THE VINDICATION OF ESTROGEN

A DR. LINDSEY BERKSON EBOOK

Stunning 19-year follow-up of the Women's Health Initiative proves, once and for all, that estrogen protects *against* breast cancer.

Summary

Estrogen was once a popular hormone, used as an anti-aging drug and even to treat breast cancer, but after the massive Women's Health Initiative[1] (WHI) study's first negative publications (July 9, 2002), many doctors and women became *estrogen-phobic*. However, a few years of very early re-analysis[2] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [14] of the WHI's data revealed lots of statistical problems that challenged these original conclusions. But that information never made headlines like the initial "bad news" did.

What was the bad news? That estrogen could cause breast cancer.

Now there has been a long time for scientists to reevaluate the data. Almost two decades.

A 19-year reanalysis[15] makes it clear that estrogen is not the enemy; rather, it *protects* breasts from cancer. Unfortunately, most doctors still haven't gotten the good news.

Even though no one knows exactly how breast cancer starts, it does not seem to be due to estrogen, but rather to *cancer stem cells*—a totally different kind of cell that has nothing to do with estrogen. Most older women, who naturally have less estrogen, have higher risks of being diagnosed with breast cancer than younger more estrogenized females. Pregnancy, which is the highest estrogen time of life in any woman, is protective against breast cancer.

Medical folks thought tamoxifen worked because it was an anti-estrogen, but tamoxifen works in various ways, not just by tamping down estrogen. In fact, tamoxifen can often raises estrogen levels. In the HABITs study (which concluded that hormones cause breast cancer), only the women on tamoxifen turned out to have higher risk of recurrences (though this was not easy to read in the depths of the study).

Recent studies have shown that estrogen protects the breast as well as safeguarding the body in many other ways. The appreciation of how estrogen is foundational in protecting health is rapidly growing. A few examples are that estrogen protects bones from fracture[16], blood vessels from hardening[17], brain from dementia[18] [19], shields mitochondria (energy-producing cells) from damage, [20] allows our bodies to benefit from lifestyle changes as it promotes epigenetics[21], makes it easier to keep a smaller waist[22], and maintains heart[23] and kidney[24] [25] [26] health. It is as close to an effective anti-aging tool as we have, maintaining life-promoting telomere length.[27]

Estrogen is not the causative factor in breast cancer, in fact, it protects against breast cancer and dementia while reducing premature death from diverse causes.

My Story

Twenty-six years ago I was diagnosed with breast cancer. This was not found by mammogram but by self-palpation while in the shower. I was the very first woman in the U.S. diagnosed with a pure mucinous cancer, a very rare cancer back then, more common now. Neither my radiologist nor oncologist had every treated a pure mucinous cancer at that time.

I was a DES (diethylstilbestrol) daughter, meaning my mother had been given this drug when pregnant with me. DES was banned in 1971 as the most cancer-causing substance ever invented at that time. DES was the first synthetic estrogen (50 times stronger than bio-available estrogen) and given to pregnant women from 1938 to 1971 as a prenatal vitamin or to stop threatened miscarriages. Many DES daughters turned out to manifest breast cancer in their mid-40's. I was one of the very first ones.

As no one had ever treated breast cancer in a DES daughter before, I kept asking, "How do you know that what you are recommending is right for me?"

They suggested I do standard protocol, like radiation. However, even though my doctors had never treated pure mucinous tumors before, or ever treated a documented DES daughter before, after several weeks of sleuthing (pre-Internet), I found the only two groups (in the Netherlands) with human studies at that time on this type of tumor.

Due to the time changes, I had to call the principal leaders on these investigations in the middle of the night and leave messages about my circumstance. As the fickle finger of fate would have it, one head investigator didn't call me back until a very dramatic moment: I was sitting on the table getting the grid put on my chest for my first radiation treatment.

This doctor/scientist firmly recommended, "If I were you, I would not do radiation. We have learned that radiation causes fibrosis, which makes it impossible to palpate a tumor in the breast if cancer returns. Totally pure mucinous tumors are never picked up by mammograms, only by palpation. If you have radiation, you won't be able to monitor yourself appropriately. That's what we advise all our pure mucinous breast cancer patients to do: not get radiation and do vigilant breast exams."

I got off the table and told the radiologist I wasn't going to do radiation therapy.

I explained to this female radiologist (wife of one of the local cancer docs) what the experienced researcher had told me. I further explained that this scientist was one of the only two research teams in the world (at that time) studying this unique tumor type. They had published a study on 95 patients with this unique tumor[28], and understood protective details for patients with this unique tumor.

The radiologist spat angrily back, "F… him!" (I kid you not.) "If you don't do this radiation, you are certainly going to die!"

That was 26 years ago.

Then my cancer doctors told me that I didn't need chemotherapy. *Hmmm*. Reading the science, it was becoming clearer to me (even way back then) that *stem cells* caused cancer

more than the daughter cells found mostly in primary tumor loads. I decided to do my own chemo. After a lot of investigation, I found a black market chemo from Switzerland (called "Ukraine") that was supposed to eradicate both daughter cancer cells and cancer stem cells, but not harm healthy cells.

So I did 40 rounds of this chemo with a willing local doctor.

Then my cancer doctors recommended tamoxifen.

But I was one-of-a-kind—a lone woman with a pure mucinous tumor and a history of DES—so it seemed they didn't really know if it would help me and this special situation… or not. They were fitting me into the same box that all other breast cancer patients were in.

So I called Craig Jordan, the man who put tamoxifen on the map. Grateful to get him on the phone, I asked: "I have this rare tumor and this rare in-utero exposure to DES. Do you think I'm really a candidate for tamoxifen?"

Dr. Jordan was thoughtful and candid, "I have to be honest with you. No one in your situation has ever asked me that. Let me look into this. I'll get back to you in a week."

To his credit Dr. Jordan indeed called back within a week and humbly explained, "If I were you, I wouldn't take tamoxifen. I think it might make DES daughters worse. Not sure, but I don't have a good feeling about it."

Stunningly enough, I still get yelled at by cancer doctors today telling me I made a mistake not taking it, even though its main scientist suggested otherwise!

After all I read, it made sense to me to take estrogen therapies, even though not one of my colleagues (functional or conventional) agreed with me. I was on my own. I waited five years just to be safe, but at year six Dr. Wright wrote me the first bioidentical script for 2-methoxyestradiol (2 MEO), which I had figured out would reverse the immunosuppressive issues started by DES in the womb. I was the first person in the U.S. to take bioidentical 2 MEO, so Dr. Wright and I had to figure out the dosage.

I also began hormonal therapies of estradiol, estriol, progesterone, and testosterone.

When I saw my breast cancer doc for yearly exams over the past two decades, she would say, "You look better than any of my other patients. But stop taking estrogen. It will kill you."

Thank god, I've been well. At my ripe age, when many are winding down, I'm still winding up. My breast cancer doctor is 20 years younger than I am, but truthfully, as smart and nice as she is, she looks 20 years older as she hasn't taken hormone therapies.

This 19-year reanalysis of the Women's Health Initiative confirms my own research. (For those who want to know, I take 125 mcg /2MEO methoxyestradiol/day, along with .35 mg estradiol/.75 mg estriol BID labially, along with 3 mg testosterone/day mucosally.)

By the way, there are a lot of nuances to taking 2 MEO. I have a webinar on it available at drlindseyberkson.com. It's hard to get. I am trying to write the monograph that the FDA requires to help move this along.

I worked at a hormone/nutritional family practice clinic, the Wiseman Family Practice clinic, in Cedar Park, TX, for six years. I asked Dr. Richard Wiseman, who had been in practice for almost 50 years, what he thought about hormones. He ran several Ironman marathons a year, looked like he stepped out of an Irish Spring commercial, and had been prescribing bioidentical hormones all those years. Dr. Wiseman said, "If you took 100 people who all exercised and ate well, you could still pick out those who were on hormones: they will have shinier skin, more youthful voices, straighter posture, thinner waistlines, look younger, and even appear more confident."

Hormones protect so many organs—from the collagen in our skin to the volume of our hippocampus (where our memories live in the brain).

I am honored to be able to write this article to spread the word that the science shows estrogen is once again okay to prescribe and safe to take.

ESTROGEN VINDICATED

Estrogen has had a bad rap for over 20 years.

Many women, upon hearing the word "estrogen," unconsciously cover their breasts with their arms in worry. Estrogen makes them think of the enemy — breast cancer. Women, physicians, and scientists alike have come to equate estrogen with being a tricky and potentially dangerous player. And many contemporary doctors and oncologists regard estrogen as fuel for breast cancer.

This is understandable when you look at the history of estrogen and the uterus. As women were being prescribed estrogen to achieve staying "feminine forever," in the 1970s the incidence of cancer of the uterus suddenly increased four to eight times more in women taking estrogen therapies versus ladies who were not taking it[29].

It was soon figured out that estrogen replacement was causing the lining of the uterus to "grow out of control"—the hallmark for cancer. This estrogenic potentially-cancerous effect was then entirely controlled by adding synthetic forms of progesterone, called progestins, to estrogen scripts. The progestins successfully blocked overgrowth and warded off the uterine cancer. The spike in uterine cancer in women taking estrogen stopped. (Bioidentical progesterone was also shown to protect the uterus from estrogen[30 31 32].) Thus, the standard of care by many mainstream doctors has been to prescribe a combo therapy of estrogens plus progestins in women that still have a uterus.

It then seemed like an intuitive leap to the idea that progestins would have the same protective effect at the breast. Thus, many women have been prescribed a combination of estrogen and progestins as hormonal therapy, thinking the progestins were protecting both the uterus and the breast.

This turns out not to be the case.

Estrogen's Roller Coaster History

For over 40 years, estrogen therapies were the biggest-selling pharmaceuticals in pharmaceutical history. Women were prescribed estrogen therapy, without any large randomized studies proving that estrogen therapies were helpful or safe (although the PEPI studies[33] were a smaller randomized study run on 847 women that showed that women on estrogen for over three years had better heart health without a rise in blood pressure or issues with insulin).

For decades doctors and patients felt that estrogen kept women "feminine forever."

Up until 2002, estrogen was the recommended standard of care for menopause. Everyone was on board the estrogen train. Prestigious medical journals, respected research institutions, and recognized expert cancer doctors all accepted the idea that estrogen was safe for breasts and that estrogen did NOT increase the risk of breast cancer.

Researchers were concluding that women taking hormone therapy were less likely to develop breast cancer. In 1987, a consensus conference reported in the *British Medical Journal*: "Well-defined epidemiological studies of estrogen therapy do not suggest an overall increase in the risk of breast cancer in postmenopausal women[34]." These results were replicated. This is the hallmark of great science—independent labs demonstrating the same results. A multi-centered report even found that women with the dangerous breast cancer genetic glitch, the BRAC1 gene, had no increased risk of breast cancer when on hormone therapies for an average of 4.3 years[35].

You heard about Angelina Jolie having both her breasts removed because she has the BRAC1 genetic mutation. Women with this genetic mutation are at a greater lifetime risk of breast cancer (as well as many other cancers) than women without this glitch. But a medical oncologist at the Sunny-brook Regional Cancer Center in Toronto studied 472 BRCA1-positive postmenopausal women, half of whom were taking hormones and half not. She concluded that "among postmenopausal women with a BRCA1 mutation, estrogen use, averaging four years, was *not* associated with an increased risk of breast cancer; in fact, in this population, it was associated with a significant *decreased* risk[36]." (I wrote about this protective effect of estrogens in BRCA1 breast cancer patients in *Safe Hormones, Smart Women*.[37])

In a 1993 editorial in the *New England Journal of Medicine*, two endocrinologists from Harvard stated, "On the basis of the available evidence, we recommend that *all* postmenopausal women be considered for hormone replacement therapy and be educated about its risks and benefits[38]."

Study after study found no consistent increased risk of breast cancer in women who took estrogen for five years, ten years, or 15 years[39]. A later Japanese study on 9,000 women replicated this data[40].

Through the 20th century, it was well accepted that estrogens did not cause breast cancer. However, the Women's Health Initiative prematurely stopped of one of the hormone study groups in July 2002.

Then everything changed.

The Women's Health Initiative (WHI)

The NIH started the WHI because Americans are getting older and sicker at a rapid rate, and the NIH wanted to know how to protect aging women while not toppling Medicare.

How old are we getting? The 65 and over population is projected to more than double from 6.4 million in 2016 to 14.6 million in 2040 (a 129% increase). By 2060 there will be over 98.2 million Americans over the age of 65. To try to protect Medicare from being unable to handle this enormous health care load, the Women's Health Initiative [41] [42] was set into motion.

The Women's Health Initiative (WHI) was organized by the U.S. National Institutes of Health in 1992 to study the health of postmenopausal women and was scheduled to be completed in 2007. The WHI was a series of a group of studies looking at aging women every which way. To date, WHI has published over 1,400 articles and funded 289 related research trials looking at various aspects of health, such as diet, bone health and nutrients, heart health, the effect of sitting on hormones and the risk of hormone-driven cancers, and, of course, very large randomized trials looking at hormone therapies.

From 1993 to 1998, the WHI enrolled 161,809 women aged 50-79 years at 40 different clinical centers.

The WHI wanted to create the first very large randomized studies on hormones. Everyone who was part of running the trials assumed the results would prove what years of giving estrogen to millions of women and previous trials had shown (though not in large randomized scientific manner): that estrogens slowed down aging and kept women younger for longer.

At 40 centers nationally, researchers ran two different groups of hormone trials, called "arms"—one with women given only estrogen and the other arm given estrogen and synthetic progesterone. Premarin, a form of estrogen found in horse's urine, was the estrogen used in the study. The other arm gave women Premarin *plus* a synthetic progestin.

July 9, 2002—a fateful day for hormones. Before the studies were supposed to end, at the five-year mark, the regulatory Data and Safety Monitoring Board recommended both arms of the study be stopped. This premature decision was not unanimous; some board members wanted to stop the study and others didn't.

This was based on results from the combo hormone study arm (synthetic progestins + estrogen), which showed, at five years of follow-up, a statistically significant increase in invasive breast cancer and an increase in heart disease adverse events.

At first blush, it looked like women on hormone replacement were at higher risk of getting the very diseases that hormones were supposed to protect against. Many were shocked. It looked like hormones were causing the very issues they were being prescribed to prevent.

Huge numbers of doctors in the U.S. stopped writing scripts for hormones. In Europe, this didn't happen as much; European doctors tend to write scripts for natural hormones or estriol, the anti-cancer estrogen, a lot more often.

Doctors and patients alike started to think of estrogen as the enemy. (If you want an in-depth, easy-to-read, detailed account of this whole unfolding, read *Safe Hormones, Smart Women*.)[43]

Due to the results of the WHI study, estrogen was getting blackballed.

Both arms of the study were finally officially stopped on February 2, 2004.

However, by this time, 2004, re-analysis by the monitoring committee was demonstrating different results than the mostly negative ones from two years earlier:

- Hormone therapies were being linked to increased risk of stroke. But this increase was very small and almost half the women had dropped out of the study, so there were a lot of statistical issues[44] and respected experts were questioning the statistical significance,
- a trend toward dementia,
- no increase or decrease of coronary disease,
- a reduction in bone fractures and
- no increased risk of breast cancer. (This fact has not gotten out to the public or to docs, and was buried on page 18 in one small paragraph of the 2004 re-evaluation.)

In fact, Dr. Leon Speroff, the iconic gynecologic physician who authored the predominant book that most gynecologists and obstetricians are trained with (*Clinical Gynecologic Endocrinology and Infertility*) and long-time professor at the University of Oregon, concluded in 2005 and again in 2008 that the 2004 results did not demonstrate the same nor agree with the first 2002 monitoring board statements.

After looking at every statistical nuance of the WHI, Dr. Speroff said [45] [46]: "Long-term postmenopausal hormone therapy is not precluded by the results reported by the WHI. There continues to be good reason to believe that there are benefits associated with treatment, including improvement of quality of life beyond the relief of hot flushes, maximal protection against osteoporotic fractures, a reduction in colorectal cancers, maintenance of skin turgor and elasticity, and the possibility of primary prevention of CHD and Alzheimer's disease."

Dr. Speroff clearly said that the WHI did not show an increased risk of breast cancer. I summarized the issues of the WHI in *Safe Hormones Smart Women*:

- Women in the second group on horse estrogen had *less* breast cancer. After 7.1 years on horse estrogen itself (without synthetic progestins), they had 18 to 44% less breast cancer depending on the re-analyses you read[47]. Breast cancer (localized to breasts) was reduced by 31% and ductal breast cancer was reduced by 29%[48] [49].
- A 10-year follow-up said the decreased incidence of cancer was persisting up to 10 years, even with an average of 5.9 years only of using estrogen[50]. Now persistent benefit is being noted up to 19 years.
- There was an apparent protective effect of the horse estrogen on breast cancer incidence in all categories for women at lower risk (who didn't have first-degree relatives with breast cancer or fibrocystic breasts).
- Women who had been on synthetic progestins in the past (before this estrogen-only study) were at greater risk. Those on estrogen only before this study did not have increased risk.
- After 7.4 years of estrogen only, younger women (50 to 59 years of age), monitored by sophisticated imaging studies, actually had slower growth of calcified plaque in their arteries, meaning they had a heart-protective effect from the estrogen [51] [52] [53].

In an article titled "Women's Health Initiative is Fundamentally Flawed," the authors (from Loyola University Stritch School of Medicine) said that the WHI findings were *wrong.* They summarized quite a large number of colleagues and experts challenging the WHI conclusions.

Fred Naftolin PhD., a scientist from Yale who was also on the executive committee of the International Menopause Society, was worried that doctors were denying women a chance to take estrogen and as a result were withholding preventative care, especially for their patients' hearts. Heart disease is the number one killer of women, not breast cancer[54].

Other re-analyses by respected well-known statisticians were also showing that women in the estrogen-only arm had 33 to 44% *less* risk of breast cancer.

But these positive reports failed to make headlines[55] [56]. Doctors and patients were not hearing the good news. The revised news. It's been shown by a shocking multi-centered study, headed by Stanford's Prevention Research Center, Department of Medicine, that one out of three randomized trials, when re-analyzed[57], come out different, often making the first conclusions wrong and thus, recommendations to patients, wrong.

But it's the first scary (even if wrong) "loud" conclusions that make headlines. These are especially difficult to get out of the medical and cultural consciousness.

Especially if litigation is involved.

Right after the first scary (and repeatedly found wrong) warnings about hormone therapies came out, Wyeth was sued by 6,000 women and had to pay out billions of dollars. Between the fear of the negative comments on hormones and the litigious atmosphere in the U.S., hormone therapy drastically dropped.

Money and fear of being sued had a lot to do with keeping the new and improved analyses from reaching women far and wide.

Avoiding estrogen therapies for any kind of high-risk women became the standard of care. The sad reality is that up to the present time, many doctors, gynecologists, and patients continue to be frightened or highly reluctant to prescribe or use estrogen and estrogen therapies. Women at high risk for breast and other hormonally-driven cancers are told that they are not candidates for estrogen therapy.

Summary of Criticisms of the WHI[58]

- The design was flawed
- It only used one protocol of hormones (not individualized or diverse options)
- The age of the participants was older, many years away from hormone exposure
- The majority of women were obese (which is a significant risk factor for breast cancer)
- Extreme number of dropouts of participants
- The recommendations could not be validly generalized to all women
- Many of the conclusions were ultimately found to be inaccurate.

Decline in Breast Cancer

One of the clinchers in the media and even in scientific studies that the WHI's conclusions were sacrosanct, was the recent decline in breast cancer incidence. Many said, "See, as women went off hormones, they got less breast cancer. This proves the HRT-breast cancer link."

I realized early on, about 2004 and 2005, that women were going to be missing out on hormones. Scouring the literature. I saw the reanalyzes that were not making headline news. I became passionate about getting the accurate science "out" so women wouldn't miss out on life-saving and breast-saving hormones. That's why I wrote *Safe Hormones, Smart Women*. All the information inside that book has been vindicated.

But as I took a deep dive into the incidence data, it became clear that breast cancer rates started to slow down *before* the WHI results came out and use of HRT went down.

The conclusion that going off hormones secondary to the WHI started the decline in breast cancer incidence is wrong. But this is not known by many, doctors, patients, or pharmacists.

Dr. Christopher L. Li, from the Division of Public Health Science at the Fred Hutchinson Cancer Research Center[59] (one of the cancer center names on the WHI 19-year reanalysis), looked at data from 13 cancer registries from 1995 to 2004 to get a handle on what was causing lowering of incidence of breast cancer cases.

They found that breast cancer rates started to go down around 1998, *well before 2002* when the WHI brouhaha hit the media. The decline, they stated, was mostly likely due to more and improved breast cancer screening. The WHI didn't start the decline, though it may have contributed to it.

WHI Details Up to 19 Years

From 1993 to 1998, more than 27,000 postmenopausal women, aged 50 to 79 years, with no prior breast cancer, enrolled in one of two randomized, placebo-controlled WHI trials implemented at 40 U.S. centers, with follow-up through September 2016.

- Women with an intact uterus received CEE (0.625 mg/day) plus MPA (2.5 mg/day) or placebo (n = 8102) for a median of 5.6 years.
- Women with prior hysterectomy received CEE alone (n = 5310) or placebo (n = 5429) for a median of 7.2 years.
- After about 19 years of follow-up, CEE+MPA resulted in a *significant 29% increased* risk of breast cancer
- Whereas CEE alone resulted in a *significant 23% reduction* in breast cancer incidence.
- In terms of deaths from breast cancer:
- There was a *significant 44% reduction* with Premarin alone.
- There was a 4*5% increase* (borderline significance) with CEE+MPA (Premarin plus the synthetic progestin MPA)

The Reanalysis

On December 13, 2019, at the San Antonio Breast Cancer Symposium (SABCS), an abstract was presented that summarized the 19-year follow-up of the Women Health Initiative. (You can read the entire abstract in the Appendix.) Medscape[60] published an article entitled "Remarkable New Data on Menopausal Hormone Therapy," summarizing the new research,

headed by lead investigator Dr. Rowan T. Chlebowski, MD, PhD, from Harbor-UCLA Medical Center, Torrance, California, and funded by the National Institutes of Health (NIH).

Chlebowski has been a consultant for AstraZeneca, Novartis, Amgen, Genentech, Pfizer, Puma, Immunomedics, and has received NIH grant funding. So Dr. Chlebowski has been studying breast cancer and hormones for a long time from many different perspectives.

The data are "remarkable," said Dr. Chlebowski. The reanalysis study concluded:

- Estrogens are breast protective a*gainst* breast cancer, while
- Synthetic progestins *promote* breast cancer, slightly but significantly. (Other animal and human studies have implicated synthetic progesterone in increasing the risk of heart disease; estrogens do not share the same increased risk[61]).

Dr. Chlebowski was asked if this should change how doctors and patients look at estrogen and how it is prescribed to menopausal women. Dr. Chlebowski replied, "Yes, I would hope so! Women considering estrogen alone should know it's safe and there may be a *breast cancer benefit* associated with its use."

Dr. Chlebowski noted that "none of the approved agents for breast cancer risk reduction . . . have been able to demonstrate a reduction in deaths from breast cancer . . . so this is a very unique finding. Women should be reassured if they had short-term estrogen exposure they are not at increased risk. In fact, the data suggest there is decreased risk."

Who is saying this besides Dr. Chlebowski?

The following esteemed institutions[62] agreed with these findings and put their names on them!

- The Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA;
- Fred Hutchinson Cancer Research Center, Seattle, WA;
- Brigham and Women's Hospital, Boston, MA;
- Stanford Prevention Research Center, Stanford, CA;
- University of Washington, Seattle, WA;
- Pitt Public Health, Pittsburgh, PA;
- Karmanos Cancer Institute, Detroit, MI;
- Stony Brook University, Stony Brook, NY;
- University of Tennessee Health Science Center, Memphis, TN;
- Albert Einstein Cancer Center, Bronx, NY;

- The Ohio State University, Columbus, OH, and
- The UF Health Internal Medicine, Gainesville, FL

Their consensus clearly states: after 19 years of the WHI being looked at from 360 degrees, there are two different types of menopausal hormone therapy — estrogen alone and estrogen plus progestin—both of which have "opposite" effects on breast cancer incidence.

Of note, these effects persist long after stopping treatment (up to ten and possibly 19 years).

The data clearly indicate that estrogen—in this case horse estrogen (conjugated equine estrogens, CEE) alone (without synthetic progestins)—significantly *decreases* breast cancer incidence and deaths from breast cancer.

In contrast, CEE plus a synthetic progestin (MPA, medroxyprogesterone acetate), significantly *increases* the risk of developing the disease. In both instances, these effects linger for decades after discontinuation.

The Physiology of Estrogen

When you understand how estrogen works in the body, you can appreciate its role in women's health.

- *Older age, less estrogen, more breast cancer risk:* As women get older and are in a less estrogenic state, they are more at risk of getting breast cancer even if they never took estrogen therapies[63]. If estrogen were carcinogenic and the main cause of breast cancer, we would expect breast cancer rates to decline with menopause, but the opposite occurs.
- *Pregnancy is protective*. Pregnancy is the highest estrogen exposure in any woman's life, with estrogen levels up to ten times more than at any other time. It is true that immediately and up to a year after pregnancy, a woman's breast cancer risk slightly rises, only to lower significantly across her lifetime. But it turns out that pregnancy—with all its huge hormonal exposure—protects *against* breast cancer in the long haul. In fact, women who are diagnosed with breast cancer during pregnancy have a similar prognosis as non-pregnant women at the same stage of breast cancer[64]. Nuns, who never get pregnant, have a higher rate of breast cancer compared to those who aren't nuns[65].
- *Not ever having a baby increases a woman's risk* of getting breast cancer by 30%[66]. The younger you are at your first pregnancy, the more lifelong protection you'll have against breast cancer. Women who give birth before the age of 20[67] have the highest protection. When I worked as a hormone scholar at an estrogen think tank at Tulane University (*Center for Bioenvironmental Research),* it was often stated at

conferences that there was no documented case of a woman getting breast cancer if she got pregnant before the age of 18. Yet the older you are when you give birth, the opposite is true. Women who have their first child after the age of 35, and have missed out on the surge of protective high levels of progesterone and estrogen (estriol) during pregnancy, have a 40% increased risk of breast cancer compared to women who have kids before the age of 20[68].

- *Pregnancy and BRCA genes*: At the annual meeting of the American Society of Clinical Oncology in June 2019, an international team of investigators reported a retrospective, case-control study of 1,252 women who had been diagnosed with breast cancer, all of whom had BRCA gene mutations. Of this group, 16% (195) eventually became pregnant and were followed over the next decade. The women who became pregnant had a longer disease-free survival than women who did not become pregnant, although both groups were matched for age, tumor size, nodal status, hormone receptor status, type of surgery, and type of endocrine therapy. The two groups did not differ in overall survival either. Interestingly, but not surprisingly, hormone receptor status of the tumor did not affect disease-free survival or overall survival among the pregnant patients. This study provides further evidence that pregnancy, which elevates levels of estrogen tenfold, does not fuel its recurrence[69] [70].

- *Estrogen as an anti-cancer agent*: Estrogen was used for years to treat metastatic breast cancer. If estrogens were carcinogenic, this would not have worked. The use of high-dose estrogen, which began in the 1940s, was the first successful breast cancer therapy. Using oral estrogens to treat breast cancer continued all the way into the late 1970s, until tamoxifen (an anti-estrogen) was introduced. When tamoxifen became the standard of care in 1974, estrogen therapy pretty much stopped.

- *Breast Cancer while on HRT:* Women diagnosed with breast cancer while on hormonal or estrogen therapies have consistently been found to have better prognosis than women diagnosed without being on hormonal therapies[71].

- *Estrogen is not initiating breast cancer:* Many doctors and women think estrogen receptor positive (ER+) breast cancer cells (having estrogen receptors on the tumors) means estrogen is feeding the cancer. But a close look at the science shows this is not most often the case, although this is not widely understood even by many cancer doctors. Estrogen receptors are found on *all* normal breast cells. Estrogen receptors on tumor cells signifies that the tumor is growing so slowly that the breast cell still has some normal cellular characteristics. It still has some characteristics of normal cells, rather than it is growth promoted by estrogen. Scientific biological studies are revealing cells that initiate tumor growth and recurrence are cancer "stem" cells[72] [73] [74] [75], which do not have estrogen receptors nor proliferate in response to estrogen. The cells of early breast cancer and ones that multiply within a breast cancer tumor are generally estrogen and

progesterone receptor negative. This is not widely known by most doctors, even cancer doctors.

Estrogens don't fuel breast cancer, stem cells do.

There appears to be a consensus that estrogen is a cause of breast cancer. But when you take a scientific analysis of existing data, including findings from the Women's Health Initiative, you see that epidemiological strength and true scientific support are not met in the case of estrogen causing breast cancer, raising serious questions about the validity of this widespread assumption[76].

The reality is that the exact mechanisms underlying how breast cancer starts are still not known[77], but evidence points to *cancer stem cells* rather than estrogen receptors on breast cells as being the responsible agent.

The human breast is made up of a number of cells. Basic breast cells are called epithelial cells, which are often guarded by myoepithelial[78] cells. Breast cells live, function, and die, meaning they have a finite life span[79]. Many of these healthy cells express estrogen receptors. The breast also contains a lot of fat cells that potentially contribute to milk production when and if the woman is breastfeeding, as well as giving shape and form to the human breast.

It had long been thought that most breast cancers arise from ductal cells, made of either epithelial or myoepithelial cells, and that this action was fueled by estrogen in *estrogen positive breast cancer*. Breast cancer tumor cells labeled as "estrogen positive" mean they have receptors that can receive signals from the hormone estrogen. The thought has been that estrogen signals fuel these cells to turn cancerous and to grow and become life threatening.

However, the cells that are estrogen positive are turning out to not necessarily be the root cause of cancers. In a report from the National Cancer Institute's Division of Cancer Etiology, published in 1991, analysis of existing data concluded that estrogens are neither direct *mitogens* nor direct *carcinogens* for mammary cells[80]. These cells are distinct from cancer stem cells, which instigate cancer and are responsible for the recurrence of cancer.

Cancer stem cells make up about 5% of breast cells[81] and are *not* fueled by estrogen. Cancer stem cells possess characteristics of both stem cells (which give rise to healthy breast cells) and cancer cells, in that they have the properties of self-renewal, asymmetric cell division, resistance to death (apoptosis – cancer cell immortality is a huge part of the nastiness of cancer), independent growth, tumorigenicity, and metastatic potential. These cancer stem cells are now thought to initiate cancer as well as drive recurrences of cancer [82] [83] [84].

Stem cancer cells are so regarded as cancer causative; they are also referred to as *tumor-initiating cells*[85] [86] [87]. Tumor recurrence is the "leading" cause of breast cancer-related death. These recurrences arise from the residual cancer stem cells that survived initial therapeutic intervention. So breast cancer stem cells are at the "root cause" of recurrence[88].

When I consult my breast cancer patients to help make their "remission" their "mission" they are taught many tools to tamp down cancer stem cell death such as consuming foods high in anthocyanin pigments which help eradicate cancer stem cells[8990].

Triple-negative breast cancers are more aggressive due to lacking receptors (because they are furthest away from normalcy of typical breast cancer cells) and they maintain more breast cancer stem cell activity[91].

Cancer stem cells have been identified in the blood, brain, bone marrow, and the breast[92] [93] [94] [95]. They can literally hide from treatment. Europe has known this for many years; in some European cancer centers they test bone marrow for cancer stem cells when someone has a diagnosis of cancer. Just taking out a tumor in a breast doesn't mean there aren't cancer stem cells lurking elsewhere in the body.

Cancer stem cells can be enabled and stimulated by various elements such as pro-inflammatory molecules[96], dysfunctional immune cells, chronic inflammation[97], or various protein structures (made up of anillin[98]) that in essence builds bridges to allow cancer stem cells to travel far and wide in the body, causing havoc wherever they go.

Avrum Bluming, MD

Avrum Bluming, MD[99] is the visionary cancer doctor who singlehandedly changed the way surgical standard of care was performed for breast cancer patients. Dr. Bluming helped stop resistance toward lumpectomy and now he is trying to do so with estrogen therapies for breast cancer patients, as laid out in his book *Estrogen Matters*.

Dr. Bluming has been in practice in Southern California for almost 50 years. Early in his practice, he started to sleuth out data that more conservative forms of surgery, such as lumpectomy and radiation without mastectomy[100], or mastectomy with less tissue removal and chemo were as protective and successful as the old disfiguring surgeries, while keeping efficacy and safety. He gathered together surgeons and cancer doctors and put on symposiums to demonstrate the data.

Dr. Bluming continues to be a visionary. He is the only oncologist who has performed a 14-year ongoing study on breast cancer patients, giving them estrogen therapy (Premarin). He first did a pilot study. Then, after much elbow grease to get permission to do a study on breast cancer patients, he gave Premarin to 248 women with breast cancer, beginning in 1992. Dr. Bluming had 100% follow-up. Every year he published a study update. In 1997 he presented the five-year follow-up. No women given estrogen were having any recurrences compared to similar (matched) breast cancer patients not on estrogen therapies[101].

Dr. Bluming put together a review that highlights the history of research on HRT[102], including a timeline of studies that have or have not found a link between HRT and breast cancer.

Drs. Bluming and Tavris, his co-author on *Estrogen Matters*, write: "Breast cancer generates more anxiety than even heart disease, even though the number of US women who died of heart disease in 2010 is over seven-and-a-half times the number who fell victim to breast cancer[103]."

A review of the statistics show that almost 90% of women with breast cancer at any stage will still be alive at five years after diagnosis. By 14 years, when Dr. Bluming's breast cancer estrogen therapy study ended, all of the breast cancer patients on estrogen therapy still did not have an increased incidence of recurrence of breast cancer compared to matched breast cancer patients not on HRT.

Studies Saying Estrogen is Bad for Breasts

After a half-century, hormone therapy's influence on breast cancer still remains controversial, even though human studies, like Dr. Bluming's, showed estrogen protects from recurrence of breast cancer and death. Part of the controversy was due to a few studies that said estrogen did in fact cause breast cancer. Besides the WHI, these were the HABITS study[104] [105], The Million Women Study[106], and a more recent study published in the *Lancet* in 2019.

The Women's Health Initiative (WHI): From 2002 to 2008, reports from the WHI claimed that hormone replacement therapy (HRT) significantly increased the risks of breast cancer development, cardiac events, Alzheimer's disease, and stroke. These claims alarmed the public and health professionals alike, causing an almost immediate sharp decline in the numbers of women receiving HRT. However, the actual data in the published WHI articles revealed that the findings reported in press releases and interviews of the principal investigators were often distorted, oversimplified, or wrong.

Re-analyses that were begun within several years had opposite findings, and a 19-year follow-up WHI analysis found that estrogen protects against breast cancer while on it and even 10 years after going off it, while progestins do the opposite. Progestins, on the other hand, increase the risk of breast cancer while on them, and for up to a decade after going off them.

The group of women in the WHI study who did experience a higher risk of breast cancer were on the combination therapy: estrogen plus a synthetic progestin. The finger must be pointed at the synthetic progestins rather than at the equine estrogens. Remember that birth control pills are also made up of synthetic progestins and they also have been linked in some studies[107] to increased risk of breast cancer.

Depending on the study, *bioidentical progesterone therapy* has been found to have no stimulating effect on breast cancer or no effect at all. Large human studies have shown that natural progesterone does not increase the risk of breast cancer like the synthetic forms

do[108] [109]. In some studies there is a protective effect. Progesterone has many beneficial actions on the body, nervous system, brain, and even breast tissue.

Ultimately, the WHI showed that estrogens do protect the breast against breast cancer.

HABITS is an acronym for Hormone Replacement Therapy After Breast Cancer—Is It Safe?[110]. This is a widely referred-to study saying that estrogens are dangerous for breasts. Yet a number of experts felt that the conclusions from this study were not warranted. Dr. Rowan Chlebowski, the lead investigator on the 19-year re-analysis of the WHI, said this isn't the last word on hormones, breasts, and women[111].

The HABITS study, run in Sweden, proposed to randomize 1.300 breast cancer survivors on HRT or not and follow them for five years. The study, like the WHI, was prematurely stopped in 2003 as more women on HRT developed a recurrence of breast cancer. But these groups, in closer analysis, did not differ in risk of metastatic disease or risk of death. Furthermore, a follow-up analysis in 2008[112] revealed that recurrence of breast cancer in women on HRT only occurred in those taking tamoxifen—an estrogen blocker! Think about that, as this "screams" out loud something different than the warnings published about estrogen.

In 2019 a meta-analysis of 58 observational studies was published in the *Lancet*, in which estrogen plus progestin and also estrogen alone were both associated with a significantly increased risk of breast cancer. Also, in the Million Women Study, both estrogen plus progestin as well as estrogen alone were associated with a significantly increased risk of dying from breast cancer.

Dr. Avrum Bluming has written that these studies did not reach the appropriate scientific conclusions based on the internal statistics or citations[113] [114] and thus millions of women and doctors have been confused about the safety of hormonal therapies.

Diving into the Statistics

Samuel Shapiro MD and colleagues from the Department of Epidemiology, University of Cape Town, South Africa, took a deep statistical dive[115] into the Collaborative Reanalysis, the Women's Health Initiative, and the Million Women Study, and concluded that the findings in these studies did *not* adequately satisfy the criteria of time, order, bias, confounding, statistical stability, strength of association, dose/duration-response, internal consistency, external consistency, or biological plausibility. Their conclusions were that HRT may or may not increase the risk of breast cancer, but the statistics on these three studies did not establish that it does.

Valerie Beral, the Head of the Cancer Epidemiology Unit at Oxford and the senior author of the paper, together with her widely respected colleagues, published the Million Women Study. This sounds very authoritative. But the Million Women Study consisted only of two

questionnaires separated by about three years and sent to over a million women. In spite of the grandiose title, only 44% of the sample responded to both surveys.

The summary below of the negative critiques of that paper is taken from several critical analyses [116] [117] [118]:

- The second questionnaire was mailed to only two-thirds of the participants, and only 65% responded (65% of 67% is 44%).
- The total incidence of breast cancer in this study was: 15,759/1,129,025 or 1.4%.
- Of these, 7,107 or 45% developed in *current* hormone users and 8,652 or 55% developed in everybody else.
- The investigators estimated that for every 1,000 women taking combination estrogen/progestin for five years, there would be an extra six cases of diagnosed breast cancer, and for every 1,000 women taking estrogen alone for five years, there would be an extra 1.5 cases.
- *The authors never explain why current use is harmful and past use is not.* Of that 1.4%, the increased risk of breast cancer was identified only in current hormone users but not in past users, even if past use had exceeded 15 years. The authors never offer a biologic rationale. This criticism has been leveled as well against The Collaborative Reanalysis[119], The Nurses Health Study,[120] and the WHI[121].
- The average time from beginning therapy to diagnosis of breast cancer was brief (1.2 years), suggesting to clinicians that, in many cases, cancer had been present before initiating treatment, and the women who filled out the second questionnaire may have been aware of a problem in the breast prompting their participation.
- The study appears to have been selecting this population with, not surprisingly, a high incidence of breast cancer.
- Just over 50% of invited women eventually had a mammogram, suggesting there could have been self-selection bias in the study population. Again, the women who were already worried there was a problem were the ones predisposed to get a mammogram and to follow up on the questionnaire.
- The study failed to take into account that a sizeable number of women switched treatments during the follow-up period – some ceased therapy (22%), others resumed their HRT (19%), and 11% initiated HRT during the study period.

In a paper published eight years after the original Million Women Study report, the same investigators reported that the admittedly small increased risk of breast cancer seen among women taking estrogen was found only among those who started it within five years of reaching menopause. For those starting it more than five years after a final period, the incidence of breast cancer was the same as that found among never users[122].

Dr. Avrum Bluming asks, how is this biologically plausible[123]? The authors' reliance on questionably generated numbers to the exclusion of biologic plausibility raises serious questions about the reliability of the conclusions they present.

Nick Panay, Chairman of the British Menopause Society, Marlow, UK, in 2012 wrote[124] the following about the Million Women Study: "I believe the use of statistics in this study is intimidating to most readers, and possibly to editors as well. I can't help but feel that these authors decide what conclusions they want to publish, and use their data to construct the desired conclusion."

Having been reading the hormone peer review literature for decades, as well as writing and teaching on the science behind hormone therapies, I completely agree!

In an editorial[125], Joanne Katsopoulos of the Women's College Research Institute in Toronto, Canada, said: "The complexity of the study design makes it difficult to appraise the results and most of us will take the results on face value."

Dr. Avrum Bluming responds to Katsopoulos this way[126]: "Read that statement again." When researchers dazzle readers with an avalanche of findings that require other professionals to "take the results on face value," something is very wrong. It is the researchers' job to make their data available—and readable—so that the data can be assessed independently. And yet Katsopoulos, while admitting it was "difficult to appraise the results," apparently had no qualms titling her editorial "definitive evidence for breast cancer." Definitive?

It's inconclusive conclusions written with authority—based on too little statistics that fly in the face of the statistics that support estrogen—that have made physicians and patients alike terrified of estrogen, a foundational hormone that could help our aging population age much slower.

Dr. Avrum Bluming continued[127]: "This huge (and complicated) endeavor presents an unbalanced picture of risks and benefits (no benefits are mentioned), and seems to value numerical results above context, ignoring data that does not fit with the easy and misleading conclusion that MHT (or HRT) is a direct cause of breast cancer.

"The authors fail to say that even if their finding of a small increased risk is valid, breast cancer is currently curable in approximately 90% of newly diagnosed patients. Additionally, they fail to provide a balanced discussion of HRT's benefits.

"We (Avrum and Tavris) regret that *Lancet* is facilitating a wide dissemination of this unbalanced and inaccurate reporting. This *Lancet* paper does not provide meaningful guidance to clinicians, and it sows confusion and fear among patients.

"The estimated incidence of breast cancer was 6.3% for never users of HRT versus 8.3% for five years of use of the continuous combination MHT—an absolute increase of 2%, or one extra breast cancer for every 50 users." (For estrogen alone, it was one in every 200 users).

The statistics do not back up the scary headlines.

"These reports alarm women, frightens them and many of their physicians away from the use of HRT, which will: (*bullets put in by Berkson for easier viewing*)

- decrease the risk of cardiovascular disease (which kills seven times as many women as breast cancer),
- decrease the risk of osteoporotic hip fracture, which is associated with almost as many deaths annually as breast cancer,
- decrease the risk of Alzheimer's Disease, for which there is currently no available treatment,
- and would improve their quality of life."

The Black Box Warning

Most of the findings linking HRT and breast cancer are weak or statistically insignificant, despite which the FDA added a black box warning to the label of Prempro (Wyeth's commercial version of HRT and the combination therapy used in one of the arms of the WHI). A caution remains on all commercial preparations of estrogen: "If you have ever had breast cancer, do not take this medication." As you can see, this doesn't correlate with the human data. However, so many lawsuits were filed and won right after this FDA black label was added that many doctors today neither understand nor do they prescribe hormones. Many are understandably fearful of getting sued.

Many oncologist, gynecologists, and researchers have been frustrated with the way the media published big scary headlines and the FDA added the black box warning. The scary statistics on HRT continue to make front-page headlines[128]. The uncovering that estrogen by itself carried no increased risk of incidence of breast cancer was placed in republished versions of the WHI in a tiny paragraph on page 18.

The father of gynecology, Dr. Leon Speroff, co-authored C*linical Gynecologic Endocrinology and Infertility*, the book that trains doctors who care for women. Dr. Speroff was aware of the bad press estrogen had been getting, but he was also aware of its benefits. Dr. Speroff published a flurry of professional articles criticizing hormone replacement being withheld from women, and encouraged doctors to keep testing, prescribing, and monitoring. Dr. Speroff reminded us that doctors had been using estrogen therapy for many decades and getting stellar results. Two randomized trials with dubious statistics should not fly in the face of years of clinical success! But fear sells. When re-analyses data emerged vindicating estrogen, it wasn't headline news.

Right before the Women's Health Initiative statistical fiasco, in 2000, Henk Verheul, a medical oncologist and now scientific co-director of the Cancer Center of Amsterdam, and

his research group wrote[129] that none of the current treatments for breast cancer—surgery, radiation, chemotherapy—were negatively affected by estrogens, even estrogens that were prescribed at considerably higher dosages than typical estrogen replacement levels. These scientists concluded, "The available studies fail to demonstrate that once breast cancer has been diagnosed, estrogen worsens prognosis, accelerates the course of the disease, reduces survival or interferes with management of breast cancer. It may therefore be concluded that the prevalent opinion that estrogens and estrogen treatment are deleterious for breast cancer patients needs to be revisited[130]."

Of the 20 studies between 1980 and 2008 that showed estrogen was not only safe for breast cancer patients but was also protective, only the HABITS study found an increased risk of recurrence in breast cancer patients on HRT. As previously stated, this risk only occurred if the women were on tamoxifen, which "blocked" the action of estrogen[131] [132].

Tamoxifen

A major argument that estrogen causes or promotes breast cancer is that tamoxifen helps to reduce or retard the growth of ER positive breast cancer by competitively blocking the binding of estrogen to the estrogen receptor on breast cancer cells[133]. Several lines of research, according to correspondence with Dr. Avrum Bluming, a California oncologist and co-author of *Estrogen Matters*, dispute this belief.

- When tamoxifen is given to premenopausal women, their natural estrogen levels increase up to five-fold[134].
- This rise in estrogen should block any competitive binding of tamoxifen, yet it doesn't. And tamoxifen's effect against breast cancer works as well in these premenopausal women as in those who are postmenopausal[135] [136] [137].
- Approximately 40% of ER+ patients fail to respond to tamoxifen[138].
- Studies have shown that tamoxifen inhibits the stimulatory effects of growth factors involved in breast cancer even in the absence of estrogen[139] [140] [141] [142] [143], pointing a finger at initiators of breast cancer other than estrogen.
- In addition, after treatment with tamoxifen, some breast cancer cells actually acquire the ability to proliferate, and low doses of estrogen have been shown capable of killing them[144] [145] [146] [147] [148].
- Finally, tamoxifen has also been shown to have a therapeutic effect on ER *negative* breast cancer cells, both in laboratory studies and in human patients[149], pointing to other pleotropic effects of tamoxifen.

In summary, tamoxifen works in a variety of ways that are exclusive of its action on estrogen receptors. Because the precise mechanisms responsible for its therapeutic effect

remain unknown, it seems inadequate and simplistic to claim that the success of tamoxifen supports the view that estrogen causes breast cancer or stimulates cellular proliferation in breast cancer[150] [151].

In 1980, Torbin Palshof from Copenhagen, Denmark, published the results of a study comparing adjuvant estrogen with adjuvant tamoxifen in the management of patients with treated breast cancer in remission[152]. From 1975 to 1978, 387 consecutive patients who were admitted to three breast cancer clinics in Copenhagen entered the study. Subjects were women younger than 70 years of age, with T1 to T4, N0 to N3, M0 breast cancers. There could be no history of previous or concomitant malignancy. Treatment involved simple mastectomy without routine axillary dissection, and postoperative irradiation. Two weeks after surgery, patients were randomized according to menopausal status to double-blind endocrine therapy for two years.

A total of 332 patients were assessable with respect to treatment. Among these, 254 were also assessable with respect to ER assay results. There was an equal distribution of patients according to stage of disease. After a median duration of observation of three years, 91 recurrences were observed.

The investigators concluded that despite the limited number of patients and time of observation, a marked effect of tamoxifen on recurrence rate was observed in postmenopausal patients; *an even higher reduction in the rate of recurrence was achieved with adjuvant estrogen*. ER assay positivity did *not* correlate adversely with prognosis among patients treated with estrogen. In fact, there were *no* recurrences among the ER-positive patients who received adjuvant estrogen therapy.

DES vs. Tamoxifen

Dr. JoAnn Manson, one of the lead researchers on the WHI, has come around to looking at estrogen in a new way. Dr. Manson said the breast protective effects seen in the estrogen-only arm in the WHI was probably due to estrogen's alter ego ability to act like tamoxifen.

But tamoxifen is an anti-estrogen. How can an estrogen act like an anti-estrogen? Oy veh. Perhaps it's medical "double speak" when the evidence does not align with the narrative.

To answer this question, we have to go back to DES (diethylstilbestrol), the most powerful synthetic and pharmaceutical estrogen ever invented, fifty times more powerful than our own naturally-made estrogen. Sir Charles Dodds, the same doctor and scientist who invented plastics (which are also estrogenic), created it.

DES was given to many millions of pregnant women for 36 years.

It was outlawed in 1971 when it was finally proven to be the most powerful endocrine-disrupting and cancer-causing drug even invented. It is now labeled a class-1 carcinogen, never to be used during pregnancy. But it was the preferred method of treating metastatic

breast cancer in the 1960s and 1970s. Metastatic cancer is when cancer cells have spread from the initial primary tumor out into other parts of the body. This is diagnosed as a life-threatening stage 4 cancer.

How can that be? The original studies showed it shrank tumors in many women with breast cancer. DES was so effective that it was described as making tumors dissolve in 30% of women treated with it.

Craig Jordan, Ph.D., said, "Large tumors would just melt away, but you needed sledgehammer doses to do it—50 times more than a woman would normally have in her body." Thus, DES was used until tamoxifen was found to work as well—not better, but with less adverse effects; DES was being linked to other nasty things. When the Mayo Clinic's 1981 head-to-head comparison of tamoxifen with DES showed similar response rates—and far fewer adverse responses in tamoxifen users—breast oncologists switched en masse to the newer agent. By that time, DES had also gained a reputation for producing a rare vaginal tumor cancer in the daughters of women who used DES to sustain their pregnancy.

The longer term follow-up studies were really mind-bending. The Mayo Clinic ran a follow-up analysis of one of its older studies comparing DES treatment to tamoxifen treatment on breast cancer patients. This follow-up study showed that some breast cancer patients treated with DES actually lived longer compared to those treated with tamoxifen. How? The Mayo Clinic researchers were able to show that estrogens, given at the right time (and the timing is a big part of this deal) can deliver signals to breast cancer cells to instruct them to "die." This is exactly what Dr. Jordan had been talking about.

Sometimes robust estrogens, like DES, can make breast cancer cells that were not responsive to drugs like tamoxifen start to respond. A Norwegian study published in 2001 showed that half of 32 breast cancer patients who had become resistant to tamoxifen or other endocrine therapies, once treated with high-dose DES then became responsive to the endocrine therapies. This meant that a woman who had become non-responsive to tamoxifen or an anti-aromatase inhibitor could be rebooted to once again respond to them by the use of a powerful estrogen.

The natural next question was: could a woman's own home-grown estrogen be protective like DES, too? The answer was yes.

Matthew Ellis, M.D., Ph.D., director of the breast cancer program at Washington University in St. Louis, answered this question and published his results. Dr. Ellis showed that giving both high-dose natural estrogen (30 mg/day) or low-dose estrogen (6 mg/day) to women with metastatic breast cancer, who had failed aromatase inhibitors, helped effectively kill breast cancer cells. These women were given oral estradiol, identical to the active form of estrogen inside a women's body. The estradiol shrank tumors in 30% of the women. The adverse side effects from the estrogen therapy, especially the lower dose, were less toxic than from chemo, and certainly less costly[153 154 155 156 157 158 159].

Interest in DES rekindled following the 1999 long-term follow-up of the original Mayo Clinic study that showed patients treated with DES had increased survival compared to tamoxifen-treated patients[160]. Then, in 2001, a Norwegian study of 32 breast cancer patients who had become resistant to endocrine therapy showed that almost half of the participants responded to high-dose DES[161].

Studies about Breast Cancer Risk and Hormone Therapy

In 1990[162], Darcey Spicer from the Kenneth Norris Jr. Comprehensive Cancer Center, USC Medical School, Los Angeles, said: "While there is a general belief that hormone replacement therapy will increase the risk of recurrence of breast cancer, there are, in fact, no data to support this notion."

A very thorough review of the research up to 1994 from cancer doctors at Rush-Presbyterian-St. Luke's Medical Center in Chicago, and colleagues in the Breast Cancer Committees of the Eastern Cooperative Oncology group, wrote: "A major concern over prescribing ERT for women with a history of breast cancer is that dormant tumor cells might be activated. There is surprisingly little clinical information to substantiate such concern.[163]"

Up to 20 scientific human studies[164] published in peer review, most of them taking place at prestigious cancer institutes, have shown that breast cancer patients given prescriptive estrogen therapy (most of the time as Premarin), in studies lasting an average of two to five years, had statistically significant "less" risk of breast cancer recurrence[165 166 167 168 169 170 171]. Quite a number of these studies also demonstrated less" risk of death from breast cancers[172 173 174 175 176 177 178 179180]. And in a number of these studies breast cancer patients had less risk of dying prematurely[181] from a wide range of non-cancer issues, called "all-cause mortality." Yet many doctors are still reluctant to recommend hormonal therapies, especially to high-risk women—those with breast cancer. (See the Appendix for details on the human trials.)

Pelin Batur MD, an internist at the Cleveland Clinic, published a review of 15 studies totaling 1,416 breast cancer survivors using hormonal therapies (most started two to four years post diagnosis) compared to 1,998 not using HRT. The women were followed for three years. Women on hormones had a 10% reduced risk of recurrence of breast cancer. There was a slightly significant decreased risk of mortality from cancer and all-causes at a seven-year follow-up[182]. Protection of estrogen continues after stopping therapies, as was stated in the re-analysis 19-year follow-up study headed by Dr. Chlebowski.

The Stockholm study was similar in size to the HABITS study. This was a prospective and randomized trial, with 188 women randomized to HRT and 190 not given hormones. There was no difference in the rate of new breast cancers, which held up over a 10-year follow-up[183 184].

A variety of scientists like Dr. LaCroix started to refer to the WHI as the first randomized trial to give evidence that if you give healthy women estrogen therapy within 10 years from the initiation of their menopause, or to post-menopausal women without a uterus, this reduced the risk of getting breast cancer.

Two other researchers agreed. Dr. Craig Jordan, the estrogen and cancer scientist who put tamoxifen on the cancer map, and Leslie Ford M.D., associate director for clinic research at the National Cancer Institute's Division of Cancer Prevention, wrote an article called "The Paradoxical Effect of Estrogen on Breast Cancer Risk." This research showed that sometimes estrogens not only prevent breast cancer, they also cause breast cancer cells to die. The ability of estrogen to do this seems to be activated by a period of lack of estrogen exposure (menopause or anti-estrogen therapy) and then re-exposure to estrogen. The absence of estrogen and then re-exposure retriggers breast cancer cells to die in some women. Dr. Jordan commented on this rebooting of response to endocrine therapies by estrogen: "After five years of anti-estrogen therapy, a switch takes place inside breast cancer cells which makes them resistant to these anti-estrogen agents. When estrogen is then used, it triggers breast cancer cell death, not growth."

Dr. Jordan is a big fan of estrogen. Presently he is a cancer director at the renowned MD Anderson Medical Center, researching safe estrogen therapies for breast cancer patients (meaning patentable).

So, research is showing that estrogens help prevent breast cancer in some women, help eradicate sleeping breast cancer cells, and help some women become responsive once again to breast cancer therapy that had stopped working.

The Benefits of Estrogen

By the early 1990s, researchers had summarized the benefits of estrogen therapies and documented them in the medical literature.

Estrogen:

- Controls menopausal symptoms.
- If given early, it helps prevent strokes and bone loss and fractures for many years, even after discontinuation.
- Significantly reduces the risk of heart disease[185],
- Significantly reduces the risk of fracture (Framingham study showed a 50% drop in osteoporosis-hip fracture[186]
- Significantly decreases risk colorectal cancer,
- Significantly reduces the risk of cognitive decline and Alzheimer's Disease. The Cache County studies (which had the bad karma to come out only months after the

WHI and was not noticed) showed that if women had been on 10 years of estrogen therapies, they had a 30 to 50% reduction in incidence of AD.

- Has now been found to have hundreds of other pleotropic effects, such as helping epigenetics[187] and protecting mitochondria (our energy organelles) from damage[188], so it helps in maintaining the energy production needed for a positive lifestyle effort.
- Helps maintain volume, plasticity, and protection from injury of the hippocampus, where memories live in the brain[189].

Now we see that estrogen *protects* against breast cancer in a woman who has not yet had it and even in those that already have[190] [191]. To age without individualized hormonal support is to age at the speed of an accelerating bullet, while hormonal therapies allow us to live younger longer and healthier.

Vindication

Let 2020 be the year that estrogen is vindicated.

I had breast cancer 26 years ago and have been on estrogen and other hormone therapies for 21 years now. I would not be the person, physician, or author that I am if I were not on hormones.

I am passionate about passing this information forward.

I get email after email from women all over the world saying that their doctor will not prescribe estrogen for them. I hope this article makes it possible for more women to enjoy the benefits of this hormone.

This article is written for women to hand to their doctors or for doctors to feel vindicated (and safe) about prescribing hormones.

Appendix I

2019 SABCS Abstracts Home Print Page

Session GS5 - GS5. General Session 5

GS5-00. Long-term influence of estrogen plus progestin and estrogen alone use on breast cancer incidence: The Women's Health Initiative randomized trials

December 13, 2019, 9:30 AM - 9:45 AM

Authors

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Abstract

Background: Breast cancer outcomes from the Women's Health Initiative (WHI) Estrogen plus Progestin and Estrogen-alone trials have been reported but issues remain regarding long-term, post-intervention influence on breast cancer incidence and the influence of time from menopause to hormone therapy initiation (gap time) on breast cancer findings.

Design and methods: Postmenopausal women aged 50 to 79 years with no prior breast cancer and with mammogram clearance enrolled in one of two randomized clinical trials at 40 US centers from 1993 to1998, with follow up through September, 2016. The randomized, placebo-controlled trial interventions were: conjugated equine estrogens (CEE, 0.625 mg/d) plus medroxyprogesterone acetate (MPA, 2.5 mg/d) (n = 8,506) vs placebo (n = 8,102) for 5.6 years (median) for women with a uterus or CEE-alone (n = 5,310) vs placebo (n = 5,429) for 7.2 years (median) for women with prior hysterectomy. Annual mammography was mandated through the originally specified completion date in both trials (March 31, 2005). Incident breast cancers were verified by medical record review. Hazard ratios (HRs) were estimated using multi-variable Cox proportional hazards models. The primary outcome for these analyses was time-specific invasive breast cancer incidence rates. In each trial, participants were instructed to stop all study pills coincident with the publication of each trial's results, in 2002 and 2004, respectively.

Results

During the intervention period, with 238 incident breast cancers, CEE-alone significantly reduced breast cancer incidence (hazard ratio [HR] 0.76 95% confidence interval [CI] 0.58, 0.98, P = 0.04). As previously reported, subgroup analyses indicated CEE-alone was particularly beneficial for women with no prior HT use (interaction P = 0.04) and women with gap time >= 5 years (interaction P = 0.01). Post-intervention, through 16.1 years of cumulative follow-up, with 520 incident breast cancers, CEE-alone use continued to significantly reduce breast cancer incidence (HR 0.77 95% CI 0.65-0.92, P = 0.005) while subgroup differences were attenuated and were no longer statistically significant. During the intervention period, with 360 incident breast cancers, CEE plus MPA use significantly increased breast cancer incidence (HR 1.26 95% CI 1.02, 1.56, P = 0.04) with increase in breast cancer incidence greater in women with prior HT use (interaction P = 0.02) and women with gap time < 5 years (interaction P = 0.002). Post-intervention, through 18.3 years cumulative follow-up, with 1,003 incident breast cancers, CEE plus MPA continued to significantly increase breast cancer incidence (HR 1.29 95% CI 1.14, 1.47, P < 0.001) while subgroup differences were attenuated and were no longer statistically significant.

Conclusions

CEE-alone and CEE plus MPA use have opposite effects on breast cancer incidence. CEE alone significantly decreases breast cancer incidence which is long term and persists over a decade after discontinuing use. CEE plus MPA use significantly increases breast cancer incidence which is long term and persists over a decade after discontinuing use. As a result of the attenuation of subgroup interactions: all postmenopausal women with prior hysterectomy using CEE-alone have the potential benefit of experiencing a reduction in breast cancer incidence while all postmenopausal women using CEE plus MPA have the potential risk of experiencing an increase in breast cancer incidence.

Appendix II

Human Trials

- At MD Anderson Cancer Center, a randomized prospective study gave 39 breast cancer survivors Premarin compared to 319 breast cancer patients not on estrogen. They were followed for 52 months and found no increased risk of recurrence in breast cancer patients on HRT[192].
- A gynecologist at the University of California, Irvine matched 125 breast cancer patients on ERT or HRT with 362 who were not given hormones. There was no increased risk of recurrence in breast cancer patients on hormone therapies[193].
- A cancer doctor reported a prospective study of 277 breast cancer survivors on ERT for an average of 3.7 years, matched with controls and no increased risk of recurrence was found[194].
- University of Texas Southwestern Medical Center compared 64 breast cancer survivors on ERT with 563 matched controls not on ERT followed for an average of 12 years and found no increased risk of recurrence with hormonal therapies[195].
- At the Fred Hutchinson Cancer Research Center at the University of Washington, they reviewed records of 2,755 women diagnosed with cancer between 1977 and 1999, 174 given HRT compared each to 4 controls and followed for an average of 3.7 years finding that HRT in breast cancer survivors had no adverse effect on recurrence or mortality. In fact, breast cancer survivors on HRT had significantly lower breast cancer recurrence rates, breast cancer mortality rates, and overall mortality rates compared to survivors not on hormones[196].
- The Medical College of Wisconsin conducted a review of nine independent observational studies and one randomized controlled trial and found that breast cancer survivors prescribed HRT had no significant risk of recurrence. Their meta-analysis had 717 survivors on HRT compared with 2,545 survivors not on HRT and they found 3% fewer deaths in survivors on ERT compared to 11.4% deaths in survivors not on hormones[197].
- Researchers from Slovenia from the Institute of Oncology in Ljubljana, compared twenty-one women with breast cancer who were treated with HRT for an average of 28 months with controls for each patient. They found no increased recurrence of breast cancer among women on hormones[198].
- University of South Wales reproductive endocrinology department followed 90 breast cancer survivors treated with HRT for an average of 18 months followed for an average of 7 years with 180 matched controls found a small but significant reduced recurrence of breast cancer among women on prescribed hormones[199].

- A gynecologist at the Women's Health Institute of the Royal Hospital for Women compared 167 women surviving breast cancer on HRT compared with 1,122 similar women not given HRT. There were no increased recurrences of breast cancer even in ER+ patients. A four year follow-up found that there was no increased risk of recurrence in breast cancer patients on HRT[200].
- A gynecologist from the University of New South Wales published a retrospective observational study of 286 breast cancer patients prescribed HRT compared to 686 breast cancer survivors who didn't get put on HRT, with some women followed for 26 years. Women on HRT had lower rates of recurrence[201]. They concluded: HRT use for menopausal symptoms by women treated for primary invasive breast cancer is not associated with an increased risk of breast cancer recurrence or shortened life expectancy.
- A cancer doctor at the Hospital Saint-Louis in Paris followed 120 breast cancer survivors prescribed HRT and each patient was compared to two matched control women, and followed for 2.4 years. There was no increased risk of recurrence of breast cancer in survivors on hormones[202].
- Researchers at the University Central Hospital from Helsinki followed 131 breast cancer survivors, 88 who took ERT and 43 who did not, for 2.6 years. There was no increased risk of recurrence in estrogen survivor users[203].
- German researchers at the Friederih Alexander University in Erlangen retrospectively reviewed 185 breast cancer patients, 64 who took HRT and 121 who did not. After five years, there was no observed increased risk of recurrence[204].

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In Health,
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About Dr. Berkson

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