

FOR NEWLY MENOPAUSAL WOMEN WHO NEED HORMONE THERAPY FOR HOT FLASHES, ONLY ONE REGIMEN HAS BEEN SHOWN NOT TO CAUSE BREAST CANCER.

WHILE PFIZER’S PREMPRO (WITH MPA) AND OTHER COMBINATION HRT REGIMENS (WITH IMITATION PROGESTERONES NETA OR LNG) DO CAUSE BREAST CANCER - PROMETRIUM® (ORAL MICRONIZED PROGESTERONE), WHEN GIVEN TO OPPOSE ESTROGEN DOES NOT:

A SUMMARY OF THE SCIENTIFIC EVIDENCE

By Michael L. Williams, updated March 10, 2010

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## **I. Executive Summary**

### **A. Important Messages**

1. The combination hormone therapy regimens (estrogen plus an imitation progesterone, or “HT”), most popular with physicians treating symptomatic menopausal women, greatly increase the risk of breast cancer, especially ER+ breast cancer. This increased risk is much higher than conventional wisdom believes. These drugs have caused more than 300,000 breast cancers in the USA alone over the past 30 years. Even now, HT is still causing about 10,000 unnecessary breast cancers per year. The single most effective action the medical profession can take to prevent thousands of breast cancer cases is to stop prescribing these HT regimens, and to prescribe the safe ones instead.

2. There is a safe companion to estrogen for women with menopause symptoms. Micronized progesterone, unlike the imitation progesterones used in HT regimens such as Prempro, does not increase the risk of breast cancer, at least when it is used for eight years or less. Evidence published since 2005 demonstrates the safety of natural progesterone and its racemic sister dydrogesterone for the breast. This new science also provides human clinical trial and animal experimental data to explain why these natural progesterones are so much safer. Most prescribers are unaware of this information. The current drug labels for Prempro and other combination HT regimens, which the drug companies have not updated on this issue since 2005, falsely state that all progestogens should be presumed to be equally dangerous (a “class effect” that is now known to be untrue). The science is solidly to the contrary.

### **B. Outline of Facts**

1. Many women, especially those in their early 50’s, suffer from moderate to severe menopausal symptoms and need estrogen supplements to eliminate hot flashes and to treat vaginal dryness and thinning. There simply is no more effective therapy than some form of estrogen supplementation.

2. But, in a woman who still has her uterus, estrogen therapy unopposed by a progestogen greatly increases the risk of endometrial hyperplasia and hormone dependent uterine cancer (cancer of the endometrium, or uterine lining).

3. The risk of estrogen-fed endometrial cancer increases with duration of exposure to the estrogen-only therapy. It is universally accepted that the mechanism of this hormone driven cancer epidemic in the 1960’s and 1970’s was by promotion of pre-existing lesions rather than initiation of completely new tumors.

4. Since the late 1970’s, all physicians have recommended that women with uteruses who are going to take estrogen supplements should also take a progestogen to oppose the estrogenic stimulation of their uterine lining.

5. The three most common progestogens used in the United States are all incomplete imitations of a woman's own natural progesterone:

(a) Medroxyprogesterone, or MPA, is the progestogen in the combination single pill, Prempro.® It is also sold as a separate pill under brand names such as Provera, Cycrin, and as generic MPA without a brand name.

(b) Norethindrone acetate, or NETA, is the progestogen in Combi Patch® and FemHrt, ® and is sold as a separate pill under generic "brand" names for single pills, such as Errin® and Aygestin. ®

(c) Norgestrel, or its left-handed isomeric half, levonorgestrel (LNG), is used in Activella,® a single combination pill of estradiol and LNG, and in Climara Pro,® a combination patch sold by Bayer. LNG was sold in the United Kingdom as a companion to Premarin in Pfizer's Prempak.®

6. All three of these imitation progesterones cause a large increase in the incidence of breast cancer in women using them longer than a couple of years. The most recent and robust studies show that Prempro, for example, increases the risk of all breast cancers more than threefold in women using the combination drug for just four years. The relative risk of estrogen receptor positive (ER+) breast cancer is even higher than 3.0 because Prempro does not feed estrogen receptor negative (ER-) tumors, but ER- tumors were not separated from ER+ tumors in this analysis. The relative risks of breast cancer from NETA and LNG are at least as high as MPA, and possibly even higher.

7. The risk of breast cancer is higher, especially in the first three years of use of Prempro or its equivalents, for newly menopausal women.

8.. Since 2005, a rapidly growing body of scientific evidence demonstrates that oral micronized progesterone (OMP), when used as the companion to estrogen therapy, does not increase the risk of breast cancer in the first five years of use, and then for those rare women who need HT longer than five years, the risk of breast cancer with OMP rather than MPA is much lower. In the first five years, OMP may even eliminate the small increased risk of breast cancer found in women using estrogen alone. It is now well accepted in Europe that the first choice of progestogen for menopausal HT is oral micronized progesterone, or for those women unable to tolerate OMP, its racemic sister, dydrogesterone (same chemical formula as progesterone, but with some subtle three-dimensional structural differences that make it more absorbable than OMP).

9.. Millions of women are still being prescribed the cancer causing imitation progestogens without being told about the safer alternatives. These women deserve to be told that there is one type of HT that has been found not to increase breast cancer in the first five years of use, while all of the others do. This information has not yet been included in the official labels for the dangerous progestins.<sup>1</sup> The labeling on this topic has not been changed since 2005, despite the enormous amount of data published since 2005 demonstrating that the "class labeling" on

progestogens sought by the entire drug industry is simply false. This false labeling contributes to about 10,000 unnecessary breast cancers in the United States alone every year.

10. The mechanism by which MPA, NETA, and LNG cause breast cancer, when used in combination with estrogen, is through promotion of pre-existing lesions, just as we know occurs with estrogen and uterine cancer. These are lesions that would otherwise stay clinically insignificant, below the level of x-ray detection, or would even regress absent stimulation by the imitation hormone drugs.

11. Many of the largest pharmaceutical companies on the planet have directed a loud and carefully orchestrated drumbeat of misinformation to the public, and especially to the target market of prescribing physicians. The drug industry has invested millions of dollars in revenues to influence the prescribing physicians' professional organizations and continuing medical education courses. Drug companies have ghost-written and planted a barrage of medical journal articles showcasing unsubstantiated benefits of their progestin drugs.<sup>2</sup> As a result, most physicians who still prescribing these drug combinations are simply not aware of the real risk of breast cancer that imitation progesterones induce. Nor are they aware that there is solid, robust evidence of a safe alternative, oral micronized progesterone, which does not increase breast cancer risk.

12. Pfizer's top ObGyn executive in charge of Prempro's labeling for its subsidiary Wyeth, testified recently that women contemplating beginning or continuing HT should be told about the evidence that Prometrium may be much safer for breast cancer risk than Prempro's MPA. However, he claimed that it wasn't Pfizer's responsibility to discuss the relative safety of other companies' products.. Instead, he declared, it was the prescribing physician's job to tell women about the growing body of data supporting safer alternative progesterones.<sup>3</sup>

13. The combination menopausal hormone therapy regimens using MPA, NETA, or LNG should be taken off the market. Until some company puts dydrogesterone back on the market in the United States, the progestogens of first choice as estrogen's escort must be micronized progesterone – the oral formulation for women who are not allergic to peanuts, and the FDA approved vaginal gel for women with peanut allergies.

14. Although this vaginal gel has not received clearance from the FDA for use in MHT to oppose estrogen, the only NIH funded ongoing clinical trial of MHT chose micronized progesterone gel instead of MPA, NETA, LNG or OMP. Currently, there are two randomized trials of menopausal HT under way. Both studies chose micronized progesterone instead of any of the three imitation progesterones. The KEEPS trial is using Prometrium®, the Solvay brand of oral micronized progesterone, which has been available in the United States since 1998. The ELITE trial, sponsored by the National Institute of Environmental Health Sciences (NIEHS), is using Crinone® gel, which contains micronized progesterone. Women should be informed of these facts, too, if they are truly giving their informed consent to treatment with hormone therapy.

**II. The current “Class labeling” on all progestogens approved for MHT is dangerously false and must be changed.**

The current labeling in place for Prempro and other HT products containing the combination estrogen plus imitation progestin has not been updated since late 2004 or early 2005.

Approved by the FDA at the urging of the drug manufacturers, the most dangerously false and misleading section of the labels states:

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. *However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.*

(Emphasis Added).

This statement, that no observational studies have found variation in risk among progestogens was true in 2004. It became false in 2005. Since then, it has become dangerously more false as additional evidence has been published showing that natural progesterone and its racemic sister dydrogesterone are much safer than MPA, NETA, or LNG for breast cancer risk, while MPA, NETA and LNG increase the risk to a much greater degree, in the first two years of use, and especially for newly menopausal women. The drug companies should immediately modify this statement and summarize the evidence presented in this treatise.

The second most dangerous and misleading statement in the Prempro label is in its black box warning about breast cancer:

#### Breast Cancer

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions (5.2), and Clinical Studies (14.6)] *In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.*<sup>1</sup>

(Emphasis added)

There now is data on OMP comparable to that of the WHI study on MPA that shows estrogen plus micronized progesterone does not have the same high risk of breast cancer that the imitation progesterones do. Pfizer argues that these multiple prospective cohort studies, which found no increase risk of breast cancer in women taking micronized progesterone, are not comparable to the WHI because they are not randomized prospective trials. However, Pfizer overstates the value of the WHI trial data. Notably, the WHI Prempro trial did not recruit

subjects who matched the typical HT user. The typical HT user is newly menopausal, or still peri-menopausal, usually in her late 40's or early 50's, and suffers from moderate to severe vasomotor symptoms (the only first-line indication for HT that is approved by the FDA).

But the typical HT users were not included in the WHI randomized trial. Instead, they wereshunted into the WHO Observational Study (OS), because the investigators knew these women would not tolerate an ineffective placebo pill for long. Because women would quit using the placebo, there would be an increase in the drop out rate from placebo (actually called the “drop in” rate, since women assigned placebo started taking HT for their symptoms). Even more important, because the WHI trial's primary purpose was to measure the expected cardiovascular benefits of estrogen therapy, the investigators had to recruit women who were on average much older than the typical user, because in the older age group, cardiovascular events were common enough that a relatively small beneficial effect would be detected. The average age of the Prempro trial recruits was 63. On average, they were nine years past menopause, meaning that most of the women in the trial no longer had bothersome symptoms of menopause.

Nevertheless, the WHI Prempro trial's dropout and drop-in rates greatly exceeded the expected rates. As a result, by the time the trial was prematurely stopped in 2002, after an average use of 4.4 years, more than 42% of the women assigned Prempro had stopped taking the drug, while 11% of the women assigned placebo had started some form of HT. In effect, the WHI trial was nothing more than a prospective observational cohort, with subjects very unlike the typical Prempro user in the actual marketplace.

The current label for Prempro should be revised to update the black box with the good news about the breast safety of oral micronized progesterone and dydrogesterone.

The current warning labels for the combination HT drugs' risk of breast cancer are also deficient in other ways. For example, the labels contain no warning that new onset of breast pain in the first year of HT use is a sign of especially high breast cancer risk. The WHI investigators published this result in 2009.<sup>4</sup> Such a warning could prevent many women from developing Prempro-induced breast cancer.

The current label also does not warn of the likelihood and magnitude of breast cancer risk from Prempro, nor that it increases steadily with duration of use. Instead, the label downplays the risk.<sup>1</sup> On page five of the current Prempro label, the section titled “5.2 Malignant Neoplasms” reads in full as follows:

*Breast Cancer*

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the Women's Health Initiative (WHI) substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin WHI substudy reported an increased risk of breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo.<sup>5</sup> Among

women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups [see *Clinical Studies (14.6)*].

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the Women's Health Initiative (WHI) substudy of daily CE (0.625 mg). In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg) was not associated with an increased risk of invasive breast cancer [*relative risk RR*] 0.80] 6 [see *Clinical Studies (14.6)*].

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. *However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.*

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

(Emphasis added).

The largest and most recent studies on newly menopausal women taking Prempro find that the risk of breast cancer in general more than triples after four years of use, and that the risk of developing an ER+ ductal carcinoma in situ (“DCIS”) or invasive tumor more than doubles at two years of use. The relative risk of developing lobular or tubular type tumors is even higher. Rather than of disclosing this information, the label mentions only the relative risk of “1.24” reported initially from the WHI trial, and implies there is no extra risk that certain types of breast cancers are caused at a rate 3-5 times higher than the background rate (200-400% increase in risk). The 1.24, or 24% increase Pfizer cites is deceptive because it is derived from the “intent to treat” analysis of the WHI Prempro trial. As explained above, one of the key weaknesses of the WHI Prempro trial is that it studied a group of women who are dissimilar to the women to whom Prempro and its label are targeted.

### **A. General acceptance that Prempro causes breast cancer**

It is now generally accepted by the medical community that Prempro causes breast cancer, and that it (or its two pill predecessor, Premarin plus Provera) caused more than 300,000 American women to develop breast cancer in the past twenty-five years -- a **much higher rate than previously thought**.

The best evidence of the scientific community's general acceptance of the causal relationship between Prempro and breast cancer are the public statements that the principal investigators of the Women's Health Initiative and other prominent studies on HT and breast cancer made to numerous media outlets on the publication of the latest WHI study data. Last year, the WHI investigators presented their new findings from the Prempro trial and observational study, and its medical implications, to the public (NEJM Feb 5, 2009).<sup>5</sup>

In this new WHI study, the investigators followed the 15,000 women in the Prempro randomized trial for an additional two and one half years beyond the first WHI Prempro trial breast cancer report, for a total follow-up of eight years. In a subset of the Observational Study, they followed another 41,449 women who had not been assigned treatment but took HT voluntarily. They reported data on 11 years of follow-up since enrollment in the Observational Study began. The cut-off for data available for this analysis was December 31, 2005.

### **B. WHI breast cancer investigators' public statements**

**Rowan Chlebowski, MD**, a medical oncologist at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, and lead author of the new WHI study, told the press:

In the last decade in which it was still widely used (1992--2002), long-term hormone therapy probably caused breast cancer in 200,000 women.<sup>6</sup>

The National Cancer Institute sponsored a study, which was published in the Journal of the National Cancer Institute in 2007. The study examined the rate of drop in breast cancer among several groups of menopausal women following the dramatic decline in HT use that began in mid-2002. The investigators estimated, based on their data and the public national data, that "the impact of the declining use of postmenopausal hormone therapy could account for an estimated 17,500 fewer ER-positive invasive breast cancers annually among women aged 50-69."<sup>7</sup>

It is tragic that prescriptions of Prempro did not fall to zero, but fell only by about two-thirds. If we could eliminate the remaining one-third of Prempro prescriptions, 9,000 or more women each year could have avoided breast cancer. Unfortunately, millions of women are still being prescribed these carcinogenic synthetic imitation progesterones and are at a substantially increased risk of breast cancer. At trial, we have been repeatedly proven to juries that the drug companies have lulled many doctors into thinking these drugs are safe, and that there are no good alternatives for the treatment of menopausal symptoms.

**Chlebowski** continued:

For longer duration therapy, this provides new evidence that the risk is higher than we previously thought. A 55-year-old woman whose mother developed breast cancer at 62 would have a 2 percent chance of developing breast cancer in five years. Doubling that risk with long-term hormone use translates to a 4 percent chance of getting cancer, or 1 in 50(sic). The risk is not one of those few-in-a-thousand things.

Estrogen-progestin appears to act as a growth factor in the body, stimulating cancer cells. But the effect seems to dissipate quickly once hormones are withdrawn. The findings should help allay lingering skepticism among some physicians about hormone therapy's role in triggering breast cancer.<sup>8</sup>

If you stop hormones, the risk of breast cancer [associated with hormone use] rapidly declines. The risk decreased rapidly in both groups after they stopped the pills, even though both groups had mammograms with similar frequency. That fact weakens the argument that the drop in breast cancer cases was due to fewer women getting mammograms. There was a rapid decline in breast cancer incidence after stopping hormones, while mammography use didn't change between the groups.<sup>9</sup>

The rapid decline in cancer rates was due not only to an overall drop in breast-cancer risk, but also to the withdrawal of excess estrogen, which may actually have served as a treatment for tiny, preclinical breast cancers. When you change from a high- to a low-estrogen environment, it's like giving breast cancer treatment. These are preclinical cancers that are below the level of detection, and that accounts for why biologically we can see such a quick effect in stopping hormone therapy.<sup>10</sup>

Another new large study of women on Prempro conducted by the new American Cancer Society was published on-line in the journal *Cancer* (*Cancer*. 2009 Mar 1; 115(5): 936-45)<sup>11</sup> just one week before the publication of the combined WHI study.

**Eugenia Calle** is the former vice president of epidemiology for the American Cancer Society. Dr. Calle and her colleagues investigated approximately 68,000 women who were cancer free at the study's start in 1992. The study followed these women until mid-2005, evaluating their HT use and their risk of breast cancer, and following them until mid-2005. The study found that the risk of breast cancer increased substantially after three years of using HT. The risk of lobular cancer from HT doubled at three years, although there was no increased risk for those who used HT for less than two years. In explaining these findings to Kathleen Doherty in the *HealthDay* interview, Chlebowski noted, "...cancers may simply be harder to detect on mammograms during initial hormone use."<sup>9</sup> "A truly safe interval can't be defined."<sup>9</sup>

**Dr. Jonathan Berek**, another major breast cancer expert, was also interviewed by the press. Dr. Berek, chair of obstetrics and gynecology at Stanford University School of Medicine, who was not involved in the study, stated:

That is a reasonable and biologically plausible explanation for why we might be seeing a more precipitous drop in breast cancer than we might expect from the normal lead time for reduction of malignancies.<sup>10</sup>

**Marcia Stefanick**, co-author of the WHI study and a breast cancer epidemiologist and professor of medicine at Stanford, told the press:

For both [WHI] groups, the risk of cancer was much more pronounced than suggested by previous data. This is very strong evidence that estrogen plus progestin causes breast cancer.<sup>12</sup>

The good news is that if you discontinue hormones, your risk drops pretty quickly. You start women on hormones and within five years, their risk for breast cancer is clearly elevated. You stop the hormones and within one year, their risk is essentially back to normal. It's reasonably convincing cause-and-effect data.

We know nationwide, breast cancer rates dropped within a year of the initial publication. We now have good evidence that, yes, this happened absolutely in association with the drop of the hormones.<sup>13</sup>

**Dr. Donald Berry** had previously published his study of population trends in HT prescriptions in the NEJM in 2007.<sup>14</sup> Dr. Berry asked to comment on these new WHI study's findings and the nearly simultaneous drop in breast cancer in menopausal women. Dr. Berry stated:

The great thing about this report is that it had individual women [his study had not had the ability to track individuals], and the randomized element. That adds credibility. The current [WHI] report didn't examine whether the cancers were estrogen-receptor positive or negative. [My] research found that much of the growth of breast cancer was due to tumors fueled by estrogen.<sup>13</sup>

**Joanne Manson**, another co-author of the new WHI study, and a professor at Harvard Medical School said:

“There was a controversy about the decline after WHI.”<sup>(1)</sup>

After disagreements emerged over the cause of the decline, the WHI researchers scrutinized women in two groups.

“In both study populations, the risk decreased rapidly after stopping hormone therapy, and in neither case was it explained by changes in mammogram screening.”<sup>13</sup>

We now have good evidence even these estimates described above are too low. A survey comparing national breast cancer incidence rates and prescriptions written for menopausal hormone therapy concluded in February, 2010, that the large declines seen in ER+ tumors in women of menopausal age in the USA since the WHI trial was halted are “likely to be underestimates.”<sup>15</sup> In this survey funded by the NIH, Harvard Medical School researchers analyzed the changes in the incidence of various types of breast cancer, stratified by age, race, and socioeconomic status. They found that the rate of decline in breast cancer was exclusively confined to ER+ tumors in wealthy white geographic areas where women were most likely to be taking HT for menopause. But in addition, the researchers found that the early cancer data contained a very high percentage of “unknown receptor status” tumors. When they estimated what the true rate of decline would have been had these “unknown” tumors been positive in the

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<sup>1</sup> In July 2002, there was a large outcry in the press about the surprise news that the Prempro trial had been stopped prematurely due to an increase in breast cancers in the women taking Prempro.

same proportion as in later tumors (when lab techniques had improved and were widespread), the true rate of breast cancer caused by HT use was likely at least 15% higher than even Chlebowski previously estimated.

Notably, the researchers concluded, “The net implication is that the actual secular decline in breast cancer incidence among these women is larger than has been reported on the basis of observed data.”<sup>15</sup>(At p. e6)

### **C. Breast cancer risk greater in newly menopausal women**

The breast cancer risk from Prempro and other HT regimens with imitation progesterones is greater in newly menopausal women than in women who begin taking the drug when they are several years past menopause. In May, 2009, the WHI investigators published yet another analysis of the breast cancer risk, as well as an analysis of the overall harm/benefit balance of both Premarin and Prempro, using combined data from both the two WHI trials (Premarin and Prempro) and the Observational Study. The purpose of this new WHI study was to determine whether the “timing hypothesis” of HT advocates was confirmed or refuted by the WHI data. It was clearly refuted.<sup>16</sup>

The “timing hypothesis” is this: The women in the WHI trials were much older than the typical HT user, who is newly menopausal. In contrast, the vast majority of women in the WHI trials were more than ten years past menopause when they first started HT. Advocates of the “timing hypothesis” believed that although the HERS (fn to original paper) and WHI trials found a cardiovascular risk (heart attacks and strokes) with HT use, it was because both studies included mostly older menopausal women, not newly menopausal. Therefore, if only newly menopausal women were studied, the cardiovascular benefits found in the observational studies would be confirmed in that subset of women.

In response, the WHI investigators tested the hypothesis by analyzing all of the data they had on newly menopausal women in the both the trials and the observational studies. The investigators found that the cardiovascular risk was still present in newly menopausal women (in Prempro users). But but more important, they found that the risk of breast cancer was also much higher in these newly menopausal women than in the older women who comprised most of the subjects in the randomized trial.

The paper is by Prentice et al. and entitled "Benefits and Risks of Postmenopausal HT When It Is Initiated Soon After Menopause." The new paper concluded, Prempro's harm-benefit balance is negative, that is, the risks clearly outweigh any benefit, whether a woman starts years or weeks after menopause:

"In summary, the results presented here suggest that the unfavorable balance of benefits and risks observed in the CEE/MPA (Prempro) trial as a whole also applies to recently menopausal women." (from the last paragraph of the study).

Note that Dr. Robert Langer is a co-author of this new WHI harms-benefits study, even though he is a consultant and expert witness for Wyeth in the Prempro litigation (which he properly discloses in the paper).

This WHI finding was confirmed by a French study published on September 14, 2009. Fournier et al., “Estrogen-Progestagen Menopausal Hormone Therapy and Breast Cancer: Does Delay from Menopause Onset to Treatment Initiation Influence Risks?”<sup>17</sup> The conclusion of this paper states:

. . . [O]ur results indicate that, contrary to what is currently hypothesized regarding the risk of heart disease, initiation of MHT [menopausal hormone therapy] close to menopause onset rather than later may not limit the increased risk of breast cancer. Instead, even short duration of use of some EP-MHT's were associated with substantially elevated risks of breast cancer when treatment was initiated close to menopause. Our finding that, for short durations of use around menopause, progesterone in EP-MHT may be safer regarding breast cancer risk than other progestagens needs to be confirmed in other settings.

In other sections of this Summary, I lay out the corroborating evidence that bioidentical progesterone in MHT is truly much safer than the synthetic, imitation progesterones used in Prempro, Activella, Femhrt, Combipatch, and Climara Pro. One major goal of this summary is to empower women to demand that their doctors familiarize themselves with this evidence, and to empower women and their doctors to demand that until these carcinogenic combination hormone therapy drugs are taken off the market, that the warnings be changed to advise women not to use the imitation progesterones as their first choice of a progestogen in MHT.

**[A note about the terminology of “risks v benefits”: the very choice of the word “risk” to characterize the harms of a drug biases the choice heavily in favor of the drug’s supposed benefit, as if there is only a CHANCE (or “risk”) that harm will occur, but a CERTAINTY that the hoped for benefits will occur. This is, of course, a false picture. Just as not all women who take HT suffer the harms found by the studies, not all of them receive benefits. Even for relief from hot flashes – the only approved first line indication for HT – not all women get relief from the drugs. A more balanced terminology would talk about the “harm-benefit” ratio, or the “risk of harm and chance for benefits.”]**

#### **D. The Myth of “1.24”**

Wyeth’s and Pfizer’s favorite mantra in the Prempro litigation to date is something they both cite repeatedly, and as frequently as possible: The “main result” of the WHI Prempro trial is the finding of a relative risk for breast cancer of “only” 1.24. Indeed, that was the reported number from the original report of the trial in 2002.<sup>18</sup>

However, Wyeth and Pfizer and their apologists in the ObGyn community were also quick to criticize the Prempro and Premarin WHI trials as critically flawed. They faulted the studies’ assessment of cardiovascular risk because the women in the study were, on average, much older than the typical new HT user in the real world outside the clinical trials. The women in the study were many years past menopause, and much more obese than the average Prempro

user. The trials intentionally recruited women older than most average new users, because older women had a much higher frequency of cardiovascular events. Had the study recruited newly menopausal women instead, the trial would have had to have been much larger in the number of subjects to see a cardiovascular benefit, which was the main goal of the study, because heart attacks and strokes are much rarer in the younger women.

Another important weakness of the WHI trial was that the women recruited did not suffer from hot flashes. Had the investigators assigned women suffering hot flashes to placebo, the women and their doctors would soon have known which subjects were taking the drug and which were not, compromising the blinding, one of the main strengths of a randomized trial, and increasing the risk of drop outs (or drop ins in this case—women suffering hot flashes on placebo would start taking HT to treat the hot flashes). Even so, there was still a great deal of unblinding among the study subjects, and a higher than expected “drop out” and “drop in” rate. That is, 42% of the women assigned to take Prempro stopped on their own instead of continuing the drug, and 11% of the women who were assigned to placebo pills switched to hormone drugs. These large non-adherence rates were greater than predicted when the study was designed. See the discussion in the first WHI Prempro trial report (pages 326-327).<sup>18</sup> In fact, because more than half of the subjects did not follow the experimental plan, some epidemiologists have suggested the Prempro “trial” is really better analyzed as just another observational prospective cohort study.

In any event, the “1.24” RR for breast cancer risk that Wyeth and Pfizer and their litigation experts constantly repeat is highly misleading and is a gross underestimate of the true risk of breast cancer from Prempro for several reasons. First, that number is the “intent to treat” result. This method counts the women who stopped taking Prempro as if they continued it, and it counts the women assigned to placebo who started taking Prempro (or similar competitor drugs containing NETA or LNG) as if they had continued on placebo. Most of the subsequent published reports of data from the WHI trials report both the “intent to treat” results and the “adherent subjects” results. For the Prempro trial, the final revised intent to treat HR was 1.24, and the adherent relative risk number was 1.49, more than double the intent to treat number.<sup>19</sup> See p. 3247.

But even more important was the study’s recruitment of women far past menopause. When women enter menopause without taking substitute hormones, their breasts go through a natural involution. That is, the ductal and lobular tissue in their breasts is literally partially degenerated by natural aging processes and absorbed, so that their breasts become less dense. It is mostly in this ductal and lobular tissue that breast cancers start and grow. The longer a woman is past menopause before she is exposed to the effects of Prempro, the less susceptible breast tissue she has. This process and these consequences for analyzing the breast cancer risk in the WHI are thoroughly discussed in a review published in 2000 by two Canadian Scientists.<sup>20</sup>

Another major reason that the WHI trial found a slightly lower risk than the Million Women Study and other European studies is that obesity masks the breast cancer risk from HT. Women in the United States, and particularly women in the WHI, were substantially more obese than the women in the Million Women Study. See the Letter to the Editor from the

principal investigators of the WHI<sup>21</sup>, and the top paragraph in the right-hand column of p. 424 of the original breast cancer report of the Million Women Study.<sup>22</sup>

This same misuse of the “intent to treat” analysis infects the descriptions of “absolute risk” that Wyeth and Pfizer and their experts and apologists in the literature like to cite. They claim, using the 1.24 hazard rate, that “only 8 new breast cancer cases per ten thousand women would be expected,” with the background rate of breast cancer being 30 per ten thousand, while the intent to treat number is 38 per ten thousand. Of course, now that we know the true relative risk for women taking Prempro in the real world is more than tripled after only four years, with an even higher risk for newly menopausal women (and the average length of time of exposure in the WHI Prempro trial was 4.4 years).

In the California Teachers Study, where the women truly represented the target market (discussed in more detail below)---80% had used HT at least for a while---the drop in absolute risk of breast cancer in women who stopped HT was 30 per thousand, not 8.

That means there are 22 excess breast cancer cases per ten thousand newly menopausal women adherent to the drug. The Wyeth/Pfizer analysis of absolute risk in the current label underestimates the real absolute risk by a factor of nearly 4.

### **III. Epidemiological Evidence that Prempro Causes Breast Cancer**

Following is a brief summary of the most recent epidemiological evidence that provides additional support for Dr. Chlebowski’s and Stefanick’s conclusion that for the past twenty five years, Prempro caused -- and continues to cause -- breast cancer in thousands of women annually.

#### **A. Observational Studies (Case Control and Cohort)**

##### **1. Women’s Health Initiative (WHI)**

It is well known that “the gold standard” for scientific evidence is the double-blinded randomized controlled trial (RCT). But it is unethical to do a RCT on humans when the outcome of interest is harm, such as breast cancer. Physicians cannot ask humans to be guinea pigs when the event under study is a serious disease. Thus, the WHI Prempro trial was approved only because the investigators believed that the risk of breast cancer or other harms, like ovarian cancer or heart attacks, was very low or non-existent. Even then, there were pre-determined levels of harm that, once reached, would cause the study to be stopped in its tracks.

That is what happened with the Prempro RCT in the WHI. After only 4.4 years of exposure (on average), the predetermined threshold for breast cancer was reached and the trial was halted. All of the women received a letter instructing them to stop taking their study pills immediately. Only a short time later, the Premarin RCT crossed the threshold for dangerous cardiovascular outcomes, and it, too, was halted early. Thus, virtually all of the scientific evidence on the harms of Prempro and Premarin are from observational studies, in which the women were not asked to do anything by the investigators except to report their exposures and outcomes as they went about their daily, ordinary lives.

The highest form of observational study evidence is the prospective cohort study design, such as the Observational Study within the WHI, the Million Women Study in the United Kingdom, the Harvard Nurses' Health Study, and many others. The next highest form of observational study is the case-control study, which is a design necessary when assessing rarer outcomes. To assess relatively rare outcomes, a cohort must include thousands or hundreds of thousands of women, but a case control study can assess associations between a rare outcome and exposure by identifying women with the disease, such as breast cancer, and then identifying other women who serve as the controls. Many of the published studies of the risk of breast cancer from HT use the case-control design.

When a drug is considered safe enough for use in a human experiment, it is the RCT design that evidence based medicine requires to prove any benefits of the drug, such as the once hoped for benefit of HT for cardiovascular protection. Observational studies are potentially misleading when used to assess a purported benefit of a therapy, because the women who volunteer to be subjects in the study may be significantly different from women in general to whom the drug is marketed. This is called "selection bias." This bias is thought to have misled investigators into what has turned out to be a mistaken belief that HT provided cardiovascular protection to women. In fact, the women who were "good" subjects of the trial – i.e., the patients who dutifully took their HT every day and saw their physicians on a regular basis -- turned out to be disproportionately concerned about their health. This created a "healthy users" bias in the observational studies of HT.

The WHI Prempro and Premarin trials revealed the truth: Not only did these drugs fail to provide cardiovascular protection, but besides causing breast cancer, they caused bad cardiovascular outcomes, too. The WHI investigators have published detailed analyses attempting to reconcile the apparently contradictory results between the observational studies of cardiovascular outcomes and the WHI trials.<sup>23</sup>

In addition to the studies discussed above, there are a few other large observational studies published recently that provide rich, robust, and detailed support for the proposition that Prempro causes ER+ breast cancer. In some individual women, these drugs can push a quiescent tumor into rapid growth and clinical emergence within a few months. In the population of new users as a whole, the risk of ER+ tumors is doubled at about 18 months of average use. The risk steadily increases with duration of use.

## **2. Million Women Study (MWS)**

The largest cohort study in the world with relevant data is the Million Women Study in the United Kingdom. The most popular form of HT in the U.K. was Wyeth's Prem-pak,<sup>®</sup> a combination of Premarin plus levonorgestrel (LNG), another androgenic, synthetic and patentable imitation of natural progesterone. In addition, some women in the U.K. used norethindrone acetate ("NETA"), another synthetic progestin. NETA was the most popular progestin in most of the Scandinavian countries, and has also been used in the U.S. as an alternative to MPA in the combination hormone therapies Activella<sup>®</sup> or Combipatch. <sup>®</sup> But

thousands of women in the Million Women Study also used MPA as their progestin, so this large cohort study had data on all three synthetic progestins combined with estrogen in HT.

None of the women in the U.K. used oral micronized progesterone, the most popular progestogen used in France. (The largest cohort study in France, the “E3N” teachers study, has found that oral micronized progesterone, unlike the non-bioidentical progestins, does not increase breast cancer risk.)<sup>24, 25</sup>

The Million Women Study (“MWS”) has generated two primary breast cancer reports so far. The first, published in 2003, analyzed the association between breast cancer and the three main types of HT (“EPRT”) used in the U.K. The breast cancers were not differentiated by histology or receptor subtype.<sup>22</sup> The report found 9,364 breast cancer cases at the time data collection stopped for this analysis. Nevertheless, the study found that in current users of EPRT the risk of breast cancer was doubled (RR=2.0). This is exactly the same overall effect, averaging durations, found by the WHI observation study above. That is, current users of Prempro have doubled their chances of getting breast cancer. Because HT with MPA, NETA, or LNG causes only ER+ tumors, the “all breast cancer” relative risk is always an underestimate of the true risk of ER+ cancers. Assuming ER+ cancers are 67% (2/3) of all breast cancer, then the basic formula to convert an “all breast cancer” risk into an “ER+ breast” cancer risk is to reverse the denominator and the numerator: A RR of 2 for a group of cancers with 1/3 not related, means there is a 3/2 multiplier needed, so the RR of ER+ tumors would be 3. If the proportion of ER+ tumors were instead assumed to be 75%, or 3/4, then the risk of all breast cancers would need to be multiplied by 4/3, and the 2 would become 2.67, etc. So far, the MWS investigators have not published their receptor data, so this type of rough adjustment is all we can do with the present data to estimate the true RR.

In the MWS, in women exposed for one year or less to EPRT, the risk was statistically significantly increased at 1.45, meaning that these drugs can cause breast cancer in some women in less than a year of exposure. This is biologically plausible because the mechanism is a *promotion* effect, not an *initiation* effect.

The risk of breast cancer steadily increased with years of exposure. The investigators compared the relative carcinogenicity of the three different synthetic progestins and found no statistically significant difference in their ability to increase the rate of breast cancer. *See* Fig 5 and text on p. 426.<sup>22</sup> The total number of women in the study who took each of the three main progestins can be determined by adding the numbers of users given for each with less than and more than five years of exposure in Figure 5. There were roughly 59,000 women who used LNG or its racemic mixture norgestrel, 52,000 who used NETA, and 24,000 who used MPA. The authors concluded that EPRT had probably caused 15,000 extra breast cancers in the UK from 1992-2002, just in women aged 50-64.

The second report from the MWS on HT (“EPRT”) and breast cancer analyzed the associations with different histological types of breast cancer, but no receptor status data were reported.<sup>26</sup> The million-plus women in the study had now been followed for another year, and there were now 14,102 breast cancer cases for analysis. These researchers found a stronger causal effect on lobular and tubular types of breast cancer than on ductal. However, even ductal tumors

(again, including ER- ductals as a diluting factor) had almost doubled in frequency in current users exposed less than five years. For lobular and tubular subtypes, the risk was more than doubled in current users exposed less than five years. See Figure 3.

### **HT with MPA, NETA, and LNG increases the death rate from breast cancer among the exposed.**

One other important finding from the original 2003 report from the Million Women Study is that hormone therapy caused a statistically significant increase in deaths from breast cancer. The number of deaths in the data at the cut off for the 2003 report was too small to segregate ERT from EPRT exposures, but for all users of any kind of HT, the risk of death from breast cancer was 1.22. *See* p.424.<sup>22</sup> With one more year of follow-up, the increased risk of death had grown to 1.30, and was still statistically significant.<sup>27</sup>

Wyeth, Pfizer and many defenders of HT argue that Prempro and similar drugs cause only the safest form of breast cancer, the most treatable and least lethal types. Generally, this is true, because ER+ breast cancers are more amenable to current anti-estrogen therapies than are ER- breast cancers. However, the apologists for MHT make an error of logic, which they repeat again and again in the review articles: The defenders of Prempro claim that the rate of death is lower for women who get the type of cancer Prempro causes because they get the safer type of tumors. The problem is, they are confusing the rate of death per woman with cancer (the rate of death per tumor) with the rate of death of women exposed to Prempro, compared to the non-exposed. The Million Women Study's finding of a higher rate of death from breast cancer in the exposed women makes sense: There were so many more breast cancers in the exposed group that breast cancer increased the death rate for all women in the study, even though the rate of death per cancer in the women exposed to HT was lower. No other cohort study but the MWS is large enough to detect this fatality rate difference, and no case control study has ever gathered enough breast cancer death cases to investigate the association.

### **3. California Teachers' Study**

In January 2010, the investigators of the California Teachers Study reported very large drops in the incidence of ER+ breast cancer, both in situ and invasive types, in menopausal women who stopped taking Prempro or other combination HT.<sup>28</sup> The California Teachers Study is a large prospective cohort study of over 133,000 California female public school teachers and administrators recruited in 1995-96 and followed for breast cancer and other health outcomes ever since. This cohort of professional women has a very high rate of mammography use and a remarkably high rate of HT use. Well over 70% of them had tried HT. In the 1995-96 survey, 60% were current users, 14% were past users, and 26% had never used HT. At the time of the second survey in 2000-2001, 58% were current users, 19 % were past users, and 23% never users. In the final survey, only 21% were current users, 52% were past users, and 27% had never taken HT (women were added to the cohort over time).

The 2010 paper analyzed the incidence of breast cancer over three time points, based on personal use data of the drugs, individual records of mammography and breast cancer. It is not just another "ecological" study. Rather, the paper explains the extra strength of its design, with

actual records of individual HT use and breast cancer diagnoses. The investigators did not match general trends in two variables based on agglomerated population level data; instead, they matched general trend data from actual individual data of both variables. "Taken together, our observations demonstrate a strong and immediate influence of HT use and cessation on breast cancer occurrence." *See p. 9.*<sup>28</sup>

When follow up for this report ended, the incidence of in situ and invasive breast cancer was assessed for the cohort in three different time periods: 1996-99; 2000-2002; and 2003-2005. The investigators had assessed HT use at baseline, in 1995-96, and again in 2000-2001. They then compared the incidence of breast cancer among HT users and past users at all three time periods.

Altogether, just over 3,000 breast cancers occurred in this cohort, 566 in situ and 2,668 invasive tumors. This paper provides powerful evidence that DCIS is related to combination HT ("EP") use. The investigators' findings, reflected in the bottom half of Fig 2, were startling:

Women currently taking EP also experienced the largest decline in rates of *in situ* cancer (percent change = -46.7,  $p = .008$ ).

The  $p$  value reported means that the findings of the study were highly statistically significant. In addition, while DCIS was dropping dramatically in past HT users, it was slightly *rising* in those who never used HT (although not statistically significant). They report no receptor data for DCIS. In addition, the researchers acknowledged they had too few cases of either type of cancer (invasive or in situ) even in this large group to measure the effect on histological subtypes (lobular, ductal, etc) or of duration of use, or type of HT. The drop in breast cancer among ERT users was evident, but it was *not statistically significant*. See figure 2 and the text.

The absolute risk revealed by these data is much larger than most review papers have acknowledged before these data were available:

Age-adjusted incidence rates for invasive breast cancer declined rapidly for women who had stopped HT by 2000-2001 ('past HT use') from 561.1 (95% CI = 432.4, 689.8) per 100,000 women in 2001-2002 to 340.0 (95% CI = 265.6, 414.4) per 100,000 in 2003-2005, an overall decline of 39.4% ( $p = .003$ ).

The study demonstrates a precipitous decline in breast cancer in HT users from 561 to 340 per 100,000 or 56 to 34 per 10,000. Recall that Wyeth boasted that the "1.24" risk implied an absolute breast cancer risk for HT of only 8 per 10,000. To the contrary, the California Teacher's Study demonstrates that the absolute risk was *at least* 22 per 10,000. That is, there were 22 excess breast cancers for every 10,000 women, or 2.2 per 100. Even this figure is an underestimate; even though most women taking HT in the middle survey had stopped by the third survey, millions of women throughout the country were still using HT. If all women stopped using HT, the number of breast cancers would fall even further, resulting in an estimated absolute risk of at least 30 per 10,000 – nearly four times higher depicted currently in the "learned" review articles.

#### **4. The MarketScan Health Insurance Data Base Study**

In January 2009, a group of epidemiologists from Boston University published a case-control study using a large private insurance claim database. They tracked HT use and breast cancer outcomes, although not by receptor or histology subtype. The study tracked “all” breast cancer, including the ER- tumor types not related to HT use, which of course, led to an underestimate of the true relative risk.<sup>29</sup> This study included 4,515 breast cancer cases and 18,058 matching controls.

For women who used combination estrogen/progestin (“EPRT”) for four years or more, the risk of breast cancer more than tripled (OR=3.10). Obviously, for ER+ tumors, the doubling time would be significantly less than four years. Most interesting, they investigators recruited the bulk of the breast cancer cases and controls after the introduction to the market of new “low-dose” Prempro (see Table 1), so one goal of the study was to determine if there was an effect of HT dose. The study could not find a difference; meaning low dose Prempro did not apparently lower the risk of breast cancer.

#### **5. American Cancer Society Nutrition Cohort Study**

Dr. Chlebowski briefly discussed this March 2009 study by Dr. Eugenia Calle and colleagues from ACS in his public remarks above.<sup>11</sup> These scientists followed a group of 68,000 American women from 1992-2005. All of them were cancer free at enrollment. The study eventually included 3,139 breast cancers. The researchers were able to analyze the data by histology (ductal or lobular, but not by receptor status), and by one year at a time of HT exposure. Although they found no increased risk in either type of breast cancer in the first two years, they reported:

[W]e observed a significant increase in risk for both types of breast cancer at 2 to 3 years of use (for ductal cancer: RR of 1.91 95% CI 1.39-2.61, and for lobular cancer: RR of 1.95, 95% CI 1.04-3.65) and for all years thereafter.

They also found that the increased risk lasted no more than two years after a woman stopped taking the drugs.

The investigators made another interesting finding. When they looked back at national breast cancer trends in the 1980’s, when EPRT was first becoming popular, they found that the proportion of all breast cancer cases with a lobular component increased from 9.5% in 1987 to 16.8% in 2002. The authors remarked:

This trend is consistent with a stronger effect of combination hormone therapy, which gained common use in the mid- to late-1980s, on lobular carcinoma than ductal carcinoma. See p 937.<sup>11</sup>

Tragically, this signal of the earliest sign of the great iatrogenic breast cancer epidemic was easily detectible in the SEER data by the late 1980’s, had anyone been watching for changes in population trends of breast cancer. Such a signal should have provoked targeted case control

and cohort observational studies to assess a potential increase in estrogen dependent breast cancer, just as it had in the estrogen dependent uterine cancer story. But because Pfizer and Wyeth and the other drug companies intentionally avoided conducting or funding any case control studies from 1980 to 2000 and beyond, the epidemic grew in fury until 2002. And the epidemic continues at a lower burn rate, since millions of women still take the cancer causing HT regimens.

## **6. The MARIE Study (Germany)**

This is a large case-control study from Germany.<sup>30</sup> The investigators recruited 3,464 breast cancer cases and 6,657 matched controls. So far, they have published two reports. The first (fn 16) contains an analysis of the associations between different types of HT and breast tumors. Unfortunately, in their analysis, the investigators combined MPA together with natural progesterone as “one type” of HT, a design they would not use today, given the French cohort studies that have found no increased risk of breast cancer in women using oral micronized progesterone in MHT.<sup>24, 25</sup> Nevertheless, among current users of MHT, the risk of ductal tumors was almost double (OR=1.75), for lobular the risk was 3.04, for ductal/lobular mixed, 3.51, and for tubular 4.19. See Figure 2a. Clearly, had there been a separate analysis for ER+ ductal tumors, or for the imitation progesterone users, or both, the risk would probably have been higher.

In a second published report on the same group of women, the authors did analyze receptor status and other tumor characteristics.<sup>31</sup> Some of the strongest causal evidence comes from these subtype analyses. For example, the odds ratio for grade 1 ductal tumors was 2.60 among current users of *all* hormone replacement therapy, including women who used estrogen only. Combining ERT and MHT data undoubtedly diluted the size of the effect. The same causal association was true for smaller tumors, and for ER+ tumors. These data are consistent with the WHI investigators’ explanation of the promotion effect of Prempro. That is, it feeds tiny, occult tumors and causes them to grow rapidly to detectable size. The effect is most seen when confined to small, ER+ tumors of low grade, and the effect is quite strong.

### **B. Epidemiological evidence that NETA and LNG also cause breast cancer at a high rate**

Observational studies of MHT with NETA or LNG as the progestogen also establish that these other imitation progesterones cause at least as much breast cancer as does MPA. For what are really accidental historical reasons, most physicians prescribing MHT to menopausal women in the Northern European countries (especially in Scandinavian countries such as Denmark, Norway, Sweden, and parts of Germany) chose norethindrone acetate (“NETA”) or levonorgestrel (LNG) as the progestogen instead of MPA, which dominated the US and Canadian and Australian markets. In the U.K., Wyeth did not market Prempro, but instead sold Prem-pak, which was a combination of Premarin plus LNG. LNG is the same imitation progesterone used in many birth control pills, and in Norplant, Wyeth’s contraceptive implantable device, which has since been withdrawn from the market. In France and other French speaking countries such as Belgium, the most popular progestogens were oral micronized progesterone or its close isomer cousin, dydrogesterone.

## **1. The United Kingdom**

The Million Women Study (“MWS”) has the richest database of users of the three main imitation progesterones used in Europe. The MWS, a cohort design, has so far reported data on a total of just over 14,000 breast cancer cases, accumulated through the data cutoff of Dec 31, 2002. fn 13. However, the data on the risks by progestogen are from the 2003 paper, which had analyzed only 9,363 cancer cases with follow up through Dec 31, 2001.<sup>22</sup>

The MWS reports no data on women using oral micronized progesterone or dydrogesterone, apparently because Utrogestan, the brand name of oral micronized progesterone sold by the French company, Laboratoires Besins International, was not licensed in the U.K. until October 2003. As a result, oral micronized progesterone arrived too late to be included in the MWS 2003 breast cancer report.<sup>32</sup> The MWS investigators had sufficient numbers of users of MPA, LNG, and NETA to conclude that these three progestogens increased the risk of breast cancer, but found that there was no consistent variation in risk among them.. See Fig 5 and the discussion about it.<sup>22</sup>

The Scandinavian countries have produced several observational studies, including both cohorts and case control designs. They consistently show that NETA and LNG are at least as carcinogenic as MPA when used in MHT, the same result found in the U.K. by the MWS.

## **2. Finland**

The largest case-control study of breast cancer and MHT use to date was conducted in Finland and published in 2009: “A case-control study on hormone therapy as a risk factor for breast cancer in Finland: Intrauterine system carries a risk as well.” The investigators analyzed nearly 10,000 breast cancer cases in menopausal women, matched with 30,000 controls.<sup>33</sup>

Of the MHT users in the Finnish study (women with a uterus who took a progestogen companion to their estrogen), 96% used one of four progestogens: NETA, 43%; MPA 25%; LNG 19%, and dydrogesterone 9%. The other 4% of the women took a variety of other progestogens, but too few to provide meaningful data.

The main findings of this study were that all three of the imitation progesterones, but not progesterone’s isomer dydrogesterone, were significantly and substantially associated with an increased risk of breast cancer, and that the increased risk was evident in women with less than three years of use. In addition, the study found one very unexpected result: women using a low dose LNG-releasing intrauterine device had the same high risk of breast cancer as the women who took NETA or MPA by mouth. It also found the risk increased with duration of use.

Curiously, the study did not address a significant bias. That is, it did not isolate current users, but rather combines past users with current users in an “ever user” category, resulting in a systematic underestimation of the true risk. Similarly, it did not report any data on ER+ or histological subtypes, resulting in an underestimation of the strength of the association in a similar fashion. Nevertheless, the study still found more than a doubling of the risk of all breast cancer for each imitation progesterone, at five years for MPA and NETA, and at 3 years for

LNG. See Table VI. In addition, it found no increased risk at any duration of use for dydrogesterone.

### **3. Germany**

The MARIE case control study, discussed above, included 3500 breast cancer cases, with 7,000 controls.<sup>30</sup> It separately analyzed the breast cancer risk in women using three categories of progestogens: “progesterone family,” which included both imitation progesterone MPA and natural progesterone and its isomeric cousin dydrogesterone; “norethisterone family;” “levonorgestrel family;” and a final category called “androgens.” The authors provide the data on risk by type of progestogen, in Fig 4. It is clear that the breast cancer risk in women using NETA and LNG was at least as high, and in fact, consistently higher than in women using the progesterone-derived” progestogens. But because the study included oral micronized progesterone and dydrogesterone in the same category as MPA, it is impossible to assess the risk of MPA by itself in the data presented.

### **4. Denmark**

In a cohort of 23,000 Danish women followed for about 5 years, Tjonneland and colleagues, in findings similar to numerous more recent studies, reported important associations between MHT consisting of imitation progesterones and ER+ breast cancers as well as lobular cancers.<sup>34</sup> There were only 423 breast cancer cases in this cohort and only 5 years of follow up on average. However, because the investigators were careful to collect past and current MHT use at study enrollment and segregated current from past users, they were able to detect more than a doubling of the risk of all breast cancer in current users, including ER+ breast cancers and lobular subtypes. Even for ductal tumors without the ER analysis, there was more than a doubling of the risk. See Tables 2 and 3. One other important finding was that for ER+ breast cancer, continuous as opposed to cyclic (or “sequential”) progestin use was more dangerous. Although these investigators did not mention or report any data on the type of progestin used in Denmark, we have another even larger Danish cohort study which does provide data that implies the progestins used by these women were mostly NETA or LNG, with a small minority using MPA.<sup>35</sup>

In the study by Ewertz et al., the investigators followed a second cohort of 48,000 Danish women aged 50 and above for ten years.<sup>36</sup> They identified 1,462 cases of breast cancer. In classifying the types of progestogen, the researchers grouped LNG and NETA into “testosterone-derived” progestins, and MPA into “progesterone-derived” progestins. Among the 8,229 women who took some form of MHT with a progestogen, only 1,221 (15%) used MPA, and 85% used one of the “testosterone-derived” progestogens, mostly NETA or LNG. See Table 3. For women taking the latter type of MHT, there was a statistically significant increased risk of breast cancer among current users of 1.53 overall. Most of the breast cancers occurred in women who were exposed to “mixed use” of different kinds of MHT, and the design of the study did not permit the investigators to tease out the effects of each type of MHT with any reasonable precision. The study defined “current use” to include women who stopped taking the drugs up to two years in the past, thus diluting the effect in true current users.

In a third Danish cohort study, Stahlberg and colleagues at the University of Copenhagen analyzed breast cancer risk among a cohort of 20,000 female nurses.<sup>35</sup> Only 224 cancers developed during the six years the study collected data. The investigators grouped all progestogens into two sets, "testosterone-derived" and "progesterone-derived." They had progestogen type data on 1,844 of the women using a combination MHT. Twenty-three percent used a "progesterone-derived" type (probably all MPA, based on the more detailed data about this category in the Ewertz study,<sup>36</sup> (described above), and 77% used a "testosterone-derived" type, mostly NETA or LNG, based again on the Ewertz study information. The study yielded two important findings. First, the risk of breast cancer among current users more than doubled even with only one year of exposure. Second, continuous use of a progestin significantly increased breast cancer risk more than sequential or cyclical use. There was no statistically significant difference in risk between the two major categories of progestogens studied.

## 5. Sweden

In the early 1990's, Magnusson and colleagues began collecting data for a relatively large case-control study of breast cancer.<sup>37</sup> Since then, the investigators have published several reports analyzing different aspects of the data. Approximately 3,300 women with breast cancer and 3,500 matched controls were recruited from the Swedish Regional Cancer Registries. Data for each woman's exposure to MHT was collected by mailed questionnaire and telephone follow-up. This was the first large study outside the United States to report on the varying associations between different MHT formulations and different breast cancer histologies<sup>38</sup> and hormone receptor subtypes.<sup>39</sup> Virtually all of the women who took combination MHT used estradiol plus NETA (in continuous regimen) or estradiol plus NETA or LNG (in sequential or cyclical regimens). When the investigators combined all estrogen/progestin MHT users, and looked at women exposed for 5 years or more, the odds ratio for ductal breast cancer was 2.3; for lobular it was 5.6, and for tubular 6.5. *See* Table 2.<sup>38</sup> When separately analyzed, continuous users had a higher odds ratio for all three subtypes: ductal 2.7, lobular 5.9, and tubular 8.2, but only the odds ratio for tubular cancers was statistically significant.

In the separate report on tumors analyzed by hormone receptor status, the investigators found, "Users of combined estrogen-progestin menopausal hormone therapy were at clearly increased risk of receptor-positive tumors but not receptor negative tumors." *See* 2485-86.<sup>39</sup> By "receptor positive," the researchers meant that the tumors' receptors were either ER+ or PR+ or both; "receptor negative" meant ER-PR- tumors. For users exposed five or more years, the risk of all three receptor positive subtypes more than doubled. *See* Table 3.<sup>39</sup>

## 6. Norway

The Norwegian Women and Cancer (NOWAC) is a prospective cohort study consisting of two groups of women. The first group of just over 35,000 women, aged 45-64, was recruited in 1991, and a second group of over 46,000 women were recruited in 1996-98. So far, the investigators have published just one report that provides information on the use of MHT and breast cancer in these cohorts.<sup>40</sup> This paper explained that most women in Norway who used combination MHT were prescribed estradiol plus NETA. Prevalence of MHT use reached a high point of approximately half of menopausal women in Norway in 2001. Table IV presents

the data for the women on estradiol/NETA combination MHT. The relative risk of breast cancer more than doubled even in women exposed to the drugs for less than five years. There was a clear increase in risk with duration of use, and an apparent stronger effect for continuous use of NETA as opposed to sequential. For users of continuous combined MHT for more than five years, the relative was 3.2. Furthermore, this finding included all types of breast cancers, so it would underestimate the relative risk for ER+ tumors. Current use clearly puts women at higher risk, too.

### **C. Ecological Studies--Rates of Prescription of MHT and Breast Cancer**

The first results of the HERS Study were released in 1998. They showed that Prempro had no protective effect for cardiovascular disease in older women. Prescriptions of Prempro (or the combination of Prempro or other estrogens plus MPA) in the U.S. immediately flattened, after a steady rise since about 1985. A group of investigators at Stanford obtained national prescription data for MHT use in the U.S. and graphed it.<sup>41</sup> After the WHI Prempro trial was abruptly stopped in July 2002, prescriptions of Prempro fell steeply for the next several months, as seen in Figures 1-3 and Table 1. (Note that the 2003 data is for the partial year only, through July 2003.)

Since 2004, several studies have been published that analyzed the relationship between prescription rates for MHT and rates of breast cancer. These studies do not have data matching individual women with their use of MHT. And they often lack data distinguishing between ERT and EPRT, let alone distinguishing between the different kinds of progestogens. Nevertheless, these studies do show a strong and consistent pattern. When prescriptions of MHT fall in a given population, so soon does the incidence of ER+ breast cancer in women of menopausal age.

The most recent and robust of these population trend studies was published in February 2010 by Harvard researcher Nancy Krieger and colleagues, discussed briefly above.<sup>15</sup> This study looked at breast cancer incidence over time, using SEER data from 1992-2005. The researchers found that the decline in breast cancer started in 1999, when the 1998 HERS study results became widely known. This decline, however, was gradual until mid-2003, when the WHI investigators announced they were halting the Prempro trial early. Suddenly, breast cancer rates dropped sharply and significantly through 2005. Most remarkable, the entire decline was confined to ER+ breast cancer in wealthy white women of menopausal age. The authors have no doubt this is an example of “iatrogenic illness,” of “iatrogenic increases in breast cancer incidence rates.” “Iatrogenic” means harm caused by the health care system: drug companies and doctors. The earlier epidemic of estrogen-dependent uterine cancer in the 1970’s caused by the rapidly growing popularity of Premarin was called by leading epidemiologists “one of the largest epidemics of serious iatrogenic disease that has ever occurred in this country.”<sup>42</sup> The Premarin epidemic was responsible for approximately 15,000 excess uterine cancers. Now, epidemiological data shows that MHT has caused hundreds of thousands of iatrogenic breast cancers.

Looking at the U.S. studies first, Ravdin and colleagues published the first national data announcing a sharp and unprecedented drop in the rate of ER+ breast cancers in this country,

confined to women over the age of 50.<sup>14</sup> The incidence began to fall in mid-2002, at the time the WHI Prempro trial results were released, and continued until mid-2003, when cancer incidence rates stabilized at a new, lower level. There was no decrease in breast cancer rates among women under 50 years of age. For women over 50, there was a 15% drop in the rates of ER+ breast cancer, but no rate change in ER- tumors. The SEER national data they had was for calendar years through 2004, which had been released in the early spring of 2007. There is a normal lag time of release of quality controlled SEER data of about 26 months. The most recent SEER data available in December 2009 is from calendar year 2006. An important question was whether this drop in breast cancer was the result of tumors that would have appeared later in the normal course of events because the tumors had been sped up to appear earlier. This would not represent a true increase in lifetime risk, but an acceleration of tumors that were going to appear sooner or later anyway. But when Ravdin et al. looked at the 2005 SEER data, there was no evidence of “catch up incidence,” meaning that the breast cancers associated with MHT use were truly excess cancers, not just earlier cancers.

This same population effect of a drop in use of MHT leading to a corresponding drop in breast cancer rates has been confirmed in other cohorts of women. More important, some of these other studies have been able to rule out a hypothesized alternative explanation put forward by Wyeth and Pfizer and their experts. The defenders of MHT argued that because menopausal women stopped going to their doctors for annual MHT prescriptions, they probably also stopped getting mammograms too, and so the drop in breast cancer rates in that age group was due to fewer mammograms detecting breast cancer, not a true drop in breast cancer incidence.

To test that hypothesis, Kerlikowske and colleagues obtained data from four different mammogram registries, in California, Washington, New Hampshire and Vermont.<sup>7</sup> They found that rates of ER+ breast cancer declined by 13% between 2001 and 2003 in women over 50, while mammogram rates did not. The WHI investigators also looked to see if a decline in mammography could explain the drop in breast cancer observed in the combined data from the Prempro trial and Prempro users in the WHI observational study.<sup>5</sup> The WHI investigators had both breast cancer incidence and mammographic use data through the end of 2005. They found that there was a sharp drop in both use of Prempro and in breast cancer incidence from before July 2002 until the end of the study period. In the women in the trial, breast cancer rates declined by 28% and in the women in the observational study, breast cancer rates declined by 48%. But the rate of mammograms did not change, so it could not possibly explain the drop in breast cancer rates.

Yet additional evidence linking the decline in breast cancer to a decline in MHT prescriptions came from California data that allowed the investigators to stratify all California counties into three groups: high, medium, and low rates of MHT use. Although the rate of breast cancer declined after 2002 in all three groups of counties, the drop in breast cancer was greatest in the counties with the most use of MHT, the lowest in the group with the lowest rate of MHT use, and in between in the middle group of counties.<sup>43</sup>

One group of investigators analyzed the demographics of the breast cancer decline Ravdin et al. had seen in the SEER data for calendar years 2002-2005. They found that the drop in ER+ breast cancers was confined not just to women over 50, but to women who were white and

affluent. There was almost no change in the breast cancer incidence during those years in minority women or in poor women.<sup>44</sup> The same population effect -- a drop in breast cancer in menopausal women following soon after a decline in the use of MHT -- has been reported in Sweden,<sup>45</sup> Australia,<sup>46</sup> Iceland/Norway/Finland/Sweden,<sup>47</sup> Germany,<sup>48</sup> Switzerland,<sup>49</sup> France,<sup>50</sup> Belgium,<sup>51</sup> UK,<sup>52</sup> and Scotland.<sup>53</sup>

#### **IV. General principles of Epidemiological Studies often misunderstood**

##### **A. Important Points to Remember About the Epidemiological Evidence**

It is important to remember several things in reading the papers summarized above:

##### **1. Many studies combined “all” breast cancers instead of analyzing hormone-dependent tumor subtypes.**

When the studies assess risk of “all” breast cancers, they will underestimate the true risk for ER+ cancers. If the investigators had analyzed and published their receptor and histology data, we know that the relative risks for ER+ breast cancers would be higher and appear sooner than for “all” breast cancers. Because ER- tumors make up roughly 25-33% of all tumors, any assessment of “all” breast cancers will systematically underestimate the risk for ER+ tumors by a factor of 30% or more. That is, if the relative risk for all breast cancer at three years is 1.7, the relative for ER+ breast cancers at three years would be well over 2.0. And if the relative risk for all breast cancers with four years of exposure is 3.06, as the study found, then the true relative risk for ER+ tumors in women with four years of exposure would be 4 to 4.5, depending on what proportion of all breast cancers one assumes ER+ breast cancers to be.

The same is true for the main histological subtypes of breast cancer. Studies that have enough total breast cancers to separately analyze the risk of ductal, lobular, tubular and other subtypes of breast cancer consistently find a higher and earlier risk of tubular and lobular breast cancers compared to ductal cancers. Again, when all types are combined, the overall risk estimate will be lower than when the subtypes are separately analyzed.

##### **2. Studies overlooked the distinction between progestogens.**

Some studies do not distinguish *at all* between types of progestogens. They fail to mention that progesterone has been found to be much less dangerous than MPA, nor do they acknowledge that the WHI results apply only to Prempro, not to Premarin plus Prometrium, and not to estradiol plus Prometrium. The Million Women Study included enough users of the three main forms of imitation progesterone (MPA, NETA, and LNG) to assess their relative differential effect and found none; the differences in RR among them were not themselves statistically significant. On the other hand, Jick’s study of the health insurance database was able to isolate just the Prempro users, which means that all of the women in the study used only the form of MHT consisting of Premarin plus MPA.<sup>29</sup> But many other studies cannot or do not report these kinds of distinctions.

### **3. Studies did not correctly define and classify “current users.”**

Some studies do a better job of capturing “current users,” which is important because we know from the WHI data in reference 8 that the elevated risk from Prempro is almost completely gone after two years past drug cessation. So, combining women who have stopped taking the drugs with those women who remained on Prempro will cause the study to underestimate the true risk. This is a major impediment of the recently published Finnish case-control study.<sup>33</sup>

## **B. Primer on Epidemiological Evidence in HRT**

Probably the most respected categorization of the levels of scientific evidence of a harm or benefit is published on the website of Oxford University’s Centre for Evidence Based Medicine.<sup>54</sup>

### **1. Randomized Clinical Trials**

If a drug is thought to be relatively safe, but its benefits are in doubt, researchers will conduct randomized clinical trials on women to “prove” the benefits. However, by design, randomized trials are literally an experiment on human subjects. Thus, if there is a suspicion that the drug will cause serious harm to some of the subjects, clinical trials cannot be done. It is unethical to experiment with potentially dangerous drugs on humans. Instead, researchers study the hazard in question by observing people who voluntarily, in their normal lives, decide to take the drug. These studies are “observational” as opposed to “experimental,” but they are the only way to ethically assess the risk of breast cancer with Prempro.

### **2. Observational Studies**

There are three main types of observational studies used to assess breast cancer risk from Prempro and other forms of MHT.

**Case-Control Studies.** The most common type of observational study is the case-control study, in which a large number of women with breast cancer are collected (the cases), then women without breast cancer are found who match the cases in age and other characteristics (the controls). The investigators then determine what percentage of women in each group used Prempro. If the percentage of women with breast cancer who took Prempro is significantly higher than the percentage of women without breast cancer, the study finds an association between Prempro and breast cancer expressed in a “relative risk” or “hazard ratio” or “odds ratio” (RR, HR or OR). Of the various types of observational studies, case-control studies are the quickest and cheapest to conduct. A good case control study can be completed in two to three years.

**Cohort Studies.** The second major type of observational study is a cohort study. Here, the investigators enroll a large number of women and then follow them medically for many years. The follow up can be retrospective (reviewing past medical history) as well as prospective. These studies are much more expensive than case control studies and take much longer to complete. Nevertheless, there are several very large cohorts of menopausal women being

followed in the U.S. and other countries that report important Prempro and breast cancer data from time to time in the peer reviewed literature. These studies are designed to follow the same group of women for many years, even decades.

**Ecological Studies.** Finally, the third main type of observational study relevant here is the “ecological” study, where the investigators analyze trends of Prempro use and breast cancer incidence in large populations of women, but without individual data. In these populations it is possible to see “intervention effects” of drugs when they cause cancer rates to go up when prescriptions go up and cause cancer rates to go down when prescriptions go down. There are several such useful studies on Prempro and breast cancer.

### **3. The design of many observational studies on menopausal hormone therapy and breast cancer leads to a systematic underestimate of true risk.**

In order to see a causal effect between a drug and cancer, it is important to define precisely what drug exposure means, and what type of cancer one suspects is connected. With Prempro, it is obvious now that its effect on breast cancer is primarily through promotion of microscopic, occult and harmless tumors into clinically significant breast cancers. The effect wears off after about two years, according to the February 2009 report from the combined WHI Prempro trial and observational study.<sup>5</sup> So studies that combine past users with current users will dilute the effect; that is, they will underestimate the true effect. Many studies in the published literature are of “ever-never users,” and they all have this systemic design defect leading to underestimation.

Similarly, we know now that Prempro acts as a growth factor for ER+ tumors, but not ER- tumors. Any study that combines both types of breast cancer into one analysis will dilute the effect on the subgroup of ER+ tumors, and will systematically underestimate the size of the causal effect. Even more obvious are studies that combine both ERT and EPRT into one analysis of “HRT.” These will also systematically underestimate the risk of Prempro, because ERT carries a much lower risk. The lower ERT effect dilutes the stronger Prempro effect.

Finally, there is a human selection bias that affects all the observational studies of HRT that recruit voluntary controls. It is known that women who take HRT are much more willing to volunteer to be controls in medical studies than women who do not use HRT. Two studies have investigated this phenomenon and confirmed it.<sup>55, 56</sup> This causes a dilution of the true effect because the controls are not representative of a true random sample of all menopausal women. They are a non-random sample of women who use HRT much more often. The recent German studies (MARIE, discussed above) actually not only acknowledged this bias, but did a substudy to estimate its effect, finding that this bias led to a ten percent underestimate of true risk.<sup>30</sup>

## **V. Additional Scientific Evidence that Micronized Progesterone Does Not Cause Breast Cancer**

**A. Human randomized clinical studies support the finding of the epidemiological studies that progesterone, unlike MPA, does not stimulate the breast.**

There are three published randomized clinical trials that analyzed breast tissue from women exposed to estrogen plus either natural progesterone or the imitation progesterone, MPA. Hofseth et al. exposed menopausal women to estrogen alone, estrogen plus MPA, or no hormones, and then analyzed breast tissue samples.<sup>57</sup> Menopausal women scheduled for breast biopsies were categorized by their intake of hormone pills in the three months before surgery: some took estrogen only, some estrogen plus MPA, and some took no hormones at all. The study found that women taking the combination had much more breast cell proliferation than women in the other two groups, and that the increase in proliferation was concentrated in the terminal duct lobular unit of the breast, where most breast cancers arise.

In the Foidart study, investigators using blinded techniques exposed women to hormones by having them spread a gel on their breasts every day for two weeks, before they were scheduled for breast biopsies. Neither the doctors nor the women knew whether they were using a gel containing estrogen only, progesterone only, estrogen plus progesterone, or a placebo. Breast cell proliferation was highest in the women who received estrogen only. The women who received progesterone alone or progesterone with estradiol had significantly lower proliferation than the women getting estrogen alone. They concluded: “progesterone administration dramatically limited the estradiol-induced proliferation of normal human breast epithelial cells.” (p 967).<sup>58</sup>

Chang’s 1995 study was similar in design to Foidart’s, and resulted in similar findings.<sup>59</sup>

Randomized clinical trials in menopausal monkeys confirm that MPA stimulates breast tissue proliferation and activates many more genetic growth pathways than does natural progesterone when combined with estrogen.

In a series of papers published by a group of investigators at Wake Forest University, menopausal monkeys were exposed to human equivalent doses of estrogen only, estrogen plus MPA, and estrogen plus oral micronized progesterone. In the study, which analyzed risk markers for breast cancer in these monkeys, the authors concluded: “Compared to placebo, E2 (estradiol) + MPA resulted in significantly greater breast proliferation in lobular and ductal epithelium, while E2 + P4 (micronized progesterone) did not . . . These findings suggest that oral micronized progesterone has a more favorable effect on risk biomarkers for postmenopausal breast cancer than medroxyprogesterone acetate (MPA).”<sup>60</sup>

In the most recent report from this group, the investigators measured how many and what kind of genes were turned on in the breasts of menopausal monkeys given the same three regimens as in the first study. “Treatment with E2 alone induced modest effects on select genes relating to epidermal growth factor receptor (EGFR) activity, which were augmented by MPA but not P4, consistent with patterns of epithelial cell proliferation . . . These findings suggest that a standard dose of oral E2 + MPA has a more pronounced effect on gene expression in the breast compared to E2 alone . . .”<sup>61</sup>

In vitro (test tubes and Petri dishes) studies of human breast cancer cell lines have found that MPA activates more and different cell receptors and genes than does bioidentical progesterone, showing that it is the androgenic properties of MPA, which progesterone lacks, that probably make it carcinogenic.

Using a specially developed human breast cancer cell line, NIH funded researchers at the University of Colorado compared the transcriptional effects of MPA and progesterone through activation of the progesterone and androgen receptors. They found both affected the PR about the same, but MPA had many effects through the AR, while progesterone had none.<sup>62</sup>

Australian cancer researchers believe they have found an explanation why MPA, when given with estrogen in MHT, is so carcinogenic. Drs. Wayne Tilley and Steven Birrell have conducted research on the androgen receptor (AR) and its role in breast cancer. The results of their study were published in a major review paper in 2007. Because MPA can bind to the AR as well as the PR and other receptors in breast tissue, they concluded that the reason MPA but not native progesterone increased the risk of breast cancer in women taking estrogen for hot flashes was because MPA interfered with the normal feedback mechanism in the menopausal breast that allows AR to dampen down the proliferation of cells when ER is stimulated.<sup>63</sup>

Drs. Tilley and Birrell have written a detailed report for the plaintiffs in the HRT litigation that explains this theory in documented detail.<sup>64</sup>

A study comparing the stimulatory effect of different progestogens, combined with estrogen, on a widely-used human breast cancer cell line found that both MPA and NETA, when combined with estrogen, significantly stimulated proliferation of the breast cancer cells, while progesterone did not, and dydrogesterone actually induced cell death. *See figure 2.*<sup>65</sup>

## **B. Primate and Other Animal Experiments**

German researchers have published new data on the comparative effects of MPA and progesterone on the uterine and breast tissues in mice.<sup>66</sup> They assessed the balance between the desirable uterine and undesired mammary gland effects for these two progestogens widely used in HRT. In the study, mice were ovariectomized, and after 14 days they were treated subcutaneously with either estradiol (100ng) or estradiol plus increasing doses of progesterone or medroxyprogesterone acetate for three weeks. Measures for progestogenic mammary gland activity were stimulation of side branching and stimulation of epithelial cell proliferation. Progestogenic activity in the uterus was assessed by measuring inhibition of estradiol-activated uterine epithelial cell proliferation. ED(50) and ID(50) values for the distinct readouts were obtained, and dissociation factors for uterine versus mammary gland activity were calculated. MPA demonstrated uterine activity and mitogenic activity in the mammary gland at the same doses. In contrast, progesterone showed uterine activity at doses lower than those leading to significant stimulation of epithelial cell proliferation in the mammary gland. The authors concluded: “Progestins do not behave the same. Use of the natural hormone progesterone, but not MPA, in combined hormone therapy might offer a safety window between uterine effects and undesired proliferative activity in the mammary gland.”

## **VI. European Consensus that Micronized, Human-Identical Progesterone Is Much Safer than the Imitation Progesterones for the breast**

### **A. French prospective cohort studies show progesterone does not cause breast cancer in menopausal women.**

There is a consensus in Europe that oral micronized progesterone and its racemic sister dydrogesterone have a much lower risk, or even no risk, of breast cancer when used in combined menopausal hormone therapy, at least for the first five years of use. A substantial body of observational scientific evidence now supports this consensus.

There are three prospective cohort observational studies comparing women on estrogen plus oral micronized progesterone or dydrogesterone to women taking estrogen only or estrogen plus one of the synthetic imitation progesterones like MPA.

The largest cohort and the one with the longest follow-up data is a cohort of French teachers or teachers' wives, known as the "E3N" cohort. So far, the investigators of the study have published three reports on breast cancer outcomes.

In 2005, the investigators published their initial results, based on 5.8 years of follow up.<sup>67</sup> The cohort consisted of 54,548 women who had not taken any type of MHT before study entry and who were followed for an average of 5.8 years. The mean duration of MHT use with OMP was 3.1 years. Most importantly, in contrast to the WHI Prempro trial, where the average age was 63 and time past menopause was 11 years, in the French study the average age at study recruitment was 52.8 years, and they continued to add newly menopausal women as the cohort aged. When the study started in 1990, many women recruited were pre-menopausal, in their 40's. The researchers found a statistically significant increase in risk of breast cancer, but only in those women taking some form of imitation progesterone. The paper stated, "Micronized progesterone may be preferred to synthetic progestins in short-term HRT." I contend that it is this published finding in 2005 that women were entitled to be informed of when contemplating whether to start or continue taking MHT. Subsequent reports from this French teachers study have strengthened this finding.

In 2007, the same group of investigators published an update.<sup>24</sup> In this follow-up, the title of the paper carried the message, "Unequal risks for breast cancer associated with different hormone replacement therapies." Now, with 8.1 years of follow up, the authors were able to confirm their original finding; that is, all of the imitation progestergones except dydrogesterone, the one closest in molecular structure to natural progesterone caused an increased risk of breast cancer. In contrast, oral micronized progesterone and dydrogesterone did not. The paper concluded, "These findings suggest that the choice of the progestagen component in combined HRT is of importance regarding breast cancer risk: it could be preferable to use progesterone or dydrogesterone."

More recently, the French investigators have published an analysis of the relative effects of progestogens on different types of breast cancer.<sup>25</sup> They found that the imitation progesterones

caused an increased risk of ER+ tumors, including ductal tumors, and especially lobular tumors. In the discussion section, the investigators reviewed and summarized studies by other scientists on women's and monkeys' breast tissue and concluded, "These studies support our findings suggesting that, when combined with an estrogen, progesterone may have a safer risk profile in the breast than some other progestagens."

The most recent report from the French Teachers Study analyzes the breast cancer risk in newly menopausal women compared to women more than 3 years past menopause. The findings are remarkable: For women taking MHT with an imitation progesterone, the risk of breast cancer is nearly doubled in less than two years of use, while for OMP users, there is no increase in breast cancer even after five years of use, and even for newly menopausal women. For users of dydrogesterone, the risk in newly menopausal women was detectable, though lower than for the other imitation progesterones. See table 3 and the discussion about it in Fournier, "Estrogen-Progestogen MHT " 2009.<sup>17</sup>

Two other, smaller cohorts of French women have reported the same effect: oral micronized progesterone is safer for the breast. The first of these is the MISSION study, which is following approximately 5,000 women over time to determine the effects of MHT.<sup>68</sup>

About half of the women taking MHT were on oral micronized progesterone, and half were using one of the imitation progesterones. The women on average exposed to HT used it for 8.3 years, and the risk of breast cancer was lower in the oral micronized progesterone group. The authors stated:

*"The safest HRT in terms of breast cancer risk is the association of cutaneous estrogen and micronized progesterone."*

P. 396 and figure 1 of Espie 2007.<sup>69</sup> They saw their results as confirming the results of the E3N French Teachers Study.

The second, earlier and smaller cohort study followed 3,175 French women for an average of 8.9 years, and found no increased risk of breast cancer in the HT users, 70% of whom used OMP or dydrogesterone.<sup>70</sup>

### **B. Review Papers Explain the European Consensus that Micronized Progesterone is safer.**

Although review papers contain no new data, they support the findings from the French cohort studies that oral micronized progesterone is significantly safer than MPA, NETA, or LNG when used as the progestational component of MHT.

There is a growing body of editorial and scientific review publications that support the conclusion that women should be advised that oral micronized progesterone is safer for the breast. Here are the best of them:

Mueck et al, "Use of dydrogesterone in hormone replacement therapy", *Maturitas* (2009) doi.10.1016/j.maturitas.2009.09.013. (Published on line ahead of print).<sup>71</sup>

Although the authors of this review paper claim no conflict of interest, they do thank Solvay for “sponsoring” the “study.” Since 1961, Solvay has marketed dydrogesterone in several countries under the brand name Duphaston,<sup>®</sup> with an approved indication for use as a progestogen in combination menopausal hormone therapy. It appears that Solvay withdrew the drug from the U.S. market in 1997, shortly after the FDA approved Prometrium for sale in the United States.<sup>72</sup>

A group of Italian gynecologists published a recent review of the epidemiology and biology of HT breast cancer risk.<sup>73</sup> Gadducci et al., “Progestogen component in combined hormone replacement therapy in postmenopausal women and breast cancer risk: A They conclude: “Some experimental and clinical studies suggest that different progestins may have a different impact on the pathophysiology of malignant breast cancer cells. HRT formulations including MPA or androgenic progestins are associated with an increased risk of breast cancer incidence, whereas micronized progesterone and dydrogesterone would not appear to influence breast carcinogenesis.” P. 812.

Another well-respected group of European gynecologists has written an even more comprehensive review of the variations in effect on women of various HT regimens.<sup>74</sup> L’Hermite et al., “Could transdermal estradiol+progesterone be a safer postmenopausal HRT? A review,” *Maturitas* 60 (2008) 185-201. These researchers conclude: “ The addition of a progestin to estrogens is required for endometrium protection and the PEPI trial has demonstrated that micronized progesterone works [222 (PEPI Study)<sup>75</sup>] as well as MPA. Another study with progesterone applied as a vaginal gel led similarly to prevention of endometrial hyperplasia in all women tested [223 (Ross 1997)<sup>76</sup>]. In addition, there is good observational data to suggest that HRT combining micronized progesterone to estrogens will not result in any increased incidence of breast cancer, in contrast to most synthetic progestins.” (Page 12).<sup>74</sup>

A third review paper by scientists who have conducted some of the clinical experiments showing micronized progesterone safer for the breast is Foidart et al., “Hormone therapy and breast cancer risk.” On page 56, the authors cited the 2005 and 2007 reports from the E3N study by Fournier as support for their statement, “... micronized progesterone or dydrogesterone used in association with oral or percutaneous estradiol may be associated with no increase in risk or lower increase in risk than synthetic progestins for at least 4 years of treatment. Recent reevaluation reveals that, even after 8 years, this treatment is not associated with an increased risk of breast cancer.”<sup>77</sup>

Another point the authors made in this 2007 review paper is that although an increased risk of breast cancer in postmenopausal women is associated with higher circulating levels of estrogens, use of estrogen-only hormone therapy does not increase breast cancer risk, at least not without many more years of exposure, compared to combination hormone therapy with a synthetic progestin. This paradox is explained by the fact that it is the concentration of estrogen in breast tissue, especially in the subset of women genetically susceptible to the growth-stimulating effects of this local estrogen, which is associated with higher breast cancer risk, rather than the level of estrogens in the circulating blood stream.

Furthermore, in the only clinical trial that assayed local breast levels of estrogen in women taking combination hormone therapy the investigators found that breast tissue levels of estradiol were 7 times higher in postmenopausal women on Prempro than in premenopausal women, and 18 times higher than in the postmenopausal control group of women.<sup>78</sup>

In addition, the plaintiffs in the hormone therapy litigation have commissioned expert reports that analyze the scientific evidence that oral micronized progesterone is a safer choice than MPA for use in menopausal hormone therapy. The authors of these reports are Donald Austin, MD, and a joint report by Australian cancer researchers Dr Wayne Tilley and Dr Steven Birrell.<sup>79, 64</sup>

**C. The only two ongoing randomized clinical trials in the U.S. studying the effects of MHT on menopausal women both rejected synthetic, imitation progestins as study drugs.**

The investigators instead opted for bioidentical progesterone. In the one study (KEEPS) that is examining the potential benefits of long-term, early initiated hrt, the investigators are using Premarin, the horse estrogen component of Prempro. However, they rejected MPA as the progestogen component and, instead chose Prometrium, oral micronized progesterone.<sup>80</sup>

NIH, specifically the National Institute on Aging, is sponsoring the other trial. The name of the study is “Early versus Late Intervention with Estrogen Trial.” (ELITE) The investigators of this study also rejected using MPA or any other imitation progesterone and opted to give women with a uterus a vaginal gel containing bioidentical progesterone (marketed in the U.S. under the brand name Prochieve® and in Canada under the brand name Crinone®).<sup>81</sup>

**D. Other authorities agree that micronized human-identical progesterone should be the progestogen of first choice for MHT.**

The French regulatory agency for drug licensing, Agence Francaise de Securite Sanitaire des Produits de Sante, states on its website (<http://www.afssaps.fr/>) that oral micronized progesterone may be safer than other progestogens in MHT:

*[T]he risk depends on the type of progestogen combined with estrogen and is smaller with micronized progesterone . . .*

The International Menopause Society states on its website (<http://www.imsociety.org/>) and in its official MHT guidelines<sup>82</sup> that there is evidence oral micronized progesterone has a lower breast cancer risk than other progestogens:

*Micronized progesterone . . . used in association with . . . estradiol may be associated with no increase in risk or lower risk than the use of synthetic progestogens for at least four years, and perhaps even eight years, of treatment. .*

Harvard Medical School Professor JoAnn Manson is one of the investigators for the WHI, and for KEEPS. In her book, *Hot Flashes, Hormones & Your Health*, Dr. Manson states, "I think it may be prudent to opt for progesterone over progestin where possible." p. 144.<sup>83</sup>

**E. Even when delivered locally in the uterus, LNG has been found to substantially increase breast cancer risk in menopausal women taking estrogen.**

In the large Finnish case-control study discussed above, the investigators assessed the breast cancer risk associated with the use of an IUD that released levonorgestrel directly into the uterus to provide protection from the carcinogenic properties of estrogen on the endometrium. To their great surprise, the investigators found that menopausal women using that system had a substantial risk of breast cancer, which nearly doubled in less than three years, and more than doubled with longer durations. *See* table VI.<sup>33</sup>

**F. The probable biological mechanism by which MHT causes cancer is promotion of pre-existing, microscopic lesions, which would have regressed or would never have become clinically manifest.**

At the beginning of this summary, I quoted several authorities' statements concerning the likely mechanism by which MHT causes cancer. The consensus is that combination MHT does not initiate breast cancer, but rather, acts as a "promoter" of existing, microscopic pre-cancerous and cancerous lesions, which would not have developed into clinically significant or even detectable tumors absent the stimulus from the hormone drugs.

Dr. Karla Kerlikowske is a professor of medicine, epidemiology and biostatistics at the University of California. In her interview with Gina Kolata of the New York Times on December 29, 2009, Dr Kerlikowske has set forth one potential explanation for the sudden rise in both HRT use and breast cancer followed by the sudden drop in breast cancer when women quit taking HRT. In a section of the longer story titled "A Nudge Over Time," Ms Kolata observed, "Cancer is supposed to take years, even decades, to develop. How, some asked, could cancer rates drop so quickly? Could it be possible that the hormone treatment somehow changed the environment of naturally occurring cancer cells and let them progress?"

Dr. Kerlikowske told her it is a possibility. "A combination of estrogen and progestin, like that in Prempro, may change the structure and activity of breast tissue, Dr. Kerlikowske finds, making breast tissue denser, a condition that has nothing to do with how breasts look or feel. Breast density is a cellular structure seen on mammograms and has long been associated with higher cancer risk. Her hypothesis is that hormone therapy can give that little bit of nudge over a long enough period to promote breast cancer," Dr. Kerlikowske said. For some cancers destined to be aggressive, she suggests, it probably makes no difference if a woman takes hormones because the cancer will spread anyway. But she thinks that "for the average person, it becomes very important."<sup>84</sup>

Several published autopsy studies have established that there is a reservoir of sub-clinical microscopic breast tumors in menopausal women. Specifically, these studies found that the

breasts of women who died with no known breast cancer revealed a high percentage of sub-clinical breast cancers.<sup>85, 86, 87, 88, 89, 90, 91, 92, 93</sup>

And a recent study from Norway has demonstrated that such lesions can naturally regress in women no longer exposed to MHT, even after they have grown to detectable size.<sup>94</sup> The investigators compared the breast cancer incidence in two groups of women. Both groups were from the same four Norwegian counties. The first group's data were collected before a breast cancer-screening program was implemented in these counties, and the second group's data was collected during and after three rounds of mammographic screening. At the end of six years, 22% more breast cancers had been diagnosed in the screened group than in the unscreened group. As the authors pointed out, since almost all breast cancers that are detected are treated, there are few case reports in the literature of spontaneous regression of breast cancers.<sup>95, 96, 97</sup> Nevertheless, in this study, the data supported the conclusion that "some invasive breast cancers detected by repeated mammographic screening would not persist to be detectable by a single screening at the end of six years. In other words, the natural course for some screen detected breast cancers may be to spontaneously regress." P. 2314.<sup>96</sup> "We believe the that the most tenable explanation of our findings is that some screen-detected breast cancers spontaneously regress." P. 2315.<sup>96</sup>

If all of the excess breast cancers promoted into clinically relevant size by MHT were destined, inevitably, to keep growing – albeit more slowly – on their own once MHT was withdrawn, we would expect to see what is called "catch-up incidence" a few years after the large drop in MHT use that followed the alarming publications of the WHI Prempro trial results in July 2002 and the Million Women Study in August 2003. That is, if MHT were only accelerating the growth of tumors that were going to appear eventually, we would expect a dip in breast cancer incidence following the large reduction in the population's exposure to the drugs, but followed by an increase back to the "natural" incidence rate. How quickly this rise incidence would appear depends on how long the increased risk from the promotional boost lasts. The careful analysis by Chlebowski and the other WHI investigators combining the data from both the Prempro trial and the observational study, showed that the increased risk disappeared almost completely in two years after women stopped taking Prempro.<sup>5</sup> Thus, if "catch-up" incidence were to occur, it should have begun to appear by the end of 2004, and certainly by 2005, in the population breast cancer rates. However, we now have SEER data through the end of calendar year 2005, and no catch up incidence has occurred. Ravdin published a short paper making this point after the 2005 SEER data became available.<sup>98</sup> This means that the breast cancers caused by MHT were truly excess cancers, cancers that would never have appeared but for MHT exposure. The annual update of SEER breast cancer incidence data normally is made public in about April of each year, with the data tallied through the calendar year ending about 27 months earlier. Thus, in April of 2010, the SEER data for calendar year 2007 should be available.<sup>99</sup>

This mechanism of promotion of pre-existing estrogen dependent lesions was proposed and is now generally accepted to explain how estrogen therapy back in the 1960's and 1970's caused an epidemic of uterine cancer in menopausal women. The epidemic was detected by two quick and inexpensive case-control studies presented at an emergency meeting at the FDA in 1975, and later published.<sup>100, 101, 102</sup> The surge in estrogen fed endometrial cancer among menopausal

hormone therapy users was also easily detected in the population trend data. Dr. Donald Austin published an often-cited paper comparing the rates of estrogen dependent uterine cancer in menopausal women in the San Francisco Bay Area with the use of ERT, and found a remarkable correlation.<sup>103</sup> Ken Rothman, one of the world's preeminent epidemiologists, published a paper calling this event "...one of the largest epidemics of serious iatrogenic disease that has ever occurred in this country."<sup>42</sup>

## **VII. Discussion & Conclusion**

Ironically and tragically, it was the need for a progestogen to reduce this cancer risk from ERT that led to the enormously larger iatrogenic epidemic of hormone dependent breast cancer in many parts of the world, but especially in the upper socioeconomic groups of menopausal women in the USA, Canada, Australia, and Northern Europe. The entire global number of breast cancers caused by the use of MPA, NETA or LNG instead of micronized progesterone or dydrogesterone, is surely well over 500,000 and counting.

### **A. Menopause conferred important evolutionary advantages on humans—it is a fundamental aspect of human life and culture.**

One other piece of junk science was also convenient to companies determined to sell a pill to every woman over the age of fifty, every day for the rest of her life: The drug industry and its advocates in the medical profession claimed that menopause was a new phenomenon of modern life, that women historically and especially pre-historically, did not suffer menopause because few if any women lived past age 50. This is a simplistic mistake in interpreting the data on average life expectancy. Just because the average life expectancy pre-1900 might have been only 45, that did not mean that a significant portion of women did not live into their sixties and seventies, long past menopause. In fact, large numbers of women always had survived past menopause and made healthy contributions to their families, clans, tribes, villages, and communities.

Indeed, there is an evolutionary explanation for menopause. The groups of our ancient ancestors who had many experienced, wise, and older women were more likely to survive because these women served as both sages and midwives. These older women no longer had to care for young children of their own. Their communal role was to help raise grandchildren and care for the tribe as a whole. Plaintiffs in the HT litigation obtained a report on this topic from one of the world's leading experts on the evolution of menopause, Kristen Hawkes, Distinguished Professor of Anthropology at the University of Utah, recently elected to the American Academy of Arts and Sciences.<sup>104</sup> Among anthropologists who have studied the issue, it is generally accepted that menopause is uniquely human among mammals, and is a critically important aspect of the survival of our species in the past few hundred thousand years. Typical of these assessments of the evolutionary purpose of menopause is this one:

“As an explanation for the origin of menopause, we can dismiss the notion that post reproductive life is the result of recent increases in life expectancies due to improved sanitation and medical care. We know from Genesis that women have lived past menopause for at least three thousand years, and during most of this time living conditions were certainly not benign. Nor is the reproductive life span solely the result

of increases in maximum life span in humans. Many investigators agree that hominid life span exceeded the current age of menopause well before the appearance of *H. sapiens*.”

Pecceit, JS, “Menopause”, in *Grandmotherhood: The evolutionary significance of the Second Half of Female Life* (Ed. Volland et al., Rutgers U Press, 2005)<sup>105</sup>

It was much more convenient for Wyeth and Pfizer to convince women and doctors that menopause was a modern problem requiring a modern solution, the laboratory imitation of a natural hormone.

**B. The Willful Ignorance of the Drug Companies About the Real Risk of Breast Cancer has been found by multiple courts to justify imposing punitive damages**

A detailed history of the state of willful ignorance fostered by Wyeth, Pfizer and other drug companies, of the effects on breast cancer of adding a laboratory imitation of progesterone to the daily pills taken by millions of women, is contained in our most recent legal brief on the justification for punitive damage verdicts against Pfizer and Wyeth.<sup>106</sup>

In addition, two courts (with four judges joining) have issued opinions explaining why these drug companies should be subjected to punitive damages for their conduct with respect to ignoring the breast cancer risk. *See In re Prempro Prods. Liab. Litig.*, 586 F.3d 547, 572 (8<sup>th</sup> Cir. 2009) (holding there was sufficient evidence upon which a jury could conclude that Wyeth acted with reckless disregard to the risk of injury). A court in Nevada also upheld the jury's finding of malice to support a punitive damages award against Wyeth in *Rowatt et al. v. Wyeth*, Cas No. CV04-1699 Dept. 9 (Washoe Cnty, 2d Jud. Dist. Ct. Nev. Feb. 19, 2008). Specifically, the court found as follows:

Here, there was substantial evidence from which the jury could conclude that Wyeth knew that its product could cause breast cancer, that it intentionally failed to conduct adequate tests, that it financed and manipulated scientific studies, and sponsored articles in professional and scientific journals that deliberately minimized the risk of cancer while over-promoting certain benefits and citing others which it knew to be unsubstantiated. The evidence also supported the conclusion that Wyeth intentionally made similar misstatements and misleading assertions in its marketing to physicians and its advertising directed to the public. *Id.* at 3.

This second hormone driven cancer epidemic in menopausal women should never have happened. It occurred because no one ever actually tried to assess the breast cancer risk from the new combination therapy---certainly not the drug companies making hundreds of millions of dollars in selling these imitation progesterones as menopausal hormone therapy. The drug companies deliberately avoided studying the risk while these drugs grew in popularity along with the companies' huge advertising, sales and marketing efforts from 1980 until 1999, when the increase in the number of combination HT prescriptions topped out and began to decline. The adverse effects of Prempro in older women with preexisting cardiac disease were announced for the first time in 1998,<sup>107</sup> with the decline in Prempro prescriptions accelerating

dramatically toward the end of 2002, after the WHI Prempro trial had been interrupted due to safety concerns. Neither Wyeth nor Pfizer conducted any case control studies to assess the breast cancer risk, even though it was these very types of studies that detected the first HT-driven cancer epidemic had been detected. It didn't take long for independent researchers to conduct case-control studies, which found an increase in ER+ breast cancer among current users of combo HT.

This summary of the scientific data demonstrates how robust the evidence is that demonstrates that the imitation progesterones greatly increase breast cancer risk. But it was not until 2005 or 2006 that many case control studies became available. The drug companies should have conducted and funded some case control studies in the 1980's and early 1990's. Had they done so, this epidemic could have been halted fifteen years sooner. Based on these studies, it is unlikely that the FDA would approved Prempro, and hundreds of thousands of breast cancers could have been avoided.

The history of Pfizer's (and Wyeth's) misconduct concerning these drugs has been the subject of intense litigation for seven years. So far, fourteen women have presented to the jury their evidence that Prempro caused their breast cancer, and in eleven cases, the jury agreed. Wyeth or Pfizer has also paid settlements to thirteen other women to avoid a trial or jury verdict. A chart of the jury verdicts and settlements to date is available at <http://www.wdolaw.com>.

But more important, several judges have concluded there is sufficient evidence of Pfizer's (or Wyeth's) misconduct to justify a jury award of punitive damages, including trial judges in Nevada, Arkansas, two in Pennsylvania, and a unanimous three judge panel of the 8<sup>th</sup> Circuit U S Court of Appeals.

Nevertheless, Pfizer and the other drug companies still tell juries that Prempro or the other dangerous combination drugs are "approved as safe and effective" by the Obama FDA. These drug companies should stop selling these drugs for HT use, and they should tell the FDA about the information in this Summary. They should apologize to the world for the hundreds of thousands of unnecessary breast cancers their misconduct caused, and they should compensate all of their victims fairly and promptly.

**C. The "iatrogenic" or drug induced breast cancer epidemic caused by imitation progesterones has slowed, but has not been stopped—thousands of breast cancers that could be prevented will continue to occur until the information in this Summary of the Science is more widely understood.**

Women who are contemplating either starting or continuing MHT using a progestogen to oppose the risk of uterine cancer should be fully informed of the data and review papers in the scientific literature that conclude the use of micronized progesterone does not increase breast cancer risk in the first five years of use, but that Prempro and its equivalents cause breast cancer, especially in newly menopausal women at an alarming rate in only two or three years of use. Tragically, millions of women are still taking Prempro or another cancer causing combination HT regimen because they are not being informed about these facts. The labels on these drugs must be updated to contain the information summarized in this paper, and

physicians need to be educated on the different risks of different progestogens. Thousands of preventable breast cancers are still occurring every year that this information is not widely disseminated.

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- <sup>3</sup> Dr. Corrado Altomare, Wyeth, Senior Medical Director of Clinical Affairs, Deposition transcript - Oct. 6, 2009, P427 L 15-21 (In Re Prempro Products Liability Litigation, 4:03CV1507-WRW).
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- <sup>7</sup> Kerlikowske et al., Declines in Invasive Breast Cancer and Use of Postmenopausal Hormone Therapy in a Screening Mammography Population, *J Natl Cancer Inst.* 2007 Sep 5;99(17):1335-9.
- <sup>8</sup> “Breast cancer risk falls after hormones halted”; The Seattle Times, Feb 4, 2009.
- <sup>9</sup> “Drop in breast cancer rates due to drop in HRT use”; HealthDay, Feb 4, 2009.
- <sup>10</sup> “Halting Hormone Therapy reduces breast cancer risk quickly”; Time Magazine Feb 4, 2009.
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- <sup>14</sup> Ravdin et al., The Decrease in Breast Cancer Incidence in 2003 in the United States, *N England J Med* 356;16:1670-1674, Feb 18, 2007.
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