

PROGESTERONE & BREAST CANCER

Bibliographies and References

- 1. 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.
- 2. 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.
- 3. 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.
- 4. 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.
- 5. 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.
- 6. 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 emphasizes progesterone's role in supporting healthy breast homeostasis and opposing the proliferative effects of estradiol in the breast, unlike synthetic progestins.

- 7. 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 percutaneous progesterone use in women with benign breast disease.

- 8. 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 surviving, 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.

- 9. 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.

- 10. 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.

- 11. 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.

- 12. Progestins and Breast Cancer.** Pasqualini JR, Paris J, Sitruk-Ware R, Chetrite G, Botella J, et al. *J Steroid Biochem Mol Biol* (1998) Apr; 65(1-6):225-35.

This review article outlines the many functions of progestogens in hormone-dependent and independent breast cancer and suggests new clinical applications for their use in the treatment of breast cancer.

- 13. 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.

- 14. 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.

- 15. 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.

16. **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.
17. **Antiestrogen Action of Progesterone in Breast Tissue.** Mauvais-Jarvis P, Kuttann F, Gompel A, et al. *Horm Res* (1987); 28(2-4):212-8.
In a review of international literature on the cellular effects of progesterone on both normal breast cells and breast cancer cell lines, the authors conclude that most data indicate progesterone and progestins have an antiestrogenic effect on the breast, as reflected in the decrease in estradiol receptor content, the decrease in cell proliferation, and an increase in a marker of cell differentiation, 17 beta-hydroxysteroid activity, which is mediated by the progesterone receptor.
18. **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.*
19. **Progesterone Concentrations – Physiologic or Pharmacologic?** Spicer DV, Ursin G, Pike MC, et al. *Fertil Steril* (1996); 65(5):1077-8.
20. **The Pattern of Hormonal Circadian time Structure (Acrophase) as an Assessor of Breast-Cancer Risk.** Ticher A, Haus E, Ron IG, Sackett-Lundeen L, Ashkenazite IE, et al. *International Journal of Cancer* (1996); 65(5):591-3.
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.
22. A family history of breast cancer will not predict female early onset breast cancer in a population-based setting.
[de Bock GH](#), [Jacobi CE](#), [Seynaeve C](#), [Krol-Warmerdam EM](#), [Blom J](#), [van Asperen CJ](#), [Cornelisse CJ](#), [Klijn JG](#), [Devilee P](#), [Tollenaar RA](#), [Brekelmans CT](#), [van Houwelingen JC](#).

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BACKGROUND: An increased risk of breast cancer for relatives of breast cancer patients has been demonstrated in many studies, and having a relative diagnosed with breast cancer at an early age is an indication for breast cancer screening. This indication has been derived from estimates based on data from cancer-prone families or from BRCA1/2 mutation families, and might be biased because BRCA1/2 mutations explain only a small proportion of the familial clustering of breast cancer. The aim of the current study was to determine the predictive value of a family history of cancer with regard to early onset of female breast cancer in a population based setting. **METHODS:** An unselected sample of 1,987 women with and without breast cancer was studied with regard to the age of diagnosis of breast cancer. **RESULTS:** The risk of early-onset breast cancer was increased when there were: (1) at least 2 cases of female breast cancer in first-degree relatives (yes/no; HR at age 30: 3.09; 95% CI: 1.28-7.44), (2) at least 2 cases of female breast cancer in first or second-degree relatives under the age of 50 (yes/no; HR at age 30: 3.36; 95% CI: 1.12-10.08), (3) at least 1 case of female breast cancer under the age of 40 in a first- or second-degree relative (yes/no; HR at age 30: 2.06; 95% CI: 0.83-5.12) and (4) any case of bilateral breast cancer (yes/no; HR at age 30: 3.47; 95%: 1.33-9.05). The positive predictive value of having 2 or more of these characteristics was 13% for breast cancer before the age of 70, 11% for breast cancer before the age of 50, and 1% for breast cancer before the age of 30. **CONCLUSION:** Applying family history related criteria in an unselected population could result in the screening of many women who will not develop breast cancer at an early age.