NOT ALL PROGESTERONES ARE CREATED EQUAL

A Review of Progesterone and Breast Cancer Risk

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The following article is a summary of some of the evidence surrounding the use of progesterone and seeks to clarify the debate as to whether all types of progesterone have the same physiological and clinical effects or whether there is indeed evidence to suggest that the synthetic progesterones (progestins) differ in effect to progesterone in its native molecular form. I am indebted to the commentary and detailed review published by Dr Kent Holtorf in 2009. Much of his article is so pertinent to this discussion that I have pasted sections of it below. Some of this is detailed science for those who have the appetite for it but I have also highlighted the key conclusion points for patients in the shaded boxes. My recommendation is for patients to read at least Section 1 of this article. Section 2 has the more detailed science together with highlights.

It is certainly true to say that a lot of confusion abounds on this topic and in my experience the majority of doctors are confused about this. As with all truth seeking, this can only come from a critical look at the published data and not from mainstream media or for that matter an expressed opinion that does not reference the published science.

The addition of synthetic progestins to oestrogen in HRT for menopausal symptoms, has been reported to increase the risk of breast cancer more than oestrogen alone (1). In breast cancer survivors progestin use is associated with an increased breast cancer risk compared with its non-use [2]. However, outside pregnancy, progesterone endogenously produced or exogenously administered does not have a cancer-promoting effect on breast tissue.
In postmenopausal women, progesterone is added to prevent the carcinogenic effect of oestrogen on the uterus [3]. In premenopausal women, the potency of the progestin in most oral contraceptive pills appears adequate to provide a protective effect against endometrial cancer. Progestagens counteract the adverse effect of oestrogens on the endometrium, the effect being greater the more days every month that they are added to oestrogen and the more obese that women are (3).

The notion that progesterone may increase breast cancer risk is based on a secondary follow-up of a French study (4) investigating breast cancer incidence in approximately 80,000 women who had oestrogen and various progestogens for hormone replacement therapy. It was suggested that progesterone increases breast cancer risk, contrary to popular thinking that this hormone is safe and protective against breast cancer.

Fournier et al's (5) originally study looked at the relationship of different progestogens (any molecule with a structure similar to the natural hormone progesterone that binds to and activates intracellular progesterone receptors), in combination with oestrogen, on the risk of developing breast cancer. In their first study they found that of all the progestogens studied, natural progesterone had the lowest risk, and this was lower risk than no treatment at all.

Their second study (5) in the same patient population as the first study (80,391 postmenopausal women), showed that the risk with oestrogen plus progesterone is less than the risk of oestrogen alone (1.7 vs 2.1, respectively), and that of all the progestogens, natural progesterone has the lowest risk. This study did not look at the effect of natural progesterone by itself, only oestrogen plus progesterone. A more accurate commentary on their data is that natural progesterone decreased the risk of breast cancer caused by long-term use of oestrogens (i.e. risk 2.1 to 1.7). These studies were based on the use of oral progesterone.

Women who have an excess of oestrogen relative to progesterone (low progesterone/oestradiol ratio), are more likely to have atypical benign breast disease which carry increased risk of developing into breast cancer (6). Low endogenous luteal progesterone levels in premenopause women (much more prevalent in peri-menopausal woman) have also been associated with increased breast cancer risk (7).

One small study (8) looked at the risk of breast cancer with topical progesterone (10-30 mg progesterone daily). This showed the breast cancer risk to be reduced by half (0.5) in those using topical progesterone for 3 years or more.

Oestrogen and Progesterone Receptor Positive Cancers

About 70% of breast cancers are ER+ (oestrogen receptor-positive), and most of these breast cancers (about 87%) are also PR+ (progesterone receptor-positive). Hormone receptor status is a significant factor in considering breast cancer treatment. There is a general view that having a breast cancer that is both ER+ and PR+ maybe worse then having ER+ alone.

Women with high levels of both oestrogen and progesterone receptors (high ER+ and PR+ status) often have the best chance of surviving. This information seems not to be passed onto patients. Whereas oestrogen can promote a tumor's growth, progesterone slows growth.
Oestrogen and progesterone receptors are proteins found in many of our cells, including cells in the breasts. Both receptors are directly involved in switching some 470 genes on and off; thereby affecting cell behaviour.

While oestrogen activates its receptor, turning on genes that stimulate cells to keep dividing, driving tumor growth sufficient progesterone **on the other hand will slow down the oestrogen fuelled growth and division of these cells**.

The late Dr John Lee, MD, author of *What Your Doctor May Not Tell You About Breast Cancer*, detailed this years ago. He maintained that when activated by progesterone, the progesterone receptors attach themselves to the oestrogen receptors stopping oestrogen turning on genes that promote the growth of the cancer cells. Progesterone activates genes that promote death of cancer cells (apoptosis) and the growth of healthy, normal cells.
A failure to grasp this important concept has led to many doctor"villainizing" progesterone and progesterone status.

A study published in the highly respected scientific journal *Nature in 2016,* led by Cambridge-based Cancer Research U.K. researcher Dr. Jason Carroll of the University of Adelaide in Australia, brought more awareness to the benefits of progesterone and progesterone receptor-status.

A reminder that the presence of both ER and PR status has typically been considered an indication of how good a woman's chances of surviving were. The belief being these cancers were more "treatable" than hormone receptor-negative cancers.

Carroll's study found that progesterone – via the progesterone receptor – is moderating how the oestrogen receptor works. They found that the progesterone receptor, in effect, "re-programs" the oestrogen receptor, changing the genes that it influences.

An abstract from the paper is shown below:
Progesterone receptor modulates ERα action in breast cancer
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Abstract

Progesterone receptor (PR) expression is used as a biomarker of oestrogen receptor-α (ERα) function and breast cancer prognosis. Here we show that PR is not merely an ERα-induced gene target, but is also an ERα-associated protein that modulates its behaviour. In the presence of agonist ligands, PR associates with ERα to direct ERα chromatin binding events within breast cancer cells, resulting in a unique gene expression programme that is associated with good clinical outcome. Progesterone inhibited oestrogen-mediated growth of ERα$^+$cell line xenografts and primary ERα$^+$ breast tumour explants, and had increased anti-proliferative effects when coupled with an ERα antagonist. Copy number loss of *PGR*, the gene coding for PR, is a common feature in ERα$^+$ breast cancers, explaining lower PR levels in a subset of cases. Our findings indicate that PR functions as a molecular rheostat to control ERα chromatin binding and transcriptional activity, which has important implications for prognosis and therapeutic interventions.

Their results suggest that hormone therapy with progesterone could be used in the treatment of ER-positive, PR-positive disease, which makes up about half of all diagnosed breast cancers.

This study highlights an important function for the PR receptor in modulating the behaviour of the ER in breast cancer. It confirms the previously published work that has suggested the same effect. See Section 2.

It is most important to note that the overall effect of **Progesterone on cancer cells was to cause the cells to stop growing as quickly**. Carroll's findings clarify *why* women who have both ER+ and PR+ potentially have a better outlook than those with just ER+ or receptor-negative cancers; assuming that is that progesterone forms part of their treatment regime.

Progesterone and HER2 in Breast Cancer

HER2 and Progesterone seem to be important in controlling metastatic dissemination of tumor cells prior to the detection of a primary tumor.

Researchers have known for some time that synthetic progestins, unlike progesterone, do not stimulate activation of the tumor suppressor gene p53 when it attaches to progesterone receptors.

P53 is a repair gene, which protects cells from cancerous change if progesterone is able to attach itself to progesterone receptors.

Maintaining healthy progesterone levels, avoiding synthetic progesterones and the down-regulation of HER2 seem to be desirable treatment objectives. While Herceptin is the drug of choice for HER2, one author has noted that daily consumption of 25 grams of flaxseed has been shown to decrease HER2 expression by 71%, which appears to outperform the drug, without the damaging effects of the drug.

- Use of progestins in breast cancer survivors is associated with increased risk of recurrence whereas progesterone use does not increase risk.
- The addition of progesterone to oestrogen negates the increase risk of breast cancer seen with oestrogen alone.
- Women who have an excess of estrogen relative to progesterone (low progesterone/estradiol ratio), are more likely to have atypical benign breast disease and increased risk of developing into breast cancer.
- Women with breast cancers with high levels of oestrogen receptors and progesterone receptors have the best chance of survival.
- Sufficient progesterone will slow down the oestrogen fuelled growth and division of breast cancer cells.
- Progesterone, not progestins, activates genes that promote death of cancer cells (apoptosis) and the growth of healthy, normal cells.
- Carroll's study published in Nature in 2015 showed that progesterone acts as a suppressor of oestrogen stimulated breast cancer cells.
- The addition of progesterone to oestrogen receptor modulation is not currently standard oncological practice.
- P53 is a repair gene, which protects cells from cancerous change if progesterone is able to attach itself to progesterone receptors. This effect is not seen with progestins.

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SECTION 2

The following is a more detailed referenced section that discusses the main topic of progesterone compared to progestins and the consensus from scientific evidence that they are not the same in their actions. I have taken the liberty of pasting key extracts from Dr Kent Holtorf's pivotal paper on the subject as I believe he has brought together the key research data on this topic. This section is for the scientist, the physician or the curious reader. I have again taken the liberty of including summary boxes to highlight the main findings from all the scientific papers cited here. These are intended to provide convenient summaries of the key points but also to highlight the key scientific conclusions for those who do not have the time or inclination to read the whole text.

Risk for Breast Cancer with Synthetic Progestins

Do synthetic progesterones (progestins) increase risk of breast cancer?

Many studies have assessed the risk for breast cancer with the use of a synthetic progestin for HRT. Despite significant variability in study design, synthetic progestins have been clearly associated with an increased risk for breast cancer.[7, 8, 58, 71-98]

The Women's Health Initiative (WHI), a large randomized clinical trial, demonstrated that a synthetic progestin, MPA, as a component of HRT significantly increased the risk for breast cancer (relative risk [RR] = 1.26, 95% confidence interval [CI]: 1.00– 1.59).[71-74] This trial confirmed results from numerous other groups demonstrating that a synthetic progestin significantly increases breast cancer risk.[7, 75, 98] In addition, higher doses of progestins, testosterone-derived synthetic progestins, and progestin-only regimens further increase the risk for breast cancer.[8, 75-77, 80, 91] The Nurses' Health Study, which followed 58 000 postmenopausal women for 16 years (725 000 person-years), found that, compared with women who never used hormones, use of unopposed postmenopausal estrogen from ages 50 to 60 years increased the risk for breast cancer to age 70 years by 23% (95% CI: 6–42). The addition of a synthetic progestin to the estrogen replacement resulted in a tripling of the risk for breast cancer (67% increased risk) (95% CI: 18–136).[98]

Ross et al compared the risk for breast cancer in 1897 women on combined estrogen and synthetic progestin with 1637 control patients who had never used HRT. Synthetic progestin use increased the risk for breast cancer by approximately 25% for each 5 years of use compared with estrogen alone (RR = 1.25, 95% CI: 1.02–1.18).[82] In a meta-analysis of 61 studies, Lee et al found a consistently increased risk for breast cancer with synthetic HRT, with an average increase of 7.6% per year of use (95% CI: 1.070–1.082), and also found that higher doses of synthetic progestins

conferred a significantly increased risk for breast cancer.[75] Ewertz et al examined the risk for breast cancer for approximately 80 000 women aged 40 to 67 years from 1989 to 2002. For women older than 50 years, current use of synthetic HRT increased the risk for breast cancer by 61% (95% CI: 1.38–1.88). Longer duration of use and the use of synthetic progestins derived from testosterone were associated with increased risk.[76] Newcomb et al studied the risk for breast cancer with synthetic HRT (80% used CEE and 86% used MPA) in more than 5000 postmenopausal women aged 50 to 79 years. They found a significant increase in breast cancer of 2% per year for the estrogen-only group (RR = 1.02/yr, 95% CI: 1.01–1.03/yr), and a 4% increase per year if a synthetic progestin was used in addition to the estrogen (RR = 1.04/yr, 95% CI: 1.01–1.08/yr). Higher doses of progestin increased the risk for breast cancer, and use of a progestin-only preparation doubled the risk for breast cancer (RR = 2.09, 95% CI: 1.07–4.07).[77]

- Synthetic progesterones (progestins) have been clearly associated with increased risk of breast cancer and this seems to be dose related
- The addition of progestins to oestrogen significantly increases the risk

Risk for Breast Cancer with Bioidentical Progesterone

Progesterone and synthetic progestins have generally indistinguishable effects on endometrial tissue. However, as discussed above, there is significant evidence that progesterone and synthetic progestins have differing effects on breast tissue proliferation. Thus, progesterone and synthetic progestins would be expected to carry different risks for breast cancer. Although no randomized, controlled trials were identified that directly compared the risks for breast cancer between progesterone and synthetic progestins, large-scale observational trials[58, 59] and randomized placebo control primate trials[16] do show significant differences. Furthermore, in contrast to the demonstrated increased risk for breast cancer with synthetic progestins,[7, 8, 58, 71-98] studies have consistently shown a decreased risk for breast cancer with progesterone.[22, 23, 25, 60, 61, 66-70, 99-101]

In 2007, Fournier et al reported an association between various forms of HRT and the incidence of breast cancer in more than 80 000 postmenopausal women who were followed for more than 8 postmenopausal years.[59] Compared with women who had never used any HRT, women who used estrogen only (various preparations) had a nonsignificant increase of 1.29 times the risk for breast cancer (P = 0.73). If a synthetic progestin was used in combination with estrogen, the risk for breast cancer increased significantly to 1.69 times that for control subjects (P = 0.01). However, for women who used progesterone in combination with estrogen, the increased risk for breast cancer was eliminated with a significant reduction in breast cancer risk compared with synthetic progestin use (P = 0.001).[59]

In a previous analysis of more than 50 000 postmenopausal women in the E3N- EPIC cohort, Fournier et al found that the risk for breast cancer was significantly increased if synthetic progestins were used (RR = 1.4), but was reduced if progesterone was used (RR = 0.9). There was a significant difference in the risk for breast cancer between the use of estrogens combined with synthetic

progestins versus estrogens combined with progesterone (P < 0.001).[58]

Wood et al investigated whether the increased breast cancer risk with synthetic progestins was also seen when progesterone was used.[16] Postmenopausal primates were given placebo, estradiol, estradiol and MPA, and estradiol and bioidentical progesterone, with each treatment for 2 months with a 1-month washout period. Ki67 expression is a biomarker for lobular and ductal epithelial proliferation in the postmenopausal breast and is an important prognostic indicator in human breast cancer.[102] Compared with placebo, significantly increased proliferation was found with the combination of estrogen and MPA in both lobular (P = 0.009) and ductal (P = 0.006) tissue, but was not seen with the combination of estrogen and progesterone. Intra-mammary gene expressions of the proliferation markers Ki67 and cyclin B1 were also higher after treatment with estrogen and MPA (4.9-fold increase, P = 0.007 and 4.3-fold increase, P = 0.002, respectively) but not with estrogen and progesterone. Inoh et al investigated the protective effect of progesterone and tamoxifen on estrogen- and diethylstilbestrol-induced breast cancer in rats. The induction rate, multiplicity, and size of estrogen-induced mammary tumors were significantly reduced by simultaneous administration of either tamoxifen or progesterone. [25]

Chang et al examined the effects of estrogen and progesterone on women prior to breast surgery in a double-blind, placebo-controlled study in which patients were given placebo, estrogen, transdermal progesterone, or estrogen and transdermal progesterone for 10 to 13 days before breast surgery. Estrogen increased cell proliferation rates by 230% (P < 0.05), but progesterone decreased cell proliferation rates by 400% (P < 0.05). Progesterone, when given with estradiol, inhibited the estrogen-induced breast cell proliferation.[22] Similarly, in a randomized, double-blind study, Foidart et al also showed that progesterone eliminated estrogen-induced breast cell proliferation (P = 0.001).[23]

A prospective epidemiological study demonstrated a protective role for progesterone against breast cancer.[99] In this study, 1083 women who had been treated for infertility were followed for 13 to 33 years. The premenopausal risk for breast cancer was 5.4 times higher in women who had low progesterone levels compared with those with normal levels (95% CI: 1.1–49). The result was significant, despite the fact that the high progesterone group had significantly more risk factors for breast cancer than the low progesterone group, highlighting the importance of this parameter. Moreover, there were 10 times as many deaths from cancer in the low progesterone group compared with those with normal progesterone levels (95% CI: 1.3–422).[99]99 Women with low progesterone have significantly worse breast cancer survival rates than those with more optimal progesterone levels.[100, 101]

In a prospective study, luteal phase progesterone levels in 5963 women were measured and compared with subsequent risk for breast cancer. Progesterone was inversely associated with breast cancer risk for the highest versus lowest tertile (RR = 0.40, 95% CI: 0.15–1.08, P for trend = 0.077). This trend became significant in women with regular menses, which allowed for more accurate timing of collection (RR = 0.12, 95% CI: 0.03–0.52, P = 0.005).[61] Other case control studies also found such a relationship.[66-70]

Peck et al conducted a nested case-control study to examine third-trimester progesterone levels

and maternal risk of breast cancer in women who were pregnant between 1959 and 1966. Cases (n = 194) were diagnosed with in situ or invasive breast cancer between 1969 and 1991. Controls (n = 374) were matched to cases by age at the time of index pregnancy using randomized recruitment. Increasing progesterone levels were associated with a decreased risk of breast cancer. Relative to those with progesterone levels in the lowest quartile (< 124.25 ng/mL), those in the highest quartile (> 269.97 ng/mL) had a 50% reduction in the incidence of breast cancer (RR = 0.49, CI 0.22–1.1, P for trend = 0.08). The association was stronger for cancers diagnosed at or before age 50 years (RR = 0.3, CI: 0.1–0.9, P for trend = 0.04).60 Preeclampsia, with its associated increased progesterone levels, is also associated with a reduced risk for breast cancer.[103]-[105]

- Progestins and progesterone have different effects on breast tissue proliferation
- In contrast to the elevated risk with progestins studies have consistently shown reduced risk of breast cancer with progesterone
- Studies show that in women who used progesterone in combination with estrogen, the increased risk for breast cancer was eliminated
- In primates biomarkers of breast cancer cell proliferation are elevated by oestrogen plus progestins but not with oestrogen plus progesterone
- Studies show that oestrogen alone increases breast cell proliferation rates but progesterone inhibits it. When given with oestrogen, progesterone inhibits the increase seen with oestrogen
- Studies show that the premenopausal risk for breast cancer was significantly higher in women who had low progesterone levels compared with those with normal levels
- Higher levels of progesterone in pregnancy seem to be associated with lower risk of breast cancers
- Women with low progesterone have significantly worse breast cancer survival rates than those with more optimal progesterone levels

Differing Physiological Effects of Bioidentical Progesterone and Synthetic Progestins

Progesterone and synthetic progestins generally have indistinguishable effects on endometrial tissue, which are not the focus of this review. Studies that compared the physiological differences in breast tissue of those on progesterone, with those on other progestins, have the potential to predict differing risks of breast cancer. While variations in methodology and study design are considerable, most of the literature demonstrates physiological differences between progestins and progesterone and their effects on breast tissue.

Synthetic progestins have potential anti-apoptotic effects and may significantly increase estrogen-stimulated breast cell mitotic activity and proliferation.[7]-[21] In contrast, progesterone inhibits estrogen-stimulated breast epithelial cells.[16], [22]-[28] Progesterone also downregulates estrogen receptor-1 (ER-1) in the breast,[27]-[29] induces breast cancer cell apoptosis,[30], [31] diminishes breast

cell mitotic activity,[7, 16, 22-24, 26-28, 31, 32] and arrests human breast cancer cells in the G1 phase by upregulating cyclin-dependent kinase inhibitors and downregulating cyclin D1.[23, 32]

Synthetic progestins, in contrast, upregulate cyclin D1[21] and increase breast cell proliferation.[7-21] Progesterone consistently demonstrates anti-estrogenic activity in breast tissue.[7, 16, 22, 24-29, 31-34] This result is generally in contrast to that for synthetic progestins, especially the 19-nortestosteronederived progestins, which bind to estrogen receptors in breast tissue (but not in endometrial tissue) and display significant intrinsic estrogenic properties in breast but not endometrial tissue.[11, 23, 35-39]

Synthetic progestins may also increase the conversion of weaker endogenous estrogens into more potent estrogens,[7, 40-45] potentially contributing to their carcinogenic effects, which are not apparent with progesterone. Synthetic progestins may promote the formation of the genotoxic estrogen metabolite 16- hydroxyestrone.[41] Synthetic progestins, especially MPA, stimulate the conversion of inactive estrone sulfate into active estrone by stimulating sulfatase,[43, 44] as well as increasing 17-beta-hydroxysteroid reductase activity,[7, 40, 42, 43, 45] which in turn increases the intracellular formation of more potent estrogens and potentially increases breast cancer risk. Progesterone has an opposite effect, stimulating the oxidative isoform of 17-beta-hydroxysteroid dehydrogenase, which increases the intracellular conversion of potent estrogens to their less potent counterparts.[34, 46, 47]

At least 3 subclasses of progesterone receptors (PR) have been identified: PRA, PRB, and PRC, each with different cellular activities.[48-52] In normal human breast tissue, the ratio of PRA:PRB is approximately 1:1.[50, 53] This ratio is altered in a large percentage of breast cancer cells and is a risk for breast cancer.[50, 53, 54] In contrast to progesterone, synthetic progestins alter the normal PRA:PRB ratio,[55-57] which may be a mechanism by which synthetic progestins increase the risk for breast cancer.

Synthetic progestins and progesterone have a number of differences in their molecular and pharmacological effects on breast tissue, as some of the procarcinogenic effects of synthetic progestins contrast with the anticarcinogenic properties of progesterone.[8, 16, 22, 24-26, 31, 33, 40, 58-70]

- Progestins, like oestrogens, have a proliferative effect on breast tissue but progesterone reduces the proliferative effect of oestrogen. This is opposite to the effect that progestins have on the uterus.
- Progestins stimulate the conversion of less potent oestrogens to more potent forms. Progesterone has the opposite effect leading to oestrogens converting to their less potent forms.
- Progesterone modulates the binding of oestrogen to its receptor and down regulates the proliferative effect of oestrogen on breast cancer cells.

Discussion

Doctors should consider both basic science results and clinical outcomes to decide on the safest, most efficacious treatment for patients. Evidence-based medicine involves the synthesis of all available data when comparing therapeutic options for patients. Evidence-based medicine does not mean that data should be ignored until a randomized control trial of a particular size and duration is completed. Rather, it demands an assessment of the current available data to decide which therapies are likely to carry the greatest benefits and the lowest risks for patients.

Progesterone has an antiproliferative, antiestrogenic effect on both the endometrium and breast tissue, while synthetic progestins have antiproliferative, antiestrogenic effects on endometrial tissue, but often have a proliferative estrogenic effect on breast tissue. Synthetic progestins show increased estrogen-induced breast tissue proliferation and a risk for breast cancer, whereas progesterone inhibits breast tissue proliferation and reduces the risk for breast cancer.

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