PROGESTERONE AND THE BREAST

BIBLIOGRAPHY AND REFERENCES

1. In Defense of Progesterone: A Review of the Literature.
Lieberman A, Curtis L. Altern Ther Health Med. 2017 Nov;23(6):24-32.

A review of the medical literature concluded that natural progesterone is protective and preventative of breast cancer and may also be helpful in preventing cardiovascular disease and stroke.

2. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. Noor Asi, Khaled Mohammed, Qusay Haydour, Michael R. Gionfriddo, Oscar L. Morey Vargas, Larry J. Prokop, Stephanie S. Faubion, and Mohammad Hassan Murad. Syst Rev. 2016; 5: 121. Published online 2016 Jul 26.

Observational studies suggest that in menopausal women taking estrogen, bioidentical progesterone use may be associated with lower breast cancer risk compared to synthetic progestins.

3. Is breast cancer risk the same for all progestogens? Stute P1. Arch Gynecol Obstet. 2014 Aug;290(2):207-9.

In this population-based case-control study of breast cancer risk in 1,555 post-menopausal women, the authors concluded that estrogen-only therapy and estrogen plus bioidentical progesterone did not increase breast cancer risk. Conversely, use of tibolone or combined estrogen-progestin therapy increased breast cancer risk when initiated within 1 year of onset of menopause.

4. Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? Fournier A1, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. J Clin Oncol. 2009 Nov 1;27(31):5138-43.

Of 53,310 women in the French E3N cohort, 1,726 invasive breast cancers were identified. Use of hormone replacement therapy containing estrogen and a progestin was associated with increased breast cancer risk when initiated within the first 3 years following onset of menopause or when duration of therapy was greater than 2 years. Bioidentical hormone replacement therapy containing estrogen and progesterone did not increase breast cancer risk.

5. Pregnancy, Progesterone and Progestins in Relation to Breast Cancer Risk. Campagnoli C, Abba C, Ambroggio S, Peris C, et al. J Steroid Biochem Mol Biol (2005) 97(5):441-50.

The authors review recent findings that show that the production of progesterone during pregnancy and the use of bioidentical progesterone in hormone therapy do not increase breast cancer risk and can even protect against the development of breast cancer.

6. Serum Sex Steroids in Premenopausal Women and Breast Cancer Risk Within the European Prospective Investigation into Cancer and Nutrition (EPIC). Kaaks R, Berrino F, et al. J Natl Cancer Inst (2005); 97:755-65.

In this large multicenter study, higher serum progesterone levels were associated with a significant reduction in breast cancer risk. Additionally, elevated serum androgens in premenopausal women were associated with higher breast cancer risk.

7. Breast Cancer Risk in Relation to Different Types of Hormone Replacement Therapy in the E3N-EPIC Cohort. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F, et al. Int J Cancer (2005); 114(3):448-54.

Combined HRT with estrogen (either oral or transdermal) and synthetic progestins was found to carry a significantly increased risk of breast cancer compared with estrogens plus oral micronized progesterone. In fact, no increase in breast cancer risk was seen in the estrogen plus oral micronized progesterone group compared with estrogen alone. This large multicenter study therefore suggests that there is a dramatic difference between the effects of bioidentical progesterone versus synthetic progestins on breast cancer risk.

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8. Endogenous Estrogen, Androgen, and Progesterone Concentrations and Breast Cancer Risk Among Postmenopausal Women. Missmer SA, et al. J Natl Cancer Inst (2004); 96(24):1856-65.

Blood progesterone levels were found not to be related to breast cancer risk in this first study to investigate this in postmenopausal women. The occurrence of progesterone receptor positive tumors was the tumor type most strongly affected by all the circulating steroid hormones measured except for progesterone. Higher levels of endogenous estrogens and androgens were significantly correlated with increasing breast cancer incidence. This suggests that circulating natural progesterone does not increase breast cancer risk.

9. Progesterone Effect on Cell Growth, Ultrastructural Aspect and Estradiol Receptors of Normal Human Breast Epithelial (HBE) Cells in Culture. Malet C, Spritzer P, et al. J Ster Biochem Mol Biol (2002); 73:171-181.

In a culture system, progesterone was found to have an inhibitory effect on breast cell growth. When given following estradiol (E2), it limited the stimulatory effect of E2 on cell growth.

10. Progesterone Receptor Activation- An Alternative to SERMs in Breast Cancer. Desreux J, Kebers F, et al. Eur J Cancer (2000) Sep;36 Suppl 4: S90-1.

This review of two placebo-controlled in vivo studies and one in vitro study emphasizes the role of progestogens (specifically, progesterone and the progestin nomegestrol) in supporting healthy breast homeostasis and opposing the proliferative effects of estradiol in the breast.

11. Percutaneous Progesterone Use and Risk of Breast Cancer: Results from a French Cohort Study of Premenopausal Women with Benign Breast Disease. Plu-Bureau G, et al. Cancer Detect Prev (1999); 23(4):290-6.

This cohort study followed 1150 premenopausal French women diagnosed with benign breast disease. Topical progesterone cream, a common treatment for mastalgia in Europe, had been prescribed to 58% of the women. Follow-up accumulated 12,462 person-years. There was no association noted between progesterone cream use and breast cancer risk. Furthermore, women who had used both progesterone cream and an oral progestogen had a significant decrease in breast cancer risk (RR= 0.5) as compared to women who did not use progesterone cream. There was no significant difference in the risk of breast cancer in percutaneous progesterone users versus nonusers among oral progestogen users. These results suggest there are no deleterious effects caused by topical progesterone use in women with benign breast disease.

12. Bcl-2, Survivin and Variant CD44 v7-v10 are Downregulated and p53 is Upregulated in Breast Cancer Cells by Progesterone: Inhibition of Cell Growth and Induction of Apoptosis. Formby B, Wiley TS, et al. Mol Cell Biochem (1999) Dec; 202(1-2):53-61.

This study sought to elucidate the mechanism by which progesterone inhibits the proliferation of breast cancer cells. Utilizing breast cancer cell lines with and without progesterone receptors (T47-D and MDA-231, respectively) in vitro, the authors looked at apoptosis (programmed cell death) in response to progesterone exposure as a possible mechanism. The genetic markers for apoptosis - p53, bcl-2 and survivin, were utilized to determine whether or not the cells underwent apoptosis. The results demonstrated that progesterone does produce a strong antiproliferative effect on breast cancer cell lines containing progesterone receptors, and induced apoptosis. The relatively high levels of progesterone utilized were similar to those seen during the third trimester of human pregnancy.

13. Progestins Inhibit the Growth of MDA-MB-231 Cells Transfected with Progesterone Receptor Complementary DNA. Lin VC, Ng EH, et al. Clin Cancer Res (1999) Feb; 5(2):395-403.

Progesterone is mainly thought to exert its effects via the estrogen-dependent progesterone receptor (PR), the effects of which may be overshadowed by the presence of estrogen. In order to study the independent effects of progesterone on breast cancer cell lines, PR expression vectors were transfected into a PR and ER negative cell line (MDA-MB-231). The growth of these cells was then studied

in response to progesterone and several progestins. Progesterone was found to significantly inhibit DNA synthesis and cell growth in a dose-dependant fashion. The results of this study indicate that progesterone and progestins independent of estrogen have an antiproliferative effect on breast cancer cells via the progesterone receptor. This suggests a possible role in the treatment of PR negative breast cancer via re-activation of the PR receptor.

14. Progesterone Inhibits Growth and Induces Apoptosis in Breast Cancer Cells: Inverse Effects on Bcl-2 and p53. Formby B, Wiley TS, et al. Ann Clin Lab Sci (1998) Nov-Dec; 28(6):360-9.

This study explored the mechanism by which progesterone inhibits breast cancer cell proliferation (growth). In progesterone receptor positive T47-D breast cancer cells, the mechanism of apoptosis appeared to be through the regulation of the genes p53 and bcl-2 by progesterone. These genes control the apoptotic process. It was demonstrated that at progesterone levels that approximate the third trimester of pregnancy, there was a strong antiproliferative effect in at least 2 breast cancer cell lines.

15. Estradiol and Progesterone Regulate the Proliferation of Human Breast Epithelial Cells. Foidart JM, Colin C, Denoo X, Desreux J, Beliard A, Fournier S, de Lignieres B, et al. Fertil Steril (1998) May; 69(5):963-9.

In this double-blind randomized study to evaluate the effects of estrogen and progesterone on normal breast cells, 40 postmenopausal women received daily topical application of a gel containing either placebo, estradiol, progesterone, or estradiol + progesterone for two weeks prior to esthetic breast surgery or the excision of a benign breast lesion. The results showed that increased estrogen concentration increased the number of cycling epithelial cells, whereas exposure to progesterone for 14 days reduced the estrogen-induced proliferation of normal breast epithelial cells.

16. Serum Progesterone and Prognosis in Operable Breast Cancer. Mohr PE, Wang DY, Gregory WM, Richards MA, Fentiman IS, et al. British Journal of Cancer (1996); 73:1532-1533.

Higher blood levels of progesterone measured during surgical treatment of breast cancers were associated with significantly better survival, especially in women who were node-positive ($P<0.01$). There was no significant relationship between estradiol levels and survival. This study demonstrated that a higher level of progesterone at time of excision is associated with improved prognosis in women with operable breast cancer.

17. Influences of Percutaneous Administration of Estradiol and Progesterone on Human Breast Epithelial Cell Cycle in Vivo. Chang KJ, et al. Fertil Steril (1995); 63(4):785-91.

The effect of transdermal estradiol (1.5 mg), transdermal progesterone (25 mg), and combined transdermal estradiol and progesterone (1.5 mg and 25 mg) on human breast epithelial cell cycles was evaluated in vivo. Results demonstrated that estradiol significantly increases cell proliferation, while progesterone significantly decreases cell replication below that observed with placebo. Transdermal progesterone was also shown to reduce estradiol-induced proliferation of normal breast epithelial cells.

18. The Proliferation of Normal Breast Tissue Implanted into Athymic Nude Mice is Stimulated by Estrogen, but not by Progesterone. Laidlaw IJ, Clarke RB, et al. Endocrinology Jan (1995); 136(1):164-71.

Normal human breast tissue was implanted subcutaneously into athymic nude mice. The mice were then treated with estradiol or progesterone such that serum levels approximated those seen in normal menstruating women.

Immunocytochemical measures were made of proliferative activity and steroid receptor expression of the tissue implants. It was found that physiologic levels of estradiol significantly stimulated the proliferation of human breast epithelial cells and increased progesterone receptor expression 10-20-fold. Progesterone failed to affect proliferation alone or after estradiol priming.

19. Double-blind Controlled Trial of Progesterone Vaginal Cream Treatment for Cyclical Mastodynia in Women with Benign Breast Disease. Nappi C, Affinito P, et al. J Endocrin Invest (1994); 15(11):801-6.

Eighty regularly menstruating women with mastodynia were studied to evaluate the clinical effectiveness of vaginally administered micronized progesterone. Subjects were randomly assigned to one of two groups, with all participating in a control cycle prior to treatment. One group received 4 grams of vaginal cream containing 2.5% natural progesterone for six cycles from day 19 to day 25 of the cycle. The other group was similarly treated with placebo. Both subjective reporting on a daily basis and clinical examination revealed a significant reduction in breast pain, defined as 50% reduction, in 64.9% of subjects receiving progesterone and 22.2% of subjects receiving placebo. Effects of breast nodularity were not significant. No side effects were detected.

20. Breast Cancer Incidence in Women with a History of Progesterone Deficiency. Cowan LD, Gordis L, Tonascia JA, et al. American Journal of Epidemiology (1981); 114:209., 083.

Infertile women were followed for 14-34 years. Those who were deficient in progesterone showed a fivefold greater incidence of premenopausal breast cancer.

21. Progesterone Induces Apoptosis in Malignant Mesothelioma Cells. Horita K, Inase N, Miyake S, Formby B, Toyoda H, Yoshizawa Y, et al. Anticancer Research (2001); 21(6A):3871-4.

Progesterone receptor gene expression was detected in a mesothelioma cell line, 211H. The administration of progesterone suppressed cell proliferation and induced apoptosis in malignant mesothelioma cells.

22. Progesterone Receptor Modulates ERa in Breast Cancer. Mohammed et al. Nature 2015.

Progesterone receptor expression modulates the behavior of estrogen receptor-alpha (ERα), which affects breast cancer prognosis. "Progesterone inhibited estrogen-mediated growth of ERα(+) cell line xenografts and primary ERα(+) breast tumor explants, and had increased anti-proliferative effects when coupled with an ERα antagonist." Higher progesterone receptor expression is associated with good clinical outcome.

Progesterone was found to significantly inhibit DNA synthesis and cell growth in a dose-dependant fashion. The results of this study indicate that progesterone and progestins independent of estrogen have an antiproliferative effect on breast cancer cells via the progesterone receptor. This suggests a possible role in the treatment of PR negative breast cancer via re-activation of the PR receptor.

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