



## Hormones and Breast Cancer

The following question is from a 52 year old patient who has been doing very well on bioidentical HRT for the past two years:

*"I am concerned about the recent reports in the media suggesting that the decrease in breast cancer cases in 2003 is linked to the dramatic decrease in women taking HRT after the Women's Health Initiative trial results were released. I feel great on my bHRT, but I am worried that I am doing myself harm. Some researchers are even saying that it makes no difference what type of estrogen or progesterin you are using, nor the route of administration. Is this true? Isn't there evidence that bioidentical HRT is potentially safer?"*

Let me respond to the first concern by quoting from a statement (issued by the International Menopause Society (IMS) in response to the media hype generated by this new data. The IMS is the largest menopause society in the world and was the lone voice of reason when the initial WHI results were released in 2002. Had its incisive analysis of the data been heeded by the media, many women would have been spared the needless turmoil that cessation of HRT caused in their lives.

"Currently, two parallel trends were observed in the United States – less breast cancer and less hormone use. However, any attempt to link both into one framework is premature and the scientific basis for such an assumption has not been established. Many important factors were not evaluated: the rate of mammography, the rate of routine visits to the primary physician, the rate of other risk factors which are relevant to breast cancer risk (smoking, physical activity, medications, e.g. SERMS). It is legitimate to speculate whether many women, after having stopped taking their hormone therapy, also stopped seeing their gynecologist regularly and so omitted their mammography examinations, leading to a decrease in diagnosed breast cancer cases. Furthermore, a careful look at the presented data on breast cancer incidence demonstrates that some decrease in rate was already apparent by 1999–2001, before the WHI scare and the massive abandonment of hormone use. . . "

"Based on the above, the IMS calls on the medical community, the media, and the public to be very cautious when interpreting the new data on trends in breast cancer incidence in the United States. It is certainly a very positive sign, which should be followed carefully, *but has little to do with the well-established data on breast cancer risk and hormone therapy that were collected in the WHI study.* During a mean follow-up of 5.2 years, the added absolute risk for invasive breast cancer in the "conjugated equine estrogen (CEE) plus medroxyprogesterone acetate" arm (of the study) was of the order of *less than one case per 1000 women-years(1).* There was no risk for women who never used hormones prior to the study and in those aged less than 60 years. Fewer cases of invasive breast cancer were actually seen in the CEE-only arm of the WHI study during 6.8 years of follow-up (2). The IMS maintains its recommendation that hormone therapy should be prescribed whenever indicated. **The use of hormones in early menopause and up to age 60 years has a very minor potential for harm, but may carry substantial benefits. Women should decide annually if they wish to continue with treatment after consultation with their caregivers.**" (emphasis added)

I encourage you to read the full statement. It can be found online at [http://www.imsociety.org/PDF/IMS\\_Press\\_Statement\\_19.12.06.pdf](http://www.imsociety.org/PDF/IMS_Press_Statement_19.12.06.pdf)

As many of you know, CEE is better known as Premarin, and medroxyprogesterone acetate as Provera. For many reasons I will discuss below, this combination is not an ideal form of HRT. But even when using this non-ideal, un-individualized form of HRT, the risk of breast cancer is not what some researchers and the media would have you believe.

Let me draw your attention again to and comment on the italicized facts:

1. In comparison to women taking the placebo pill, those taking Premarin and Provera experienced **one extra case** of breast cancer per 1000 women each year of the trial. This is the more relevant way of looking at the oft quoted 24% increase risk of breast cancer.
2. There was **no increased risk** in women who had never taken HRT before the trial or who were less than 60 years of age. This category is representative of the vast majority of women who are confronted with making the decision about whether to start HRT around the menopausal transition. This rarely reported, incredibly important statistic is why the IMS, and now virtually all other medical bodies, agree that women can take HRT for at least 5 years around the menopause with no increased risk of breast cancer. In other words, for most women taking HRT at the time WHI results were released, there was no reason to stop them.
3. In women with a hysterectomy taking Premarin alone, there were actually **fewer cases of invasive breast cancer** compared to placebo over the 6.8 years of the trial.

What does this tell us? Well, if taking Premarin for up to 5 years around the menopause doesn't increase a woman's risk of breast cancer and may even reduce it somewhat and taking Premarin and Provera at the same time slightly increases the risk, then the logical conclusion is that Provera caused the increase in risk. This isn't just my speculation. The authors of the JAMA article presenting the Premarin alone data said the same thing in their conclusion:

"Thus, cross-study differences in the study cohorts do not explain the differences in breast cancer effects seen and **the results strongly suggest a role for progestin in relation to increasing breast cancer risk.**" (2) (emphasis added)

Why, then, haven't the headlines been, *Provera increases a woman's risk of breast cancer*? I believe that this is how the headlines should have been written and instead of going off of HRT altogether, women should have gotten off of Provera. Alas, that is not how it went. Instead, the headlines were, "HRT is Dead" or some sensationalistic version of this. While it's easy to blame only the media for this, the problem lies deeper and comes from a concept that many physicians and researchers have been slow to abandon—*class effect*.

To understand this concept you first have get some terminology under your belt. There are two main classes of hormones a woman produces during the normal menstrual cycle and are replaced in HRT—they go by the names 'estrogens' and 'progestins.' There is no actual molecule called 'estrogen;' rather it is a general term that is used when talking about a group of molecules that can lock into estrogen receptors and cause them to alter the behavior of estrogen-sensitive cells. 'Estradiol' is the name of the principal estrogen product of the human ovary, and estrone and estriol are metabolites of estradiol. Premarin is a molecule that consists of at least 12 horse estrogens and only one human estrogen, estrone. Similarly, there is no actual molecule called 'progestin;' rather progestins are a group of molecules that can lock into progesterone receptors and alter the behavior of progestin-sensitive cells. 'Progesterone' is the name of the principal progestin of the ovary. 'Medroxyprogesterone acetate' is the generic name for the progestin Provera which has been the most commonly used progestin in the United States for HRT. Other progestins such as levonorgestrel, norethindrone acetate, and norgestimate are commonly used in bill control pills. Progestins are a class of molecules that have *similar* effects in progestin-sensitive tissues; estrogens are molecules that have *similar* effects in estrogen-sensitive tissues.

Physicians and researchers who generalize the WHI results to all forms of HRT are clinging the concept that all molecules of a particular class have the *exactly* the same effects in all tissues and it really doesn't matter which one you use. So they contend that if Provera causes an increased risk of breast cancer, then progesterone does as well. Or, if Premarin caused an increase in blood clots

in post-menopausal women, then so does estradiol. The problem is that there is ample data to suggest that this is just not true. Let's take a look at some of it.

There are a number of different kinds of evidence that progesterone is different and may have a safer profile than Provera in many tissues. The first kind of evidence is in vitro—experiments done with isolated breast cells in a laboratory. Kramer et al found that progesterone stimulated a non-malignant breast cancer cell line less than Provera and other progestins and concluded by saying, "Therefore, the choice of progestin may be important in terms of influencing a possible breast cancer risk."<sup>(3)</sup> Ghatge et al, looking at the effect of Provera (which they call by its generic name MPA) in breast cancer cells in vitro, concluded, "Our comparison of the gene regulatory profiles of MPA and progesterone suggests that, for physiologic hormone replacement therapy, the actions of MPA do not mimic those of endogenous progesterone alone."<sup>(4)</sup> This is direct molecular biological evidence that progesterone and Provera are different.

In vivo evidence is the next type of evidence. In a randomized, double-blind study of women undergoing breast surgery for benign conditions, Foidart et al found that those who applied topical progesterone to the breast for 14 days before surgery found a decrease in the stimulation of breast cells in the excised tissue.<sup>(5)</sup>

Cohort studies are a way to look at large numbers of women using one form of therapy versus another. Plu-bureau et al found that 1,150 French women who applied progesterone topically on their breasts to reduce breast tenderness over the menstrual cycle did not have any increase in breast cancer over 12,462 person-years of follow up.<sup>(6)</sup> In Europe, transdermal estradiol and progesterone are used more frequently than Premarin and Provera. Following a cohort of 3,175 French women for on average 8.9 years who used mostly transdermal estradiol and progestins other than Provera, de Lignieres et al found that there was **no increased risk of breast cancer**.

In the largest cohort study to date, Fournier et al assessed the risk of breast cancer associated with HRT use in 54,548 postmenopausal women who had never taken any HRT 1 year before entering the E3N-EPIC cohort study (mean age at inclusion: 52.8 years).<sup>(7)</sup> The women were followed for on average 2.8 years, so this is considered short-term HRT. With regard to breast cancer risk their results were similar to the WHI results overall. Women on a synthetic progestin (not progesterone), had a statistically significant 20% increased risk of breast cancer over those not on any HRT. Women on estrogen, of any type, did not have a significantly increased risk. However, because the study cohort included a large number of women on progesterone, the researchers could analyze the data for the effect of progesterone versus synthetic progestin and found that there was no increased risk of breast cancer in women on progesterone. All of the excess risk of breast cancer was in women taking synthetic progestin and this difference was highly statistically significant. The authors concluded by saying: "Our results suggest that, when combined with synthetic progestins, even short-term use of estrogens may increase breast cancer risk. **Micronized progesterone may be preferred to synthetic progestins in short-term HRT**. This finding needs further investigation." (emphasis added)

These studies are part of the growing evidence that the class-effect concept that considers all progestins to have exactly the same effects in all tissues is untenable. If your gynecologist or internist makes a class-effect argument when she tells you there is no difference between progesterone and Provera (I often hear, "It *is* progesterone"), show her these studies.

Keeping all this in mind, I wholeheartedly agree with the last sentence—we do need more studies. These are not large, randomized, placebo-controlled trials like the WHI. They don't prove cause and effect, but they certainly are reassuring. The problem is that there are only two major trials<sup>(8)</sup> in the works to debunk the class-effect concept in HRT and their results won't be available for at least 7 years. And neither trial is large enough to look at breast cancer risk. When the results are in and show there is a cardiovascular benefit (and I am confident they will show benefit), there will be larger, longer-term studies to look at breast cancer risk.

Until longer-term, controlled-trial data is available with bioidentical HRT, women facing menopause should be reassured by all the data we have, that their risk of breast cancer from using HRT without Provera for up to 5 years, is likely to be minimal or non-existent.

For reasons explained in another section

([http://www.physioage.com/about\\_hormones/by\\_which\\_route.php](http://www.physioage.com/about_hormones/by_which_route.php)) of this website, if the bioidentical HRT also employs transdermal estradiol, then most of the other adverse events such as blood clots, strokes, gall bladder disease, and increased triglycerides and c-reactive protein, are likely to be eliminated as well. This results in a risk-benefit equation that is quite beneficial for most women undergoing the menopausal transition and quite likely for continued, long-term therapy.

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1. **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama*. 2002;288(3):321-33.
2. **Stefanick ML, Anderson GL, Margolis KL, et al.** Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *Jama*. 2006;295(14):1647-57.
3. **Kramer EA, Seeger H, Kramer B, Wallwiener D, Mueck AO.** The effects of progesterone, medroxyprogesterone acetate, and norethisterone on growth factor- and estradiol-treated human cancerous and noncancerous breast cells. *Menopause*. 2005;12(4):468-74.
4. **Ghatge RP, Jacobsen BM, Schittone SA, Horwitz KB.** The progestational and androgenic properties of medroxyprogesterone acetate: gene regulatory overlap with dihydrotestosterone in breast cancer cells. *Breast Cancer Res*. 2005;7(6):R1036-50.
5. **Foidart JM, Colin C, Denoo X, et al.** Estradiol and progesterone regulate the proliferation of human breast epithelial cells. *Fertil Steril*. 1998;69(5):963-9.
6. **Plu-Bureau G, Le MG, Thalabard JC, Sitruk-Ware R, Mauvais-Jarvis P.** Percutaneous progesterone use and risk of breast cancer: results from a French cohort study of premenopausal women with benign breast disease. *Cancer Detect Prev*. 1999;23(4):290-6.
7. **Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F.** Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2005;114(3):448-54.
8. **Harman SM, Brinton EA, Cedars M, et al.** KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric*. 2005;8(1):3-12.