Estrogen and Breast Cancer

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In September 2012, a jury in Salt Lake City, Utah awarded a breast cancer survivor $5.1 million in a court case against the pharmaceutical company, Wyeth (also known as Pfizer), alleging that the use of Premarin-Provera (Prempro) was responsible for the development of her breast cancer.[1] This is one of many lawsuits against Wyeth, since the Women's Health Initiative trial (WHI) was published in 2002. The general matter for this case is whether Wyeth withheld data and failed to inform the public concerning the risk of breast cancer with the use of the synthetic hormones, Prempro. There have been over 10,000 cases filed against Wyeth, which has paid $896 million to resolve over 6,000 lawsuits. Furthermore, they have set aside an additional $330 million to resolve the remaining lawsuits.

Despite the knowledge Wyeth had of the increased risk, they made no effort to alert the public. For several years, Prempro was marketed without an advisory label or black box warning. This warning would discourage any woman from taking the drug, but it also resolves any future litigation for Wyeth, as they would not be blamed for a failure to warn the public.

While Prempro now contains a black box warning label, it is puzzling that millions of women still take it in spite of recognized harm. What is even more puzzling is that physicians continue to prescribe Prempro, even when safer alternatives are available. Wyeth downplays the harm of synthetic hormones by marketing against safer hormone alternatives. In this review, I will explain the literature and science demonstrating breast cancer, the chance of risk, and the process of how the jury came to award a plaintiff verdict in this and other cases filed against Wyeth.

Failing to Warn the Public

Any cigarette carton carries a warning that smoking tobacco will kill you. Yet for many years, the tobacco industry misled the public and hid the overwhelming amount of research that proved tobacco causes cancer and heart disease. Until the tobacco industry issued warning labels on their products, several lawsuits were filed against them for their failure to warn the public. These labels are meant to pardon the tobacco industry from future lawsuits. Similarly, the black box warning on the Prempro label prevents any future lawsuits against Wyeth and they can no longer be held accountable for failure to inform.

In spite of the scientifically-proven harm, the former president of the North American Menopause Society (NAMS), Dr. Wolfe Utian, at a recent NAMS meeting advised physicians to continue prescribing conventional hormones and avoid prescribing natural or bioidentical hormones. The continual promotion of Prempro and simultaneous marketing against the safer alternatives can be seen as points of contention against Wyeth. At first, many healthcare providers (myself included) may have felt sorry for the pharmaceutical company in being sued. However, once I heard firsthand the comments Dr. Utian made to denigrate bioidentical hormones and still recommend conventional HRT, I realized the promotion was instigated by Wyeth and therefore agreed with the jury.

I believe a jury of physicians most likely would not find judgment against Wyeth, due to the fact that breast cancer can be caused by factors other than synthetic hormones. Therefore, it is impossible to sort the blame. However, a jury that does not consist of physicians or medical experts, who understand the intricacies of cancer and hormones, can easily find fault based on the inappropriate actions taken by Wyeth.

Wyeth, ACOG, NAMS, and many of us well-read physicians know perfectly well that there is a safe alternative to Prempro. When the pharmaceutical industry markets against the safer alternatives, they are putting their profits ahead of women's health. It is unsuitable to continually bash the bioidentical hormone industry and promote a scientifically-proven harmful, conventional hormone therapy. Regardless, the public knows of the harm and typically refuses to take harmful synthetic HRT, even if their doctor

recommends it. Everyday more physicians are turning to safer alternatives, primarily based on patient demand. Physicians are certainly ignoring the promotion of Wyeth and the medical academies, as this is evidenced by the large number of doctors attending HRT training seminars. These physicians value the safety supported in the literature and want to be educated in the use of bioidentical hormones.

Risks & Benefits of Various Hormone Therapies

For physicians who have attended HRT training courses, it is quite obvious which hormones provide the best protection as is seen from the medical studies. However, the inexperienced physician and patient may not understand the reasoning behind preferred hormone therapies. I have included a review of the medical literature that supports why we do what we do. This will provide greater understanding of the risks and benefits of various hormones, and perhaps help us better comprehend the jury's decision in this case.

A recent article that appeared in the Lancet Oncology journal demonstrated that women in the WHI trial who received estrogen-only (Premarin without Provera) experienced a 23% lower incidence of breast cancer when compared to the placebo group.[2] This translates to suggest that there was a decrease in breast cancer risk in women who took just estrogen "Unless it was shown that Provera was only taken for a short period of time, blame should have been shared with the physician." without Provera. Research from the WHI also demonstrated that the use of estrogen-only did not result in an increased risk of breast cancer, but was actually associated with a decrease in breast cancer.[3] These results are difficult to grasp seeing that everyone believes estrogen causes cancer. Estrogen may stimulate cancer to grow once cancer is established; however, estrogen does not cause it to occur in the first place. As is mentioned in the article published in Lancet Oncology, Premarin has become less popular in recent years, because many patients have switched to estradiol - a natural bioidentical estrogen that resembles estrogen naturally found in the body.

The addition of Provera to Premarin is what causes the harm of Prempro's association with breast cancer. Provera is added to Premarin to protect against uterine cancer, but it has also resulted in an increase in stroke, heart attack, deep venous thrombosis, deep vein thrombosis, pulmonary embolism, breast cancer, and diabetes. Provera is generally prescribed to protect against uterine cancer, because the uterus is the only organ that seems to like it. All other organs – the heart, brain, blood vessels, and visceral fat – do not like Provera.

In the case of Mrs. Okuda versus Wyeth, it is most confusing that she took both Premarin and Provera after she had a hysterectomy at age 47. The only reason to use Provera is to protect the uterus against uterine cancer. The treatment is never indicated in women who have undergone a hysterectomy. The question remains as to the length of time Mrs. Okuda took Prempro, as opposed to just Premarin. Taking Prempro for a short period of time most likely would not influence the development of her breast cancer and it would be impossible to predict the effect Prempro would have for a short duration of time. This would make a vote in favor of Wyeth in this settlement. Yet, whose fault was it that she was taking Provera? Since she should not have been prescribed Provera in the first place, her increased risk could be blamed on the physician. What were they thinking? Unless it was shown that Provera was only taken for a short period of time, blame should have been shared with the physician. Unfortunately, we are not told the length of time that Mrs. Okuda took Provera.

Prempro & Breast Cancer Risks

Understanding the above complexities indicates how difficult it would be to render judgment in this case. In the post-commentary section of this article, I found the *comment* made by the "sanityinutah" reader most interesting, as they referred to the difficulty in having an uninformed jury that has no understanding of the medicine, science, literature, or pathophysiology of HRT. I believe the jury truly had no idea as to whether or not the hormones were responsible for the cause of breast cancer in Mrs. Okuda, nor should they have been able to comprehend all the aforementioned facts. I also believe that the jury voted against the drug company, not necessarily for the patient, Mrs. Okuda. I say that simply because 50% of the cases have been won by the pharmaceutical company and 50% have not. Once it can be shown that a drug company failed to warn of potential danger, particularly if they had good evidence ahead of time or hid data, then the jury

would most likely vote in favor of the patient. Wyeth “failed to disclose, misstated, downplayed, and understated” the risks of Prempro, which lost the case for them.

So, now what? It is firmly proved in science and the courts that Prempro contributes to the increased risk of breast cancer. Do current warning labels pardon Wyeth from further wrongdoing? Apparently so, because this pharmaceutical company continues to manufacture and advertise Prempro. Why would a pharmaceutical company continue to manufacture Provera or Prempro with these inherent risks? Experts now recommend the HRT regimen should only be taken in the lowest dose and for the shortest period of time to control menopausal symptoms, after which time the HRT regimen should be stopped in hopes of avoiding any harm. Knowing the scientific facts, it seems unreasonable for a physician to continue prescribing Prempro. However without estrogen, women lose all of the tremendous health benefits and may suffer an increase in morbidity and mortality from estrogen deprivation.

Does Estrogen Cause Cancer?

What about estrogen-only? There is no evidence in recent medical literature that shows prescribing estrogen without a progestin increases the risk of developing breast cancer. The WHI trial and other recent studies amazingly prove a decrease incidence of breast cancer in women taking estrogen-only. In the CORA study, there were fewer cases of breast cancer in the estrogen (estradiol) group when compared to the placebo group.[4] To date, a lawsuit has not been brought against any pharmaceutical company with the claim that taking estrogen-only caused breast cancer. All studies demonstrate a decrease in morbidity and mortality, which encourages physicians to recommend estrogen for all women. Preliminary "There is no evidence in recent medical literature that shows prescribing estrogen without a progestin increases the risk of developing breast cancer." Preliminary data from the recent completed KRONOS study of hormones found no increased risk of breast cancer in women taking estrogen and progesterone.[5] The recently published DANISH study also demonstrated no increased risk of breast cancer in women taking estradiol for ten years.[6] These results should be in the headlines of every newspaper. Yet, this research is not negative sensationalism and uninteresting to the media.

To this day, the most powerful scientific studies demonstrate that estrogen does not cause or stimulate the development of breast cancer. A recent study entitled “Aromatase Inhibitors: A Time For Reflection” critiqued the commonly prescribed estrogen-blockers termed aromatase inhibitors, which are commonly used in patients with breast cancer to block estrogen receptor sites on breast cancer cells.[7] This renders the cancer cells to be insensitive to any stimulatory effect from estrogen. Estrogen does not cause cancer to occur; however, once breast cancer develops, estrogen can stimulate its growth as the tumor becomes estrogen-sensitive. In women with active cancer, this is an important treatment modality to prevent estrogen from stimulating breast cancer cells to grow.

These aromatase inhibitors have become standard care in women with breast cancer and are usually continued for five years after breast cancer is diagnosed. Pharmaceutical companies are pushing these drugs to be continued beyond the five-year recommendation with the hope and intent of preventing any further recurrence of breast cancer. So far, studies have demonstrated a very small decrease in the recurrence of breast cancer when these agents are used indefinitely. However, this article published in the journal Menopause refutes these suggestions and recommendations to continue the use of estrogen-blockers indefinitely. The study claims there is increased harm in blocking estrogen long-term, along with an increase of morbidity and mortality associated with loss of estrogen.

Remember that in the WHI trial the use of estrogen-only provided protection against breast cancer with an incidence of eight less breast cancer cases per 10,000 women treated with estrogen-only and that is the same protection against breast cancer as seen with aromatase inhibitors. Studies show that both medicines are equal for cancer protection. Estrogen-blockers increase the symptoms of menopause, whereas estrogen therapy eliminates those symptoms and improves quality of life. The aromatase inhibitor article goes on to say, "Estrogens play a critical role in multiple systems. The loss of estrogen is associated with an accelerated loss of bone, an accelerated progression of atherosclerosis and MI. If estrogen is started at menopause, there is a 60% reduction in coronary calcification, a 50% reductin in MI, and a 35% reduction in overall mortality. Estrogen deprivation causes decrease in cognition, mood, and memory. There is

accelerated expression of neurodegenerative disease like Alzheimer's and Parkinson's disease. Evidence shows that neurodegenerative disease can be prevented by estrogen replacement."

Alternative Treatments for HRT

Is there an alternative to Provera if the patient wants uterine protection without the risks and complications observed with Provera? By now, we should understand and appreciate all of the benefits of estrogen, but we cannot provide estrogen without some type of estrogen opposition to protect the uterus. This is provided by Provera and it is the sole purpose of this prescription. If Mrs. Okuda had taken Premarin (estrogen) with natural, micronized progesterone instead of Provera, would she have filed against Wyeth? Certain medical academies claim that there is no difference between synthetic and bioidentical hormones; yet, I've never heard of a breast cancer patient sue when taking Premarin with micronized progesterone.

Are we missing something here? A recent article demonstrated an increased relative risk of breast cancer with use of Provera, in comparison to progesterone with no increased risk.[8] Interestingly, the new progestin, norethindrone, which is the recommended replacement for Provera, has a two-fold increased risk of breast cancer.[9] This is even worse than Provera and makes it seem unreasonable that a physician would prescribe a medicine proven to increase breast cancer risk, when the data supports a safer alternative – micronized progesterone. Another study, the EPIC-E3N trial has found consistent results for over 10 years that demonstrate an increased risk of breast cancer with the addition of a progestin and a decreased risk in breast cancer with the use of progesterone.[10] The implications of this study are enormous. Which hormone regimen would you rather take?

While ACOG and NAMS currently recommend that HRT only be taken in the lowest dose for the shortest period of time, it would be more appropriate to inform women on the many studies that demonstrate neither estradiol or progesterone have been associated with an increased risk of breast cancer. This combination is safe and effective. However, OB-GYN academies do not clarify these findings, which cause us to disdain pharmaceutical companies and the medical academies they support. I personally find the denigration of the bioidentical hormone industry by these medical academies to be erroneous. Micronized progesterone's proven record of safety has worldwide implications for women's health.

Jury's Reasoning for Opposing Wyeth

I personally do not believe that taking Provera for a short period of time had anything to do with Mrs. Okuda development of breast cancer. From my many years of research, writing, and teaching, I have gained a sound understanding of the published literature and science surrounding HRT. The very small increased risk of breast cancer that is associated with Provera, the short duration of Provera use (no statement was made as to how long it was taken), and the protective effect of Premarin-alone makes the increased risk of cancer in this case relatively small. Nevertheless, I can understand the jury's reasoning to vote against Wyeth, based on the unsuitability of their prior actions, refusal to acknowledge the scientifically-proven risks, and disregard to advise the public of the risks. My personal dissatisfaction for Wyeth is based on their continual denial of a safe alternative, persistent marketing of harmful synthetic hormones, and continued production of a medicine shown to be harmful to women's health. Fortunately, the public is becoming more aware of these deficiencies and is now refusing to accept synthetic hormone prescriptions.

The European studies demonstrate that the majority of physicians and patients avoid synthetic HRT, such as Prempro, in which the majority of women are taking the bioidentical hormones estradiol and progesterone. Interestingly, the pressure on drug companies that exists in Europe does not exist in the United States. For now, I expect Wyeth will continue to be reproved with large jury awards and front- page headlines. Perhaps the major harm in this controversy is that women may still refuse to take estrogen out of media induced fear; and thereby, suffer the consequences of estrogen depletion.

Closing Thoughts on Wyeth Lawsuit

Which HRT would you prefer – conventional or bioidentical hormones? How would you have voted on the jury? In this article, I suggested that there should have been shared responsibility between the

pharmaceutical company and the physician who prescribed Provera, when it was unnecessary for the patient to take it after a hysterectomy. This case would have never existed if Mrs. Okuda had not been prescribed Provera. Based on the foregoing paragraphs discussing the benefit of progesterone and lack of breast cancer risk, perhaps the third responsible party is the medical establishment that fails to acknowledge a scientifically-proven alternative. There is very adequate evidence to support a strong preference for micronized, natural progesterone over synthetic progestins. ACOG and NAMS may consider a safer alternative, instead of standing by the pharmaceutical industry to support the continued administration of problematic progestin. Until the OB-GYN academies acknowledge the alternatives, there will continue to be disapproval of the pharmaceutical industry and filed lawsuits.

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