

- The Early Breast Trialists Group meta-analysis of 55 clinical trials with 30,000 women reported that 5 years of TAM after Rx for (ER+) BC:
- Tamoxifen reduced the risk of breast cancer **recurrence** by **47%**.
- Reduced the risk of death from breast cancer by **26%** (1). Das, Gokul, 2025

Das, Gokul M., Chetan C. Oturkar, and Vishnu Menon. "Interaction between Estrogen Receptors and p53: A Broader Role for Tamoxifen?." Endocrinology (2025): bqaf020..

Preventive: Oral Premarin Alone

- In 2018, Dr. Zexian Zeng from the Northwestern University Feinberg School of Medicine searched the Northwestern Medicine Enterprise Data Warehouse for menopausal HRT use. Dr. Zexian Zeng studied breast cancer risk associated with various HRT preparations:
- **Premarin-alone** use is associated with an impressive **69 percent reduction in risk for breast cancer**. This result far exceeds the results obtained with estrogen-blocking drugs, tamoxifen and AI.

96) Zeng, Zexian, et al. "Conjugated Equine Estrogen and Medroxyprogesterone Acetate Are Associated with Decreased Risk Of Breast Cancer Relative To Bioidentical Hormone Therapy And Controls." PLoS One 13.5 (2018): e0197064.

Preventive: Oral Premarin Alone

- Dr. Zexian Zeng writes:
- CEE [Premarin] Alone is associated with decreased breast cancer risk (HR =**0.31**),
- Bioidentical Estrogen Alone is associated with decreased breast cancer risk **(HR =0.65**).
- Synthetic Estrogen Alone is associated with increased breast cancer risk (HR =1.49)

96) Zeng, Zexian, et al. "Conjugated Equine Estrogen and Medroxyprogesterone Acetate Are Associated with Decreased Risk Of Breast Cancer Relative To Bioidentical Hormone Therapy And Controls." PLoS One 13.5 (2018): e0197064.

Ranking Hormone Formulas by Carcinogenicity

Most Preventive: Adding Testosterone to the HRT:

- In 1999, Puthgraman K Natrajan from Augusta, Georgia studied 50 breast cancer survivors on HRT which included testosterone pellets in 40 of the 50 patients.
- The HRT/testosterone users had an **81% reduction in mortality compared to non-users.** (60)

60) Natrajan, Puthgraman K., et al. "Estrogen Replacement Therapy in Women with Previous Breast Cancer." American Journal of Obstetrics and Gynecology 181.2 (1999): 288-295.

Ranking Hormone Formulas by Carcinogenicity

Most Preventive: Vaginal E2 or CEE (alone)

- In 2001, Dr. George Peters from Texas studied 8 patients using vaginal estrogen alone after breast cancer followed for 11.4 years. There were **no cancer recurrences and no cancer deaths in this group**. (61)
- In 2002, Dr. Eva Durna from Australia reported a group of 32 vaginal estrogen users with an **82 percent reduction** in breast cancer recurrence compared to non-users. (13)

61) Peters, George N., et al. "Estrogen Replacement Therapy After Breast Cancer: A 12-Year Follow-Up." Annals Of Surgical Oncology 8 (2001): 828-832., 13) Durna, Eva M., et al. "Hormone Replacement Therapy After a Diagnosis of Breast Cancer: Cancer Recurrence and Mortality." Medical Journal of Australia 177.7 (2002): 347-351.

Ranking Hormone Formulas by Carcinogenicity

Most Preventive: Vaginal Biest/Progesterone with Testosterone

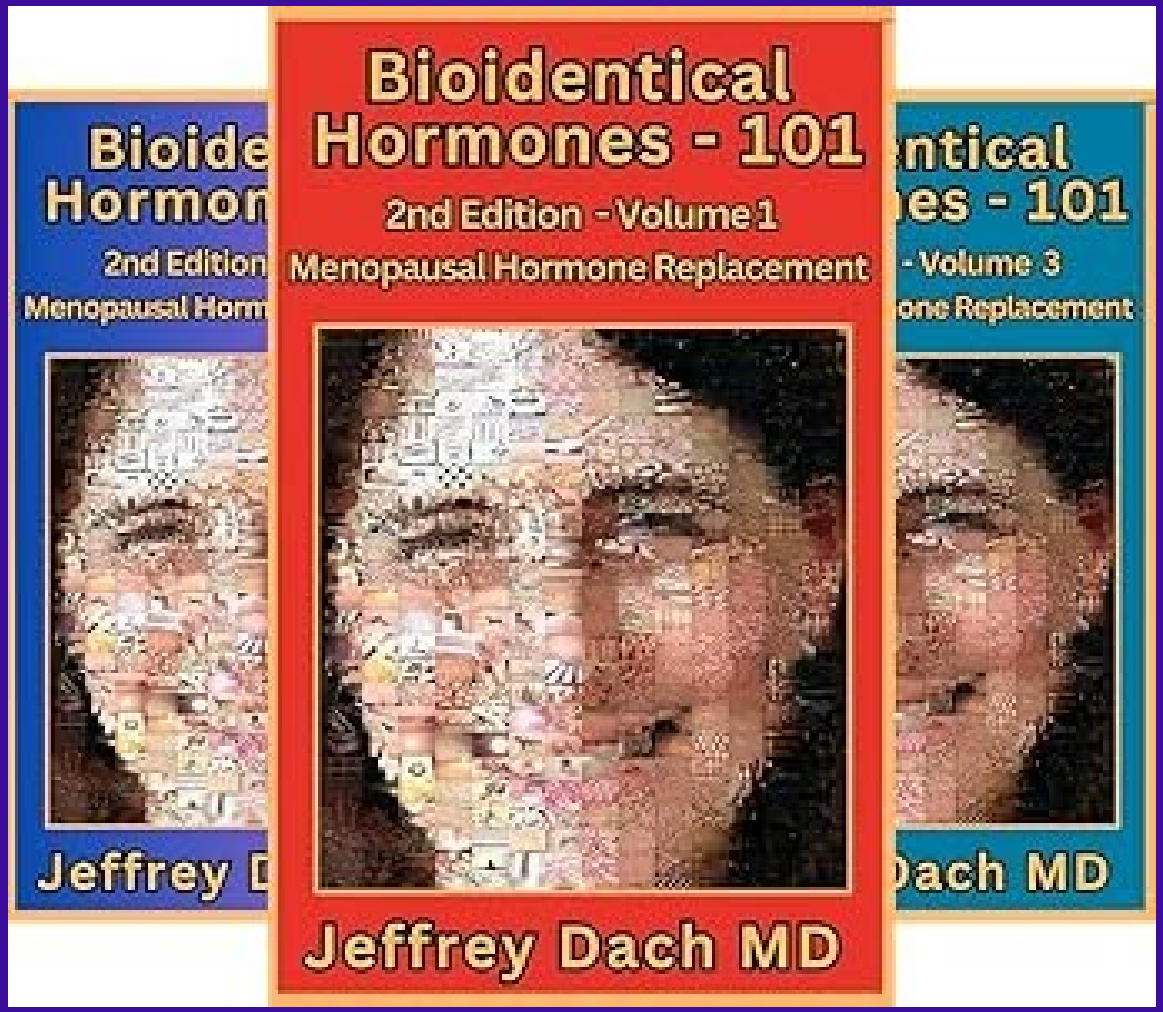
- Bi-est contains 20 percent estradiol E2, and 80 percent estriol (E3).
- The E3 binds preferentially to ER-Beta and is breast cancer preventive.
- Progesterone and Testosterone both act as a proliferative break on ER-alpha activity.
- Testosterone metabolite 3-beta-Adiol preferentially binds to ER-beta.
- The vaginal route of delivery may more closely mimic the protective hormone levels of pregnancy.
- This is the preferred formula used in my office.

Dach, Jeffrey *Bioidentical Hormones 101* Second Edition (2005)


STOP

Part Four – Jeffrey Dach MD

Hormone Replacement for Breast Cancer Survivors



Zsuzsanna Suba MD PhD, Semmelweis University in Budapest:

- Medical science has misunderstood the connection between estrogen signaling and the development of breast cancer.
- Mainstream medicine ignores the role of estrogen in DNA stabilization and maintenance of genome stability.
- Estrogen works closely in association with the BRCA gene, a tumor suppressor gene involved in DNA repair, cell cycle control, apoptosis, and genome stability.

Zsuzsanna Suba MD PhD

13) Suba, Zsuzsanna. “Rosetta Stone for Cancer Cure: Comparison of The Anticancer Capacity of Endogenous Estrogens, Synthetic Estrogens and Antiestrogens.” Onc Rev 17 (2023): 10708.
14) Suba, Zsuzsanna. "DNA Damage Responses in Tumors Are Not Proliferative Stimuli, but Rather They Are DNA Repair Actions Requiring Supportive Medical Care." Cancers 16.8 (2024): 1573.
21) Suba, Zsuzsanna. “DNA Stabilization by The Upregulation of Estrogen Signaling In BRCA Gene Mutation Carriers.” Drug Design, Development and Therapy (2015): 2663-2675.
22) Suba, Zsuzsanna. “The Pitfall of The Transient, Inconsistent Anticancer Capacity of Antiestrogens and The Mechanism of Apparent Antiestrogen Resistance.” Drug Design, Development and Therapy (2015): 4341-4353.
23) Suba Z. DNA Stabilization by The Upregulation of Estrogen Signaling In BRCA Gene Mutation Carriers. Drug Design Devel Ther. 2015;9: 2663–2675.

The Three Phases of Antiestrogen Administration

- In 2015, Dr. Zsuzsanna Suba: mechanism of antiestrogen resistance. (TAM or AI)
- First phase, preservation of estrogen signaling indicates successful antiestrogen therapy with tumor regression.
- Second phase, the tumor appears stable with no progression.
- Third and final phase, the tumor cell's ability to compensate by upregulating ERs and aromatase enzyme is exhausted leading to rapid proliferation, metastatic disease, and death,

29) Suba, Zsuzsanna. “The Pitfall of the Transient, Inconsistent Anticancer Capacity of Antiestrogens and The Mechanism of Apparent Antiestrogen Resistance.” Drug Design, Development and Therapy 9 (2015): 4341.

HABITS Study, What Went Wrong?

- **Tamoxifen Resistance !**
- **Anti-Estrogen Resistance !**

29) Suba, Zsuzsanna. “The Pitfall of the Transient, Inconsistent Anticancer Capacity of Antiestrogens and The Mechanism of Apparent Antiestrogen Resistance.” Drug Design, Development and Therapy 9 (2015): 4341.

HABITS Study, What Went Wrong?

- **Patients with breast cancer recurrence were all taking tamoxifen** which blocked the estrogen receptors, so giving exogenous estradiol (E2) is a futile gesture. The exogenous estrogen can not reach the blocked receptors.
- **The first phase of tamoxifen resistance** is a desperate attempt by the breast cells to upregulate estrogen receptors and estrogen signaling. **When this fails, the cancer cell switches from estrogenic to androgenic signaling.**

29) Suba, Zsuzsanna. "The Pitfall of Antiestrogens and Mechanism of **Antiestrogen Resistance**." Drug Design, Dev and Ther 9 (2015): 4341.

HABITS Study, What Went Wrong?

- Dr. Charles Dai (2023), AR (androgen receptor) can bind to the same DNA regions as the ER (estrogen receptor).

42) Dai, Charles, and Leif W. Ellisen. “Revisiting Androgen Receptor Signaling in Breast Cancer.” The Oncologist 28.5 (2023): 383-391.

HABITS Study, What Went Wrong?

- **In 2021, Dr. Theresa E. Hickey**
- In-vitro breast cancer study finding AR (androgen receptor protein) was detected at 42% of estrogen-stimulated ER-binding sites on chromatin.
- Thus, androgens are upregulated to replace deficient estrogen signaling during anti-estrogen treatment. In addition, androgen signaling, much like estrogen, can induce apoptosis within breast cancer cells.

40) Hickey, Theresa E., et al. “Minireview: The Androgen Receptor in Breast Tissues: Growth Inhibitor, Tumor Suppressor, Oncogene?” Molecular Endocrinology 26.8 (2012): 1252-1267.

41) Hickey, Theresa E. et al. The Androgen Receptor Is a Tumor Suppressor in Estrogen Receptor-Positive Breast Cancer. Nat. Med. 2021, 27, 310–320.

Blocking Both Estrogen and Androgen Signaling

- What happened when the HABITS trial patient on tamoxifen was given the synthetic progestin, norethisterone, an androgen receptor-blocking drug?
- Assuming that androgens represent an alternate estrogen signaling pathway, we can now speculate what happened.
- Tamoxifen blocks the estrogen receptors, and the cancer cell will then try to compensate by upregulating ER-alpha.
- When this fails, androgen signaling is upregulated as an alternate pathway.
- The norethisterone synthetic progestin drug blocks this alternate pathway.

29) Suba, Zsuzsanna. “The Pitfall of Antiestrogens and The Mechanism of Apparent Antiestrogen Resistance.” Drug Design, Development and Therapy 9 (2015): 4341.

Blocking Both Estrogen and Androgen Signaling

- According to Dr. Suba's three phases of antiestrogen administration, I speculate that these two drugs, tamoxifen and progestin together completely blocked all ER signaling, and exhausted the cancer cells' ability to compensate, thus leading to tamoxifen resistance and aggressive cancer progression.
- Resulting in a 300 percent increased cancer recurrence. This is bad.

29) Suba, Zsuzsanna. “The Pitfall of the Transient, Inconsistent Anticancer Capacity of Antiestrogens and The Mechanism of Apparent Antiestrogen Resistance.” Drug Design, Development and Therapy 9 (2015): 4341.

Time to Re-Examine Clinical Strategy for Breast Cancer Risk Reduction

- In 2021, Dr. Rowan Chlebowski Professor of Medicine and Chief of Medical Oncology and Hematology at UCLA Medical Center agrees with Dr. Zsuzsanna Suba:
- The use of antiestrogens for primary prevention of breast cancer is a medical mistake !

89) Chlebowski, Rowan T., et al. "Breast Cancer Prevention: Time for Change." JCO Oncology Practice 17.12 (2021): 709-716.

Dr. Rowan Chlebowski Primary Prevention No Mortality Benefit from TAM or AI

- Endocrine-targeted agents (tamoxifen and aromatase inhibitors) reduce [the incidence of] estrogen receptor (ER)–positive, progesterone receptor (PR)–positive cancers **without reducing deaths from breast cancer.**
- In the Women's Health Initiative randomized, placebo-controlled trial evaluating CEE conjugated equine estrogen (N = 10,739), **deaths from breast cancer were reduced 40%.**
- **"These findings suggest that reexamination of breast cancer risk reduction strategies and clinical practice is needed. "**

89) Chlebowski, Rowan T., et al. "Breast Cancer Prevention: Time for Change." JCO Oncology Practice 17.12 (2021): 709-716.

How to Prevent Breast Cancer?

- In 2015, Dr. Zsuzsanna Suba reviewed the pitfalls of anti-estrogen treatment as a prevention and treatment of breast cancer.
- Both estrogen and anti-estrogen treatments result in extreme up-regulation of estrogen signaling, the key mechanism for prevention and treatment of breast cancer.

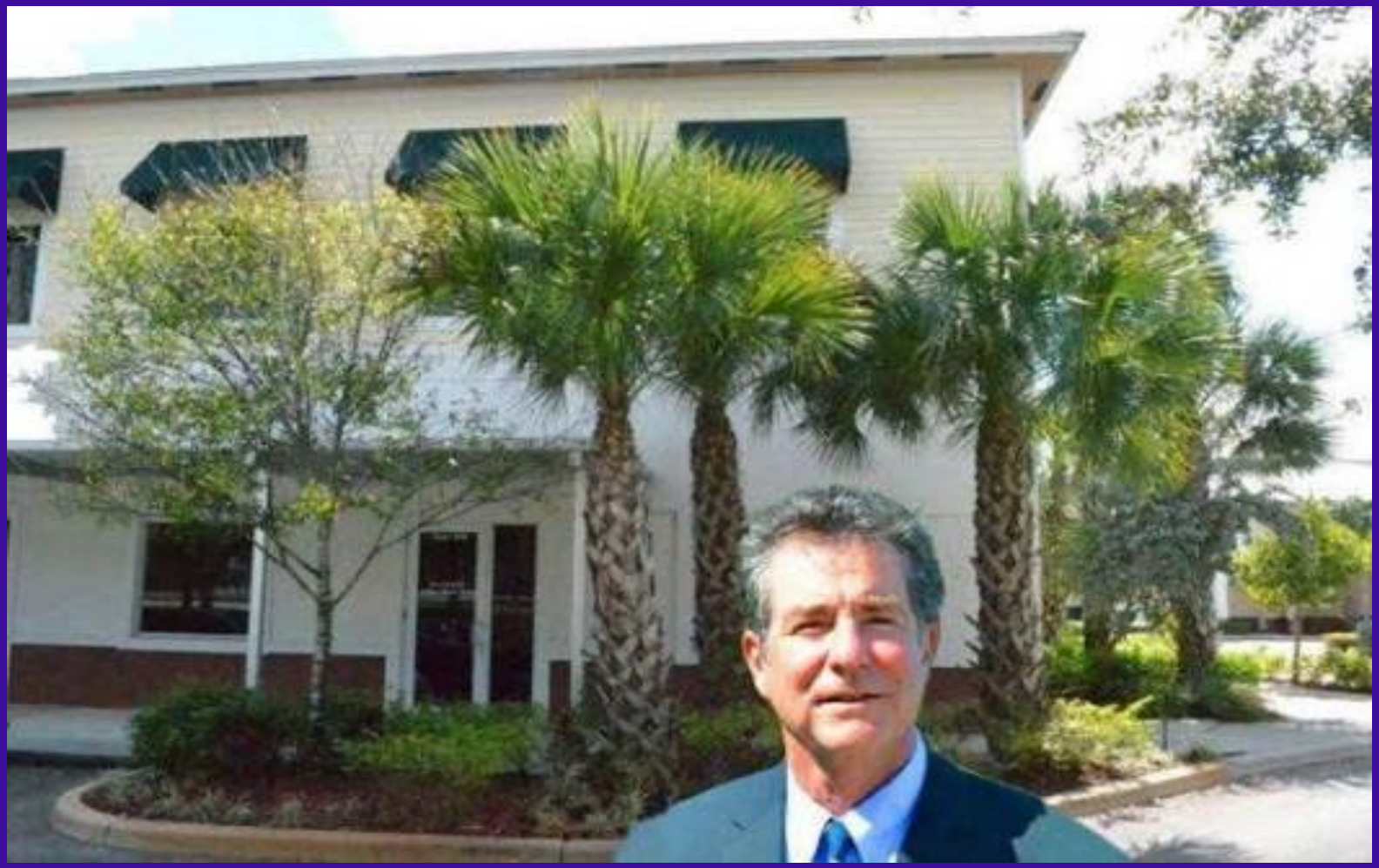
29) Suba, Zsuzsanna. “The Pitfall of the Transient, Inconsistent Anticancer Capacity of Antiestrogens and The Mechanism of Apparent Antiestrogen Resistance.” Drug Design, Development and Therapy 9 (2015): 4341.

How to Prevent Breast Cancer?

- Dr. Suba writes:
- whatever type of available endocrine therapies may be used, including estrogen, antiestrogen treatment, or oophorectomy, an **extreme upregulation of ER signaling** seems to be the crucial mechanism of successful prevention and treatment for breast cancer. (29) (114)

29) Suba, Zsuzsanna. “The Pitfall of the Transient, Inconsistent Anticancer Capacity of Antiestrogens and The Mechanism of Apparent Antiestrogen Resistance.” Drug Design, Development and Therapy 9 (2015): 4341.

Thank You – Any Questions?



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