ESTROGEN MATTERS IN WOMEN

A Summary of ESTROGEN MATTERS, published in 2018 by Dr. Avrum Bluming, an oncologist, and Carol Tavris, a social psychologist
https://sciencebasedmedicine.org/estrogen-matters

Estrogen replacement stops hot flashes cold and is a veritable Fountain of Youth . . . .. Estrogen replacement is dangerous: it kills women. . . . . It prevents heart disease. . . . . It causes heart disease. The message keeps changing. What are we to believe?

Avrum Bluming is an oncologist whose practice has been 60% devoted to breast cancer. Carol Tavris is a social psychologist, feminist, and skeptic who writes the column "The Gadfly" for Skeptic magazine and whose many books include the classic *Mistakes Were Made (But Not by Me)*. They were alarmed by the many misunderstandings about menopausal hormone replacement and they collaborated to set the record straight with an extensively referenced new book, *Estrogen Matters: Why Taking Hormones in Menopause Can Improve Women's Well-Being and Lengthen Their Lives – Without Raising the Risk of Breast Cancer.*

Background

Back when I was practicing in the 1970s and 80s, it was standard practice to offer menopausal women replacement hormones. But doctors were not prescribing willy-nilly. The evidence at that time showed that it was by far the most effective treatment for hot flashes and other menopausal symptoms. The evidence at that time showed that estrogen reduced the risk of osteoporosis and heart disease. In my experience, it was not being prescribed just to prevent those diseases, but prevention was seen as an extra added benefit for women who needed estrogen to control menopausal symptoms. There was a small risk of blood clots and other adverse effects, but the benefits were thought to outweigh the risks.

Hormone replacement therapy (HRT) came in two flavors. Women with an intact uterus were given a combination of estrogen and progestin, since unopposed estrogen was known to cause cancer of the uterus. Women who had had a hysterectomy could safely take estrogen alone (ERT). Estrogen was contraindicated for women who had had breast cancer.

As of the 1990s, the evidence indicated that estrogen reduced the risk of heart disease by 40-50%, hip fractures by 50%, colon cancer by 50%, and Alzheimer's by 35%.

A 1997 article estimated HRT would prolong life by 3 years.

The Women's Health Initiative (WHI)

Then came a bombshell. In 2002, the results of the WHI study were trumpeted in headlines with the message "*OOPS! We were wrong. Hormones do more harm than good!*" They were essentially saying "*Hold your horses!*" (an apt expression since the most commonly prescribed estrogen, Premarin, is made from pregnant mares' urine).

This study had a huge impact because it was a gold standard study: large, randomized, prospective, placebo-controlled, and double-blinded. Subjects were randomized to receive either hormones or placebos and were followed for 15 years. It was published in one of the most prestigious medical journals. The study was stopped early when it detected an increase in breast cancer, coronary heart disease, stroke, and pulmonary embolism in women taking estrogen and progestin. The study was seen as definitive evidence that HRT was dangerous, that the risks outweighed any benefits.

Thousands of women were scared into going off their hormones. Sales of Premarin dropped from $2 billion to $880 million. Some of these women tried other remedies and then went back to Premarin because it was the only thing that worked for them. Doctors learned to prescribe more selectively, and sales started rising again. The new mantra was "*the smallest dose for the shortest time*".

What did the WHI really show?

The media misrepresented and misinterpreted the WHI findings, giving the impression that HRT was killing women. Not so. Over 10,000 person-years, women on estrogen plus progestin had 7 more coronary events, 8 more strokes, 8 more pulmonary emboli, and 8 more invasive breast cancers than women who didn't take hormones; but they also had 6 fewercolorectal cancers and 5 fewer hip fractures. In the estrogen-only group, there was a decreased risk of coronary heart disease and breast cancer. And in both groups there was **no increase in overall mortality**. These women were getting more of some diseases and less of others, but they weren't dying any faster.

Over the years since the initial report, there have been a number of follow-up studies of the same cohort of women, introducing nuance and even reversing some of the findings. Bluming and Tavris report those findings in detail and they describe how the original WHI study was flawed.

Menopausal symptoms

Many troublesome symptoms are reported by menopausal women: hot flashes, loss of sexual desire, painful intercourse because of vaginal dryness, difficulty sleeping, palpitations, unexplained and uncharacteristic anxiety attacks, difficulty concentrating, fuzzy thinking, and more. DeLuca's book The Hormone Myth questions how many women experience these symptoms and to what degree. And whether all of those symptoms are really due to low hormone levels or might be due to other factors in their lives. It's undeniable that some women do experience severe menopausal symptoms that interfere with their activities and reduce their quality of life, and that estrogens are by far the most effective treatment. The WHI did not address these symptoms at all; in fact, the WHI patients averaged 63 years of age, past the age when menopausal symptoms are most likely. Surely relief of debilitating symptoms should be factored into any discussion of the risk/benefit ratio for an individual patient.

Breast cancer

By 2000, numerous studies had shown that estrogen did not increase the risk of breast cancer, not even in high-risk BRCA1 patients; in fact, there was evidence that it reduced the risk.

The fear of breast cancer rested on two studies:

1. 1989 study in Sweden showed 440% increase in risk of breast cancer among women who had been on HRT. But it found no increased risk in women taking estrogen alone. And the 440% was based on 10 women who developed breast cancer instead of the expected 2.2. With such small numbers, it could have been a statistical fluke. And it was not even statistically significant!

2. 1997 Lancet study showed no significant increase in breast cancer among women who had taken HRT in the past, no matter how long they had taken it. But it found an increased risk in women who were still taking HRT and had used it for 5 or more years. The increased risk was small: 0.6 cases per 100 women after 10 or more years.

The Women's Health Initiative found a 26% increase in risk of invasive breast cancer in women taking combined estrogen and progesterone. But the fine print said that the 26% figure "almost reached nominal statistical significance." In other words, there was no significant increase. And there was no increased risk in women taking estrogen alone, not even a non-significant increase.

The WHI continued to do follow-up analyses and publish updated findings:

- In 2006 a follow-up analysis of the same cohort of women found no increased risk with combined estrogen-progesterone treatment. This time, the news didn't make headlines.

- In 2008, another follow-up found a nonsignificant increase in all-cause mortality and no increased mortality from breast cancer.

- In 2010, another follow-up showed an increase in breast cancer deaths (2.6 vs. 1.3 per 10,000) in women on HRT compared to placebo. But this was not statistically significant.

- In 2018, the WHI investigators announced that the dose of estrogen in vaginal creams is not associated with an increased risk of breast cancer

The Million Women Study followed, reporting an increase in breast cancer with both estrogen alone and combined estrogen/progestin. But only in current users, not past users. Bluming and Tavris ask, "If estrogen is a major risk factor in breast cancer, why would having taken it for years not be a problem but taking it at the time of study be a risk?" Birth control pills contain the same hormones, and most studies have shown no association with breast cancer. And survival rates for women with breast cancer are higher if they were taking oral contraceptives at the time of diagnosis.

They provide a table of risk factors that have been associated with breast cancer. Estrogen reduces risk (0.77 relative risk), the WHI reported an increase in risk with estrogen and progesterone (1.24 or 1.26 relative risk). Other things that increase risk include fish intake (1.14), multivitamin use (1.19), alcohol (1.26), French fries (1.27), night shift work (1.51), increased carbohydrate intake (2.22), left-handedness (2.41), and electric blanket use (4.90).

They go on to discuss research pitfalls like data mining and substratification analyses, which in one case led to the finding that aspirin had an adverse effect on mortality for patients born under the astrological signs of Gemini and Libra but was beneficial for patients born under all other signs. A 2000 study from the National Cancer Institute found no increased risk with estrogen alone, and an increased risk with combined therapy, but only in women who had used hormones in the four years prior to diagnosis and who weighed ninety pounds or less.

Even though some research indicates a 2% increase in breast cancer, other research shows that women on HRT live longer and have a lower death rate from breast cancer.

They stress that correlation is not causation. So how can we approach the mosaic of findings with breast cancer? They show how each of the Bradford Hill criteria for causation supports the finding that smoking causes lung cancer. Then they show that the hypothesis that estrogen causes breast cancer fails to meet any of the Bradford Hill criteria.

They say, "it is time to relegate the "common knowledge" that ERT and HRT cause breast cancer to the dustbin of discredited ideas along with the theories that radical mastectomy is the best treatment for primary breast cancer, that anger causes peptic ulcers, and that stress causes tuberculosis."

Osteoporosis

They explain that bone density (as measured by DEXA) is not the same as bone resilience (a more clinically meaningful factor that can't be measured). Osteopenia has no medical meaning; it doesn't predict risk of hip fracture. The authors chastise Big Pharma for promoting medications that are less effective and cause more side effects than estrogens. Meds like Fosamax should be used for osteoporosis, not osteopenia. The bisphosphonates can even cause hip fractures.

No therapy is more effective than ERT and HRT in preventing osteoporotic fractures of the spine and hips. It reduces risk by 33-50%. But it requires ten years and possibly lifelong treatment. Women age 65-74 had a 63% reduction in hip fractures, but if they stopped taking estrogen the reduction quickly dropped to 18%.

Bluming and Tavris don't recommend estrogen for osteoporosis prevention in all women: the vast majority will not develop osteoporosis or die from it. But the research is persuasive that high-risk women would benefit from continuing to take estrogens.

Alzheimer's disease

Alzheimer's disease is common and devastating, and the available treatments only ameliorate some of the symptoms but do nothing to slow the progression of the disease. There is evidence that we already have a powerful preventive: decades of research have indicated that estrogen helps preserve the cognitive ability of postmenopausal women and reduces the risk of Alzheimer's.

In 2003, the WHI Memory Study found just the opposite. Estrogen plus progesterone doubled the relative risk (1.8% vs 1%) of dementia in women over 65. Bluming and Tavris say that finding was statistically significant but neither compelling nor clinically relevant. The absolute risk was small, the subjects were not all healthy and were not representative of the typical user, the sample size was small, and the increased risk was found only in women over 75 and in the first year of use, suggesting pre-existing dementia. And there was no increase in the mild cognitive impairment that should precede dementia. The reports tended to neglect the finding that there was not a statistically significant increase in risk with estrogen alone. A 2004 follow-up reported that the increased risk was only in women who were cognitively impaired at the outset, not in women who were cognitively healthy. Bottom line: the finding of a small increase in dementia risk could not be extended to all forms of HRT or even to the women most likely to start HRT.

There is abundant evidence, including evidence from animal and lab studies, that estrogen started early in menopause can prevent or delay the onset of dementia, including Alzheimer's. And it has even more benefits for the brain: it stimulates the growth of nerve cells, promotes brain plasticity, enhances the action of glial cells, improves cerebral blood flow, and much more. Numerous clinical studies support those benefits, and three large meta-analyses found that HRT was associated with a 34% decreased risk of dementia and a 40% decreased risk of Alzheimer's.

Heart disease and stroke.

The evidence shows that when HRT is started soon after menopause, it can reduce the incidence of heart disease and strokes.

Pre-existing breast cancer

Conventional wisdom says women who have had breast cancer should not take estrogen. That conventional wisdom was never actually supported by any good evidence. Bluming's breast cancer patients wanted relief of their menopausal symptoms, so he started looking into it. He found that neither lowering estrogen levels by removing ovaries or raising levels by becoming pregnant had any effect on the recurrence of breast cancer. He did his own study and found that HRT had no effect on the recurrence rate. Numerous other studies subsequently confirmed his findings, with only a single study pointing the other way. In fact, there is evidence that HRT may reduce the recurrence rate and prolong survival.

Progesterone

Estrogen alone appears to be safer than estrogen plus progestin. They discuss the difference between progestins, progesterone, and micronized progesterone, which appears to be the safest form.

Colon cancer

There's another added benefit. Data from the WHI study showed that women on any form of HRT had a 30% lower risk of colon cancer. Other studies have shown that HRT in pill form (as opposed to the patch) is associated with a lower risk of colon cancer and a lower mortality rate from colon cancer if they do get it. Most, although not all, studies confirm these findings.

Ovarian cancer

Oral contraceptives reduce the rate of ovarian cancer by up to 80% and the reduced risk persists for nearly 20 years after the pills are stopped.

Hormone replacement had been killing women?

When the results of the WHI study were publicized, the prescription rate for HRT fell by 70%. The incidence of breast cancer declined in the next 8 months, but this can't be attributed to fewer women taking estrogen. It takes longer than 8 months for cancer to develop, and the decline actually started three years prior to the WHI announcement. And in Norway, even though women went off HRT at the same rates, the rate of breast cancer diagnoses did not decline.

Many people seem to be committed to the ideas that a natural phenomenon, menopause, has been medicalized and that hormones cause cancer. When researchers have conducted re-analyses that contradicted their earlier conclusions, they have typically waffled, looking for other explanations, seemingly unable to say anything good about HRT. Cognitive psychologist Daniel Kahneman calls this "theory-induced blindness", where adherence to a theory makes people unable to see its flaws or accept new evidence.

Taking the lowest dose for the shortest time?

There is no scientific basis for the recommendation to take the lowest dose for the shortest time. The North American Menopause Society advises clinicians to move away from this simplistic advice and instead prescribe the dose and formulation that meet each patient's needs and concerns based on the woman's age, time of menopause, and any unique health risks she might have. The book provides a long list of organizations that endorse the continued use of HRT after the age of 65.

Criticisms of the WHI

The WHI was widely trusted because it was a large gold standard trial. But Bluming and Tavris show that in this case the gold standard had feet of clay. They list ten key problems:

1. It was rushed into publication before most of the co-investigators had even seen the draft. There is reason to think some of them would have objected. Later one of them published a blistering account of the violations of the scientific process.
2. The initial finding that HRT increased the risk of breast cancer was not statistically significant.

3. The subjects were not representative of menopausal women: their average age was 63.
4. The sample was not representative of healthy women. Nearly half were current or past smokers; more than a third had been treated for high blood pressure; fully 70 percent were seriously overweight or obese.
5. The findings were inconsistent and contradictory: in 2002, a nonsignificant increase in risk, in 2006 no increase in risk; and women taking estrogen alone were subsequently found to have a lower risk.
6. Some of the findings were the result of data mining.
7. They claimed that estrogen didn't even help alleviate menopausal symptoms, but there was no basis for that claim: they had not studied women who were actually having menopausal symptoms.
8. Initial claims that HRT increased the risk of heart disease were later reversed: women who started HRT in the first ten years following menopause actually had a reduced risk of heart disease.
9. Reports of an increased risk of stroke were the result of statistical manipulations. When the data were independently analyzed, the supposed increased risk of stroke vanished.
10. Many of the WHI investigators have continued to promote alternatives to HRT that they incorrectly maintain are just as effective. Most of their suggestions are no better than placebos.

What's more, some of the investigators had voiced their stated agenda to prove that hormones were harmful.

Despite revelations about the WHI's flaws, many people still consider WHI the definitive proof that hormone replacement does more harm than good. Even John Ioannidis, a notorious critic of research that is paid for by industry, and author of an important study showing that most published research is wrong, believes that the data implicating hormones as a risk of breast cancer are strong and scientifically reliable. He and Bluming have agreed to disagree.

Understand, then advise

They suggest a new maxim. Instead of *primum non nocere*, (first do no harm) *primum certior fi, tunc mone* (first understand, then advise).

This book is a refreshing change from the usual book that promotes an agenda by concentrating on one side of a divisive issue. As a male, Bluming is not a candidate for HRT; his only agenda is to help his patients. And Tavris is not a candidate either: at her age, she is well past the ten-year window of opportunity. They rigorously present the evidence on both sides and the disagreements among scientists. And they don't presume to tell patients what they "should" do. They advocate individualizing decisions based on many factors such as the severity of menopausal symptoms and the patient's risk of osteoporosis, heart disease, colon cancer, etc.

Estrogen is the only really effective treatment for hot flashes and other symptoms of menopause. It has a large effect on the quality of life as well as many other health benefits. The authors say the real question is notwhether it helps, but whom it helps and when. There appears to be a critical window of opportunity: the decade following the onset of menopause.

They quote Sir George Pickering: "If you are a clinician, you must believe that you know what will help your patient; otherwise, you cannot counsel, you cannot prescribe. If you are a scientist, however, you must be uncertain — a scientist who no longer asks questions is a bad scientist."

Bluming says:

"The practice of oncology thus requires a constant dance between what we know and what we must learn; perhaps that's why we say that surgeons perform surgery but physicians practice medicine."

Conclusion:
Estrogen vindicated

Once considered a veritable fountain of youth, estrogen replacement got a bad rap with the Women's Health Initiative study. This book is an exhaustively researched and meticulously reasoned vindication of hormone replacement therapy. Estrogen matters: it's the most effective treatment for hot flashes and other symptoms of menopause, and when started early and used continuously, it has important health benefits and can actually prevent some of the adverse events it was thought to cause. Bluming and Tavris tell estrogen's story in a way that is both accessible to the general public and appropriate for professionals. What's more, they provide valuable insights into understanding research and how even the best randomized controlled studies can lead to unjustified public fears and injudicious clinical recommendations. Very enlightening!