Makary Marty, "OMG HRT The untold story of hormone replacement therapy," Blind Spots. NYC, NY: Bloomsbury Publishing, 2024: 17-37.

CHAPTER 2

OMG HRT

The untold story of hormone replacement therapy

Truth, they say, is all too frequently eclipsed but never extinguished.

—TITUS LIVIUS

For most of the 20th century, hormone replacement therapy (HRT) was celebrated as a medical miracle. Millions of women using HRT found relief from the symptoms of menopause. HRT, which is estrogen with or without progesterone, alleviated hot flashes, reduced brain fog and depression, and even helped women sleep better. Not only did women *feel* better on HRT, but studies found they were also less likely to develop Alzheimer's and bone fractures, and they had a 50% lower risk of dying of a heart attack when they started HRT within ten years of menopause.[1] Overall, HRT has been shown to increase a woman's longevity by three years. Millions of women around the world have felt better and lived longer, healthier lives thanks to HRT.

But then in 2002, something happened.

Doctors from the NIH held a press conference to announce a surprising discovery. HRT, they said, causes breast cancer. Their conclusion was based on a 16,608-woman study they had just completed with Harvard and Stanford researchers. "These findings are the first confirmation from a rigorous clinical

trial that taking estrogen plus progestin increases the risk of breast cancer," lead author Dr. Jacques Rossouw said, adding that HRT resulted in "a 26% higher incidence of breast cancer." He didn't release any of the study's data but claimed the study had been stopped early because of this concerning finding. The shocking announcement scared women around the world, and doctors, too. HRT was instantly deemed a carcinogen and abandoned.[2] Women flushed their pills down the toilet and doctors stopped prescribing them.

The media clapped like seals congratulating the researchers. Reporters amplified the study's conclusion, even though they had not yet seen the actual data. *Time* magazine put a woman on its cover with an ominous headline: "The Truth about Hormones: Hormone-replacement therapy is riskier than advertised. What's a woman to do?" The researchers were celebrated as savvy medical detectives whose discovery would rescue millions of women from a dreaded cancer.

There was just one problem: The study had NOT shown that HRT causes breast cancer.

The actual publication, which appeared in the *Journal of the American Medical Association* (*JAMA*) one week after the press conference, did not support the headlined conclusion. It reported no statistically significant difference in the rates of breast cancer among the women on HRT compared to those who took a placebo. The authors had misrepresented their data. But amazingly, hardly anyone noticed. The message that HRT causes breast cancer stuck. And that message is still believed by most doctors to this day.

Not everyone drank the Kool-Aid. I was a resident at the time. One of my mentors, known for her impartiality, pointed out to me the massive discrepancy between the study announcement and the published data.

"Is this a Jedi mind trick?" she asked me in disbelief. "This may be the greatest farce in modern medicine."

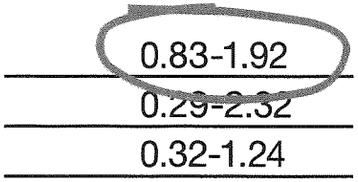
I asked her to walk me through the data in the publication. She pointed out that the rate of early breast cancer (what we call carcinoma in situ) was stated in the article to be no different with HRT. The rate of invasive breast cancer was slightly higher in the HRT group than the placebo group, less than 1 additional nonfatal breast cancer diagnosis per 1,000 women treated in a year, but given the large size of each group, only a valid statistical test would determine if the difference was real—or just random

noise in the data. That's how science is done. It's Research 101. No journal or legitimate scientist would ever accept claims of a higher rate in one group over another group if the statistical test applied found no difference.

I checked the statistical test in the publication. It was a standard test. We call it an "odds ratio confidence interval." When a confidence interval is wide and includes the number 1.0 in the range, it is considered nonsignificant, meaning there is no difference between the groups being tested. *Always*. In this study, the confidence interval was so wide, you could drive a Mack truck through it. More importantly, it also included the number 1.0 in the range.

"Marty, it's amazing," my mentor exclaimed. "The study showing that HRT causes breast cancer does not show that HRT causes breast cancer!"

As time went on, my mentor and I were baffled that no one was speaking up. We wondered when a prominent doctor would finally and publicly point out the false claims made by the NIH researcher. *Surely someone will expose this*, we thought. *There can't be that many people who don't understand statistics.*



Published confidence interval of the adjusted risk of invasive breast cancer for women taking HRT compared to placebo
(*Journal of the American Medical Association*, July 17, 2002)

We were wrong. The few doctors who spoke up were crowded out. U.S. prescriptions for HRT plummeted by 80%, and they remain low to this day. Tragically, a generation of millions of women were deprived of a life-changing treatment.

A cruel irony came to light in follow-up studies. They found that participants who took estrogen alone had lowered their risk of breast cancer by 23% and lowered their risk of breast cancer death by 40%. That benefit diminished over time after women discontinued HRT.

Yet to my utter amazement, to this day, many doctors still believe that HRT should not be prescribed because it causes breast cancer. If you ask them why, they will almost certainly cite this famous study—the most expensive clinical study in history—known around the world as the Women's Health Initiative (WHI). The NIH had spent approximately $1 billion in taxpayer dollars on the study.

The Incredible Backstory

When I set out to investigate how the WHI debacle happened, doctors close to the study told me I should talk to Dr. Robert Langer, a University of California San Diego epidemiologist and preventive medicine expert who was also a WHI investigator. He has been outspoken about how the WHI lead authors misled the public. I reached out to him to learn more.

When we met, Dr. Langer explained that most of the coauthors of the WHI study had been bamboozled at a meeting held on June 27, 2002, just weeks before the study was published in *JAMA*. He walked into the regularly scheduled biannual meeting of the study's 40 principal investigators (one leader from each participating site) at the beautiful new Sofitel Chicago hotel. They were greeted with pleasantries. They had no idea what was about to hit them.

"Welcome to Chicago," the meeting began. Dr. Langer and a researcher from Hawaii were a bit bleary-eyed coming from western time zones.

"You can throw out the agenda we sent you. Things have changed," they were told. The lead biostatistician went on to explain that the study's independent board recommended stopping the HRT trial. Dr. Langer and the other 39 principal investigators (PIs) were told that a small group of the study's leaders had already written the research article, and it had already been accepted for publication at *JAMA*, the most widely read medical journal in the United States.

"Proof" copies of the article were then handed out to the PIs in the room.

The PIs couldn't believe it. Coauthors are always given ample time to review a paper before it's submitted for publication. The investigators objected, stunned by the highly unusual, top-down approach. They were given 20 minutes to read the study. But as they read it, the researchers pointed out misleading language in the article and spotted problems with its conclusions.

Dr. Rossouw, the head of the entire study, tried to calm the researchers by inviting them to make suggested edits and return their marked-up drafts to him before lunch. He said he would have a courier run over any changes to the journal's offices, only a few blocks from their meeting in Chicago.

"By noon?" The researchers objected. It was already 10:30 A.M. Most of the PIs didn't bother making edits. But Dr. Langer told me how he and a few others used the next hour to make major revisions to the article. They submitted their edits before the noon deadline. But after lunch, they were informed that the courier had returned with the message: It was too late. The article had already been typeset and printed. The journals were stacked at the warehouse, ready to be shipped.

This meeting was a charade.

The focus of the meeting then turned to the proposed press release, titled: "NHLBI [a division of NIH] Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit."[3] The PIs' ire boiled over. Remember, these are respectable researchers with MDs and PhDs. Dr. Langer, the most vocal among them, got into a shouting match with Dr. Rossouw.

"If this is what you put out to the press, there's no turning back," Dr. Langer told him.[4] He explained that breast cancer is the biggest hot-button issue in America, adding that "if you stir baseless fear around something so sensitive, you can't put that genie back in the bottle."

Dr. Langer told me, "Marty, it was clear to me that if that press release was put out there, it was game over. And that's exactly what happened."

Over the next several years, Dr. Langer would take issue with other WHI studies and even resign as a coauthor of some of the papers. "It was obvious that the agenda in subsequent reports was to preserve the storyline and save face, given how large and expensive the study was," he explained. His internal resistance did not go unnoticed.

In 2009, Dr. Langer received an email informing him that he was being removed as chair of a WHI committee and banned from involvement in any future WHI publications on HRT. When he asked why, he received the following email response from a WHI leader:

> The PIs have reached a consensus on interpretation of our data and prefer that our publications not be contradictory.

In other words: *We will not tolerate dissent.*

Reflecting on the ordeal, Dr. Langer wrote in 2017 that "highly unusual circumstances" surrounding the early termination and reporting of the trial resulted in the "misinformation and hysteria" that persists today. In a different medical journal, he said that "good science became distorted and ultimately caused substantial and ongoing harm to women for whom appropriate and beneficial treatment was either stopped or never started."[5] When I spoke with him, he shared with me that being fired from the WHI "was at the time very troubling and stressful. Now I see it as one of my proudest moments."

In 2023, Dr. Langer and others published a detailed article condemning "the WHI's reporting of nonsignificant results as if they were meaningful, a misinterpretation of its own data, and the misleading assertion that the WHI's findings have reduced the incidence of breast cancer in the United States."[6] He and his coauthors concluded that, "A generation of women has been deprived of HT [hormone therapy] largely as a result of this widely publicized misinterpretation of the data."

Why did the study's small group of leaders hide data from their coauthors? It may be because the lead author, Dr. Rossouw, had made up his mind before the study began. He had written six years prior to the WHI publication, "It is time to put the brakes on the hormone bandwagon."[7] Well, he did.

I reached out to Dr. Rossouw at his Maryland home to get his take on what went down at that Chicago meeting. He acknowledged that the publication had been hurried and contentious. "That created some unhappiness," he said. "It created a very uncomfortable meeting . . . but we got over it."

My biggest question was about statistical significance. A finding is either statistically significant, which means we can make medical decisions based on it, or it's not. I asked Dr. Rossouw point blank: Was the breast cancer link in his study statistically significant?

"It touched on significance but wasn't quite significant," he replied. "It was nominally significant. It was not significant after being adjusted for multiple looks at the data."

Huh? What a strange way to acknowledge that it was not. I have never heard someone spin a nonsignificant result like that before in my career. It made no sense. I then asked him if his trial or any trial has ever shown

that HRT was associated with an increase in mortality due to breast cancer. He said no.

Amazing.

Months after the publication of the WHI's HRT study, a noted oncologist, Dr. Avrum Bluming, invited one of the three lead investigators, Dr. Rowan Chlebowski, to give a lecture at California's Medical Center of Tarzana. Dr. Bluming told me the audience was not impressed by the non-statistically significant "evidence" presented.

During the Q&A portion after Dr. Chlebowski's lecture, a physician in the audience challenged the WHI investigator, politely asking, "About your claim of the increased risk of breast cancer for women on HRT, I was under the impression that if the confidence interval included the number one, that it was not particularly meaningful."

Dr. Chlebowski responded saying, "Yeah, yeah, you know, that's right. And you know what happens? What happens is, if it's an important question and if it's a big study . . . and you can't do it again because it costs too much money, then they'll say that's the best data there is and then . . . the statistical police have to leave the room."[8]

The audience was silent, flabbergasted by the glib dismissal of universally accepted research standards. There were no more questions.

Dr. Garnet Anderson, the study's statistician, had gone on record saying that when it's an issue as important to women as breast cancer, we intentionally set the bar low.[9]

Other leading authors, like Dr. JoAnn Manson, gave many talks and interviews about the study following its publication. In 2023, when asked directly about the controversial findings, she claimed "it approached" nominal statistical significance. If I ever claimed an association in my research because something "approached" significance, it would be rejected on the spot.

I reached out to Dr. Manson and spoke with her for more than an hour by Zoom. I found her to be very friendly and quite charming. In our conversation she referred several times to the "increased risk of breast cancer," balancing it with other benefits of HRT.

I challenged her statement that HRT causes breast cancer and pulled up the exact numbers and odds ratios from her 2002 publication. I asked

her to show me where the increase in breast cancer was found to be significant. "I completely agree with you that there is some concern that the sequentially monitored confidence interval wasn't the focus," she told me.[10] It wasn't clear to me if she was officially reversing her position that HRT causes breast cancer, so I again displayed the results from her publication and asked her if she'd like to go on the record to say that the study did not show that HRT increased breast cancer. "The finding is very borderline," she said. I moved on to ask her about the Chicago meeting of the study authors. "It's a super sensitive topic. It's like one of the bleakest times of my life, thinking about that meeting," she replied. She didn't elaborate.

In the year following the WHI publication, some of the lead authors claimed credit for the decrease in U.S. breast cancer rates. But a closer look revealed that the decline had begun in 1999, three years before the WHI publication. Actually, rates of breast cancer went up by 0.5% annually after the 2002 publication, the year that HRT use plummeted. Regardless, Drs. Chlebowski and Anderson have claimed credit for preventing over 100,000 diagnoses of breast cancer.

Dr. Sarrel

To get the real story on HRT, I reached out to Dr. Philip Sarrel, a leading expert on estrogen. An emeritus professor of obstetrics and gynecology and of psychiatry at Yale, he graciously gave me hours of his time. He told me that he had been invited to be one of the WHI study's investigators when it was being organized, but after examining the study design and seeing several red flags, he had declined to participate in protest. He had also been amazed by how little the cardiologist leading the study had appeared to know about the field of reproductive biology.

Dr. Sarrel explained all the medical nuances on the topic. A true scientist at heart, he described how estradiol (the body's natural form of estrogen) is "oxidized" to produce nitric oxide, a molecule that dilates blood vessels, keeps them healthy and elastic, and prevents heart disease. As early as the 1890s, doctors noticed that women who had their ovaries removed developed early heart disease. Then in 1953, researchers from the Mayo Clinic

studied young women who had their ovaries removed in their 20s. They all went on to develop early heart disease, including one woman who died of a heart attack at age 28.[11] In that study, among women under age 60, the average time from removing ovaries to death was 11 years. The Mayo Clinic researchers challenged the medical establishment at the time by suggesting that hormones are not just for reproduction, they also affect blood vessel health and thus, overall health.

Hormones may also be good for neurons. I was fascinated when Dr. Sarrel explained how some research on estrogen comes from the octopus, an emotionally intelligent animal that thrives on estrogen. After about a year or two of life, its estrogen levels drop precipitously, it stops eating, and it dies. What's also amazing about the octopus is that its estrogen-rich body is majestically coordinated and smart. Its eight arms can perform separate tasks independently. It can navigate mazes, solve math problems, remember, and predict. It can even use tools and take apart just about anything from a crab shell to a lock.[12] Its estradiol is believed to optimize its body's many neurons.

In the end, Dr. Sarrel concluded that the WHI cardiologists didn't understand hormones but they "made the loudest noise, so they got their message through." He has since committed his life to explaining the real science of HRT and its many benefits.

Doctors Who Refuse to Prescribe HRT

I began asking doctors who treat menopausal symptoms if they offer HRT to their patients. The prescription is simple: estrogen + progesterone if a woman still has a uterus, or estrogen alone if a woman had her uterus removed. (The progesterone helps protect the endometrial lining of the uterus and prevent uterine cancer.) Remarkably, most doctors told me they tried not to prescribe HRT because they worried about the risk of breast cancer. Some would prescribe it but only if the menopausal symptoms were extreme. Even then they would reluctantly prescribe "as little as possible for as short of time as possible," hoping the whiff of estrogen wouldn't trigger breast cancer. This, even though no randomized trial or credible

study has ever shown that HRT increases a woman's risk of dying of breast cancer.

Yet to this day, the dogma lives on.

I reached out to Dr. Bill Queale, a Maryland primary care doctor that I trust. I like him because he reads everything. It turns out he is in the minority of physicians who know the truth about the faulty HRT data. "Marty, the estrogen-causes-breast-cancer idea was beaten into us so bad, it scared the crap out of most of us," he said. He estimated that a majority of the doctors in his field nationally still hesitate to prescribe it for that reason.

Perplexed as to how many doctors have been persuaded by the unsupported claims of the WHI lead authors, I began to ask women experiencing menopausal symptoms what they were being told by their doctors about their symptoms. Most were never offered HRT, or even told about the option. A few others had told me they heard it can cause breast cancer. I pointed out to them that when I recently spoke to Dr. Rossouw, the head of the WHI study, he admitted to me that the breast cancer risk was not statistically significant and that HRT was "a reasonable treatment for younger women."

In many of my discussions about the data, it struck me that the *fear* of HRT-induced breast cancer was not a scientific discussion. It's become a belief system.

Doctors who really want to believe HRT causes breast cancer will sometimes cite poorly designed studies, like the so-called "million women study." This study sounds like a clinical trial that had a million people in it, but it didn't. Instead, it was a questionnaire sent to a million women. Most women never even responded. It was also mailed to women after they had a mammogram (presumably some had the mammogram because of a suspicious lump or other concern) so it surveyed a skewed, nonrepresentative sampling of women. Others who insist HRT causes breast cancer will sometimes point to follow-up studies reported by WHI researchers. But after women were unblinded in the original study, and those on HRT were told they had a higher breast cancer risk, some religiously began an aggressive hunt for breast cancer, even if it was indolent. Other flaws in the follow-up studies have been documented in the medical literature.

As time has passed since the original WHI study, critics have pointed out even more flaws in its design and execution. For example, the study

used horse urine estrogen and synthetic progesterone, not the bioidentical forms commonly used today.

In looking at the total body of medical research on the topic, the data are overwhelming. In analyzing 30 trials with a total of 26,708 women participants, HRT was not associated with an increase in cancer mortality, according to a study by researchers from Santa Clara Medical Center, Stanford, and the University of California San Francisco. Conversely, women who took HRT lived longer. In the subset of 17 trials in which women began HRT before age 60, "HRT was associated with a reduction in total mortality of 39%."[13]

The data are clear. HRT saves lives.

A Humbling Day

Sometimes patients walk into clinic with a real medical mystery. One of the most humbling cases I saw as a student was that of a 52-year-old woman that came to the surgery clinic with a three-year history of new-onset abdominal discomfort, palpitations, depression, and numbness and tingling. We doctors huddled to try to crack the case.

One doctor rattled off the need for a CT scan, a cardiac stress test, and a litany of blood tests. Another doctor wanted to do nothing because the patient had dismissed her symptoms as mild. A third doctor, always worried about malpractice liability, insisted that we get a consultation from a cardiologist, psychiatrist, neurologist, and sleep medicine specialist. He enthusiastically offered to make the referrals himself because he knew good people in each field. Incidentally, all three doctors were male.

Then, finally, a female medical student cut through the chatter and solved the enigma by interjecting two words: "It's menopause."

What? I thought. *Really?*

We had spent fewer than 15 minutes talking about menopause in medical school. I know because a female classmate, Jennifer Rosen, had complained about how the curriculum virtually skipped over the topic, as most of the rest of the class (mostly male) rolled their eyes. Could it really account for all these symptoms, some of which were severe?

Menopausal symptoms, we were told—by male professors—were merely mild hot flashes and night sweats, affecting just some women, and lasted about two years. But in fact menopausal symptoms affect 80% of women, can be severe, and last an average of 7.5 years.[14]

The patient was sent back to her primary care doctor, who cured all her symptoms with estrogen and progestin. She came back to the clinic just to tell us how much better she felt and to thank us. She had been relieved of her debilitating medical problems.

I was blown away.

Dr. Sarrel explained to me that "because of the WHI, there was little medical education about menopause. Because WHI suggested there was no safe treatment for it." That may explain why only 20% of OB/GYN residents surveyed some ten years later reported being taught about menopause in their training.[15]

Sadly, medical school education is slow to change. That's because the curriculum of every U.S. medical school is controlled by a private company that has a monopoly on accrediting medical schools and writing examinations. It's called the Association of American Medical Colleges (a company discovered to have given $500,000 to a dark money group in 2018.)[16] Because American medical education is controlled by a slow, political, distracted, and centralized authority, medical schools propagate outdated groupthink. It's not like college education, where each university can rapidly add new courses and adapt existing curricula to new scientific thinking.

A Closer Look

I saw how quickly HRT treated the immediate symptoms of menopause right before my eyes. It was one of the most vivid and rewarding fixes I had seen in medicine, the type of stuff that makes us look good as doctors. The power of HRT to alleviate the symptoms of menopause has never been controversial. But what about its long-term benefits? In reviewing the literature and talking to colleagues, I learned something amazing. There are vast and well-established benefits for a woman who starts taking HRT

within ten years of experiencing menopause. HRT reduces the risk of a host of medical problems.

Let's briefly explore some of the big ones. As you will see in the next few pages, *even if* the WHI would have shown that HRT increases the risk of breast cancer, the long-term health benefits of HRT are so profound that they would far outweigh that increased risk.

Reduces Cognitive Decline (Better than Billion-Dollar Drugs)

Women taking estrogen have a 35% lower incidence of Alzheimer's. That's according to a University of Southern California study of more than 8,800 women. "Estrogen replacement therapy may be useful for preventing or delaying the onset of Alzheimer disease in postmenopausal women," the study concluded.[17]

Let's put this benefit in context. For every woman diagnosed today with breast cancer, two are diagnosed with Alzheimer's. Keep in mind that breast cancer is 90% curable. Alzheimer's has a 0% cure rate.

Researchers have long noted an association between hormones and cognition. A 2009 Mayo Clinic study of women who had both ovaries removed before menopause—thereby cutting off their hormone production—found they had an increased risk of depression and anxiety, dementia, and Parkinson-like symptoms.[18]

Other studies have identified a potential mechanism of action: Estrogen supports neuron development and maintenance throughout life.[19] More recently, a 2023 UK study of 1,178 postmenopausal women found that women who took HRT had improved memory.[20]

Danish researchers randomized 343 women in early menopause to receive HRT versus placebo and followed them for up to 15 years. They found that taking HRT for even just two to three years reduced the risk of cognitive impairment by 64%.[21] Wow.

Compare that to the hot new Alzheimer's drug, Leqembi, approved by the FDA in 2023. Leqembi was reported to slow cognitive decline in women by 12%—at an annual cost of $26,500.[22,23]

But unlike HRT, the new Alzheimer's drugs have major risks (a 13% risk of brain swelling and a 17% risk of brain bleeding), which is why there is a black-box warning on the drug's label. Those are not trade-offs I would have ever recommended for my aunt Aida, who succumbed to the cruel disease. HRT is a thousand times safer and a fortieth of the cost. I do sometimes wonder if, had my aunt taken HRT, her cognitive decline could have been prevented or delayed.

As an aside, I decided to read the entire 2023 *New England Journal* study that led to Leqembi's FDA approval. I discovered that the reported 12% reduction in Alzheimer's progression in women was *not* statistically significant (*déjà vu* of the WHI study). The results for women—who make up two thirds of the people with Alzheimer's—did not appear anywhere in the printed article, which was funded by the drug's manufacturers. I found them deep in the study's supplemental material online.

It is strange to me that America will spend billions on a drug to treat Alzheimer's, but pennies to study what actually prevents it.

Less Likely to Break a Bone from a Fall or Car Accident

Falling down is a common cause of death. Sure, the death certificate will often cite some other cause like pneumonia, but after age 65, a fall often triggers a cascade of events that can be lethal. It can be a wrist fracture causing loss of independence or an ankle or hip fracture causing immobility. In fact, the one-year mortality following a hip fracture is 22%.[24]

Remarkably, HRT lowers the risk of a fracture by 50 to 60% according to a randomized trial published in the *New England Journal*.[25] There are not a lot of ways a woman can increase her bone density and reduce her risk of a hip fracture, but HRT is one. In fact, without HRT, it doesn't matter how much calcium and vitamin D a postmenopausal woman takes for the strength of her bones. HRT helps make bones stronger.

Another study that tracked nearly 3,000 women for decades found that postmenopausal women who had taken estrogen had a 35% lower risk of hip fracture.[26] This reduced risk is especially beneficial for older women. Among women aged 80 and older, 1 in 3 will have a hip fracture as a result of osteoporosis.[27]

These benefits of HRT were known to doctors before the WHI report was released in 2002. In 1984, the NIH convened a Consensus Development Conference on Osteoporosis that met for two days of presentations by experts. The panel concluded by making strategy recommendations for addressing osteoporosis, listing first among them "ensuring estrogen replacement in postmenopausal women."[28]

Bone fractures kill women. To put this risk in context, the number of women who die each year from a hip fracture (about 40,000) is roughly equal to the number of women who die from breast cancer. As I write this book, my mom just had a close call. She fell while walking and fractured two bones, requiring surgery. Mom experienced menopause just as the WHI study came out in 2002. Her doctors never suggested HRT to her. I can't help but wonder this week if her pain, surgery, medical bills, and temporary disability could have been avoided had she been on HRT.

Prevents Heart Attacks

Heart disease is the leading cause of death in American women. HRT reduces that risk by about 50%.

What? you're probably asking. Honestly, I was shocked too. I didn't even know it was that high because we hardly ever talk about it in the medical community. I've heard a million talks and public health campaigns demonizing saturated fat, extolling CPR, and advocating putting a defibrillator in every mall in America, yet I've *never* heard one about HRT. But the data are abundantly clear.

Researchers from the University of California San Diego and Johns Hopkins did a thorough review of the research literature and concluded that most studies of HRT "show around a 50% reduction in risk of a coronary event in women using unopposed oral estrogen."[29] By comparison, statins—which are currently used by 40 million Americans—lower the incidence of heart attacks by 25 to 35%.[30]

Another study, published two years before the WHI study, looked at 70,000 postmenopausal women over 20 years and found that HRT reduced the risk for major coronary events by almost 40%.[31] What other intervention reduces the risk of the number one cause of death in women by that much?

Another powerful observation is that women who stop taking HRT have a 26% increased risk of a fatal heart attack in the first year after stopping HRT, according to a large Finnish study.[32]

Furthermore, in 2012 Danish researchers published the results of a ten-year randomized controlled trial in over a thousand women who had recently experienced menopause. They found that HRT reduced the risk of heart attacks and other major heart problems by 52%. The authors also pointed out that prolonged use of HRT did not increase the risk of breast cancer or stroke.[33] Finally, a 2015 review of the entire body of literature on the topic by the Cochrane Library found that women who started HRT within ten years of menopause had half the rate of "death from cardiovascular causes and non-fatal myocardial infarction" and no increased stroke risk.[34]

For the heart benefits—and nearly all health benefits, for that matter—the key is that HRT must be started around menopause (or within ten years of its onset). That's when a woman's level of estrogen naturally drops and her blood vessels begin to gradually narrow and harden, a process fostered by lower levels of nitric oxide and by normal aging. The narrowing and hardening over the first ten years after menopause may be irreversible. This explains why the WHI study did not show the better cardiac outcomes seen in other studies. WHI participants started HRT at an average age of 63. That's too late.

HRT, started around the menopausal years, helps keep the walls of blood vessels soft and dilated. A consistent finding by experts I trust is that it's ill-advised to start HRT more than ten years after menopause. For women who can start HRT within ten years of menopause, those same experts will often keep women on it for life, if no complications or risk factors develop.

Reduces Colon Cancer Risk

When I've had to break the bad news to women that they have colon cancer, it sometimes leads to a long conversation with them about its causes. Some

have asked if there was anything they could have done differently in their life to have prevented it. My standard answer has been no, nothing. But in 2009, three big studies reported that HRT can reduce the risk of colon cancer.

The first study looked at 56,000 women over two decades. Researchers from the University of Minnesota and the NIH found that the women who took HRT had a 25 to 45% decreased risk of colon cancer, depending on the type and duration of HRT used.[35] Another study, by the American Cancer Society, analyzing 67,000 women, found that HRT use was associated with a 24% decreased risk of colorectal cancer.[36] Finally, the *Journal of Clinical Oncology* reported in a study of more than 2,600 Israeli women that HRT was associated with a 63% reduction in the risk of colorectal cancer in post-menopausal women.[37] The microbiome, the bacterial layer that lines the gut, may also play a role, a topic we'll explore in the next chapter.

Other Surprising Benefits

One reason couples stop having sex when a woman goes through menopause is because of vaginal dryness, making sex painful for some women. Estrogen reduces vaginal dryness. Incidentally, women also report that HRT alleviates the dryness they notice in their nose, mouth, eyes, and scalp. Doctors tell me they have saved marriages by prescribing HRT to women. "The mental health improvement is palpable," one of them told me.

HRT may also help prevent diabetes. WHI researchers, with all their skepticism about HRT, reported in 2004 that women on HRT had a 21% lower risk of diabetes.[38] One possible mechanism for the reduction in diabetes is that women on HRT feel better, may be more active, and thus have less of the weight gain typically seen with menopause. That could be why a systematic review published in 2017 found that HRT delays the onset of Type 2 diabetes.[39,40] While the data are considered less definitive than for the other benefits of HRT, the potential implications are significant. One in seven U.S. women has diabetes.[41,42]

Finally, because HRT helps with bone density, there is also a dental benefit. A 2017 study found that severe gum disease was 44% lower in women who were taking HRT.[43] Another study by South Korean

researchers found that postmenopausal women had a higher risk of gum disease, and that HRT could reduce its incidence.[44] Yet another little-known health benefit of HRT.

Overall, HRT may do more to improve the health of women over age 50 on a population level than any other medication in history.

A Few Notable Exceptions

While HRT has a long list of dramatic short-term and long-term health benefits, it is not for everyone. Some oral forms of estrogen have been suggested to slightly increase the risk of a blood clot. But this is not the case for transdermal estrogen. The very low risk of a blood clot is akin to that of oral contraceptive pills. Women with risk factors for developing a blood clot may be advised against the oral form.

For some women with endometriosis, estrogen can make it worse. Furthermore, some women who take HRT may not tolerate it because it can cause a resumption of bleeding or irritability and moodiness. Not everyone does well with it. Also, as above, no one recommends starting HRT more than ten years after menopause. Women should also be aware that the type and quality of estrogen and progesterone matter. There are "pill mills" carrying HRT made with poor quality control. Some clinics say they only offer surgically implanted pellets for HRT when women should really be offered all options, including topical, oral, and implantable.

For these and other reasons, the recommendation to take HRT should be nuanced, rather than a one-size-fits-all recommendation. Nevertheless, the vast majority of women in the world benefit from HRT when started in the first ten years after menopause.

Lowering Drug Costs

As I write this book, the FDA just approved the first medication to treat hot flashes, Veozah.[45] Already I'm noticing a barrage of Veozah ads on TV. While the ads do not have the standard people dancing and singing,

Veozah does market itself as hormone-free. The obvious question that comes to my mind: Why would a healthy woman take this new medication to treat one menopausal symptom when she could take HRT to treat the same symptom and get the full spectrum of short- and long-term health benefits?

For a woman who can't take HRT, such as someone with a predisposition to blood clots or someone with active breast cancer, Veozah seems like a great medication. But otherwise, it makes no sense to me. Plus, it's much more expensive than HRT. A one-year supply of Veozah costs $7,386 at my local Costco.

As politicians scratch their heads trying to figure out how to lower drug costs in the U.S., here's a simple idea: The best way to lower drug costs in the U.S. is to stop encouraging patients to take expensive drugs when there are less expensive alternatives.

The Aftermath and Legacy

Drs. Avrum Bluming, Carol Tavris, Phil Sarrel, and others have dedicated their lives to educating doctors about the truth about HRT. Dr. Sarrel is among a group of experts from around the country who now run a foundation to educate women and physicians about the best data on the topic.[46] Visana is another group helping women navigate the healthcare system to find good care.

The leaders of the WHI have done tremendous damage to public health. Dr. Sarrel and a team of researchers published a study that estimated that up to 91,000 women have died prematurely from HRT avoidance in the first decade after the infamous WHI press conference. Dr. Sarrel told me that in the last ten years, there have been at least another 50,000 premature deaths due to the misinformation put forth by WHI leaders.[47] Looking back, telling women to avoid HRT because it causes breast cancer may have been the biggest error in modern medicine.

Women deserve an apology.

Yet, inexplicably, the dogma is still alive and well. This year, the U.S. Preventive Services Task Force, an influential board of doctors in America,

renewed its guidance to avoid HRT to prevent chronic conditions because of the risk of breast cancer. The Task Force's statement read, "The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal persons." In response, strong articles by Dr. Langer and others pointed out the fallacy of the recommendation and urged them to take a hard look at the evidence.[48,49]

Today

Lead author Dr. Jacques Rossouw went on to be named one of *Time* magazine's hundred most influential people in 2006.[50] *Time* wrote that he and others "deserve a round of applause for their role in the WHI's myth-busting operation." As of my submitting this book manuscript, Dr. Rossouw, at age 81, is still a volunteer scientist at the NIH.[51]

I asked Dr. Rossouw if he had any regrets. He reaffirmed that he believes that HRT causes breast cancer. He did add that he wishes he would have stated "more loudly" in his press release that HRT is "a reasonable treatment for younger women" to treat menopausal symptoms. "I made sure to tell women that the absolute risks are small . . . may be less than one in a thousand . . . That didn't get picked up. You know how the media operates, they want bad news."

Dr. JoAnn Manson, another lead author of the WHI, went on to be promoted and is now the chief of Preventive Medicine at Brigham and Women's Hospital and a professor of epidemiology at the Harvard T. H. Chan School of Public Health. She is celebrated as the fifth most cited researcher in medicine.[52]

To her credit, Dr. Manson has walked back some claims made by WHI investigators and has been open to discussing the study with critics.[53] In 2016 she admitted in an article in the *New England Journal* that "reluctance to treat menopausal symptoms has derailed and fragmented the clinical care of midlife women, creating a large and unnecessary burden of suffering."

In a 2023 interview with Dr. Manson, Dr. Peter Attia remained polite while pressing her, but he concluded the interview by telling her, "I still remain somewhat sad, because I think there's a lost generation of women.

There's 20 years of women that entered menopause who were denied HRT due to the ignorance of their physicians and the irresponsibility of the media. And I look at women like my mother and mother-in-law who were entering menopause just as the WHI was coming to its conclusion, who suffered unnecessarily . . . How many millions suffered unnecessarily?"[54]

When I told Dr. Langer about Dr. Attia's frustration, he took it a step further. "We are about to lose the opportunity to help the next generation of women if we don't work hard to provide honest findings to women and doctors."

Dr. Garnet Anderson, the WHI study's statistician, went on to be named senior vice president and director of public health sciences at Fred Hutch, the highly regarded cancer center at the University of Washington, where she also holds an endowed chair. Her bio on the center's website boasts, "In 2002, she and her WHI colleagues reported that menopausal estrogen-plus-progestin therapy increased the risk of breast cancer . . . Subsequent analyses led by Hutch colleagues estimated these changes prevented 126,000 breast cancer diagnoses and saved approximately $35.2 billion in direct medical expenses." As I was writing this book in early 2023, I happen to notice a statement Anderson and a WHI colleague had published in the *New York Times* in response to an article by staff writer Susan Dominus. The title of Dominus's article, published on February 1, 2023, was "Women Have Been Misled About Menopause." In her response a few weeks later, Anderson shamelessly wrote, on behalf of the WHI steering committee, that the worldwide decrease in the use of HRT "undoubtedly has saved millions of lives and billions of U.S. healthcare dollars."[55] I wish that were true.

It would be good for the people involved in propagating the HRT-causes-breast-cancer absolutism to show some humility. It's not too late. But we've heard no apologies from the 40 WHI investigators, except for Dr. Robert Langer.

From time to time, a woman will ask me how she can find a good primary care physician or internist. I sometimes suggest that she start by asking candidates how they feel about treating menopausal symptoms with HRT. If the doc responds with "I don't prescribe it because I worry about the risk of breast cancer," my recommendation is clear. Keep looking.