

## FEATURE STORY

# The HRT Connection

BY ELIZABETH WHITTINGTON

*Are breast cancer rates dropping because of the HRT decline, or are other factors at work?*

Throughout the 1990s, breast cancer rates steadily rose. Then in 2003, the number of cases made a clear downward turn—14,000 fewer women were diagnosed with breast cancer than in 2002, a drop of nearly 7 percent. In women age 50 to 69, those numbers dropped nearly 15 percent for estrogen receptor-positive breast cancer, which makes up about two-thirds of all breast cancers.

Many researchers pointed to a significant period in history that may have created a reversal of the steady upward trend—the end of the Women’s Health Initiative [WHI] study examining the effects of hormone replacement therapy, or HRT, in postmenopausal women. At a time when a third of all women over 50 were taking HRT, the study’s results were front-page, primetime news and became the catalyst for millions of women to question whether HRT was not only ineffective in its presumed benefits, but actually increased their risk of several diseases, including breast cancer.

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Estrogen-only replacement therapy gained popularity in the 1960s and '70s, but when it was linked to uterine cancer, progestin was added to counteract the risk. So, the '80s and '90s saw a shift to combined estrogen and progestin. The medical community prescribed combined HRT to women going through menopause, especially those suffering from symptoms such as hot flashes. Many women had been taking the drug for 10 years or longer with the idea that it was preventing heart disease and improving bone health.

But in 2002, the part of the 16,608-woman WHI study looking at HRT was stopped early after the group taking combined HRT was found to have a higher risk of heart disease, stroke, blood clots, and breast cancer than women taking placebo.

After only five years—the study was planned for eight—researchers pulled the plug. The substantial media coverage—headlines read “Should Anyone Take Hormones?” and “The End of the Age of Estrogen”—led 38 percent of women prescribed any type of HRT to stop taking it. Sales of the two most popular HRT drugs, Prempro (estrogen plus progestin) and Premarin (estrogen), dropped after bringing in more than \$2 billion in 2001.

Early in her career as an internist, Maura Dickler, MD, prescribed HRT to women at risk for heart disease. “Some women sought it out, but many were told of the potential benefits and then opted to take it,” says Dr. Dickler, now a breast cancer oncologist at Memorial Sloan-Kettering Cancer Center in New York. “WHI really hit home for me, in that we were really misdirected for a long time by epidemiological studies suggesting a benefit of HRT.”



Molly Lindell questioned her decision to stay on HRT when she was diagnosed with breast cancer two years after the release of the WHI results. Photo by David C. Dalton.

When the WHI results were announced in July 2002, Molly Lindell had been taking combined estrogen and progestin for five years to alleviate her hot flashes, which she says were coming every 45 minutes and disrupting her work as a long-term care nurse. Lindell, of St. Clair Shores, a suburb of Detroit, educated herself about the study results and weighed the risks and benefits of continuing HRT. Although it increased the risk of breast cancer by 26 percent, it also showed a slight decreased risk of colon cancer. Both of Lindell’s parents died of colorectal cancer, and she thought a lower risk of colorectal cancer outweighed the possibility of breast cancer.

“It was an educated guess,” she says. Then in 2004, she was diagnosed with stage 2 breast cancer, which caused her to doubt her decision. “I was in a panic and thought this is what caused it,” Lindell says. “I couldn’t imagine continuing to take them.” Lindell, like thousands of other women who were diagnosed with breast cancer after years of HRT use, asked themselves if HRT was the cause. But the answer may have less to do with causing breast cancer and more to do with helping the disease grow.

While the WHI study found that combined HRT was associated with a higher risk of breast cancer, women taking estrogen-only HRT had no increased risk of breast cancer. (Estrogen alone increases the risk of uterine cancer, so the therapy is limited to women who have had hysterectomies.) A closer look at the statistics reveals that the 26 percent increase with combined HRT amounts to only an additional eight women developing breast cancer out of 10,000 women per year who use it, and the risk appears after five years of continuous use.

But when the numbers were put in perspective, the big picture looked much different since millions of women were filling prescriptions for combined HRT. “Women in the population who have been on estrogen and progestin should not be unduly alarmed. However, even small individual risks over time, and on a population-wide basis, add up to tens of thousands of these serious adverse health events,” explained Jacques Rossouw, MD, WHI’s acting director, in a statement announcing the end of the HRT part of the study in mid-2002.

## Making the Connection

Nearly five years later at this past December's San Antonio Breast Cancer Symposium, Peter Ravdin, MD, PhD, a research professor in the Department of Biostatistics at M.D. Anderson Cancer Center in Houston, presented an analysis that he and colleagues say statistically shows the 6.7 percent drop in breast cancers between 2002 and 2003 was primarily the direct cause of the WHI findings.

Between 2001 and 2003, prescriptions for estrogen and progestin therapy dropped by half, to 33 million prescriptions filled—accounting for an estimated three million women who stopped the combination therapy. Estrogen receptor-positive breast cancer, a disease fueled by estrogen, saw the biggest drop.

Estrogen-blocking therapies, such as tamoxifen, are effective in about half of estrogen receptor-positive breast tumors. Dr. Ravdin and colleagues deduced that taking away HRT, a hormone-promoting therapy, would have the same anti-cancer effect. Depriving potential tumors of those cancer-growing hormones may explain why the breast cancer drop was so sudden after women were off HRT for a short period of time, which Dr. Ravdin says surprised even him. Because the effects of anti-estrogen therapy appear after about a month, Dr. Ravdin's group proposed that the effect of taking HRT away could slow down or stabilize the cancer growth in the same amount of time.

Many experts believe HRT affects the progression of pre-existing cancers too small to be detected by screening. Because most breast cancers take years to become detectable, combined HRT may only speed up the growth to make tumors detectable by screening. Remove HRT and the tumor growth slows down or stops altogether. "If you look at it that way, you are kind of treating pre-cancers," Dr. Ravdin says. Whether HRT affects initiation of these cancers remains unknown.

## A Cause for Mammography?

Almost immediately after Dr. Ravdin's presentation, other explanations for the breast cancer drop surfaced. Among the most convincing were reports about the decline in mammography rates.

A report published in *Breast Cancer Research* by Ahmedin Jemal, PhD, and colleagues at the American Cancer Society indicates mammography use declined during the time leading up to the WHI study, which could have led to the decrease in diagnosed breast cancers. Following a steep increase in mammography use—rates went from 29 percent in 1987 to 70 percent in 2000—some experts say mammography reached a saturation point in the population, and subsequently began to decline.

Using cancer incidence data from the National Cancer Institute, the investigators also tracked a decline of invasive breast cancer incidence from 1999 to 2003, but

say the decrease was not significant until 2003. Jemal and colleagues wrote that the decrease in HRT use could not account for the decrease in breast cancer cases before 2002 or in women 75 and older, and was only a contributing factor to the decrease after 2002.

While mammography rates did decrease 3.2 percent in women age 50 to 64 between 2002 and 2003, Dr. Ravdin says that doesn't explain why the drop in breast cancer incidence was greater in estrogen receptor-positive cancer (14.7 percent) compared with estrogen receptor-negative cancer (1.7 percent) in 50- to 69-year-olds. "That would suggest something was not driving the estrogen-positive breast cancers any longer," he says.

Nancy Breen, PhD, at the National Cancer Institute led an analysis published in *Cancer* in June that examined the drop in mammography rates from 2000 to 2005. The investigators uncovered something interesting: The group with the largest drop in mammography use was 50 and older, white, educated, insured, and had an income well above the poverty level. While theories behind screening declines usually include barriers to access and lack of emphasis on screening, the characteristics found in Breen's study mirror the sociodemographics of HRT users. Experts suspect previous HRT users consequently had fewer appointments with their physicians resulting in fewer recommendations for screening.

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After bringing in more than \$2 billion in 2001, sales of two popular HRT drugs, Prempro (estrogen plus progestin) and Premarin (estrogen), plummeted following the release of the Women's Health Initiative results.

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"What was striking about that was, it wasn't just the age group, but also many of the categories of women who historically have been the most likely to use mammography," Breen says, suggesting access may not be the problem.

The messages women receive about mammography may also be less clear, Breen says. High rates of false positives, the controversy over whether women 40 to 49 should be screened, and other issues may cloud the importance of mammography. "I think a key point that shouldn't be lost is that mammography does detect breast cancer early at a point or at a stage that it can be treated well and survival is very high," Breen says.

Karla Kerlikowske, MD, principal investigator at the San Francisco Mammography Registry and professor of medicine and epidemiology and biostatistics at University of California in San Francisco, says the M.D. Anderson analysis was interesting but wondered if the declining mammography rate played a part. A drop in mammography use would also result in a quick decline of breast cancer cases, simply because doctors may not be finding them, she says. And while fewer HRT users may have led to fewer breast cancers in women over 50, the decline may also have something to do with these women not getting regular mammograms, which Breen's study suggests.

To further examine the major cause in the breast cancer decline, Dr. Kerlikowske and colleagues used data from screening mammography registries from 1997 to 2003—more than 600,000 mammography examinations in women age 50 to 69—and found the decrease in HRT use among women who had mammograms

correlated to a decrease in invasive breast cancers, most significantly in ER-positive breast cancers. The results of Dr. Kerlikowske's study, published in the *Journal of the National Cancer Institute* in August, is another puzzle piece that points to the decline in HRT use—not mammography—as the cause of fewer breast cancers.

While the declines in HRT and mammography use are the two most likely possibilities for the breast cancer decline, other contributing factors, such as chemoprevention, may have played a small part. Tamoxifen, approved in 1998 to prevent breast cancer, and Evista (raloxifene), an osteoporosis drug approved in 1997 that has also shown efficacy in breast cancer prevention, may have contributed to the drop. However, adverse side effects, such as blood clots and endometrial cancer with tamoxifen, led many women, even those at high risk for breast cancer, to stay away from the agent. The FDA is currently considering Evista for approval as a breast cancer preventive agent.

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Steadily rising since the mid-1980s, breast cancer incidence in women 50 and older dropped by 6.7 percent between 2002 and 2003.

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### What It Means for Survivors

“I think most people who are on HRT and then diagnosed with breast cancer want to know if that's the cause, and we know that for most women on HRT who get breast cancer, most of them would have developed breast cancer anyway,” says Halle Moore, MD, a breast oncologist at the Cleveland Clinic in Ohio, but adds that some of these cancers may have remained small enough to never be detected or pose a threat.

In a National Institutes of Health study, published in 2002 after the WHI study, data suggest the risk of breast cancer begins to return to normal within six months of stopping HRT, but research continues. Although women in the WHI study were told to stop taking their HRT pills, they are still being followed. A report is expected later this year about the influence discontinuing HRT has on breast cancer risk.

Dr. Moore reminds survivors that even women who never took HRT are at risk for breast cancer, and whether a woman develops cancer in her lifetime depends on a variety of factors. “Those risks will persist, but it's always impossible in one individual to determine whether their cancer occurred as a result of the HRT or would have happened anyway.”

While physicians encouraged some women to take HRT for bone or heart protection, many women were prescribed the therapy to alleviate symptoms of menopause. When the WHI study ended, dosages were lowered for many women while others looked to HRT alternatives.

And while some physicians feel HRT is still beneficial when taken at small dosages and for a short period of time, women with a history of breast cancer are usually told it is not an option because of the risk of recurrence. The M.D. Anderson analysis is consistent with the idea that HRT encourages the growth of

breast cancer, says Dr. Ravdin, “both within the breast and it also appears to stimulate the growth of micrometastatic disease as well, so it increases the risk of recurrence.”

Currently, few randomized, controlled studies have looked at recurrence in survivors using HRT because of the known risk it poses to them. Even in the WHI study, women with a history of breast cancer were excluded from participating.

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While a significant decline was seen in ER-positive breast cancers--a disease fueled by estrogen--in women age 50 to 69, little change occurred in ER-negative cancers during the same time.

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In 2004, a Swedish study planned to examine HRT use in 434 survivors for five years. The study, published in the *Lancet*, was stopped three years early after women in the HRT arm developed breast cancer at three times the rate of the non-HRT arm (26 cases compared with seven cases). Critics of the study point to its flaws—it was not blinded or placebo-controlled, and had enrolled less than half of the 1,300-participant goal set. Even still, the medical community widely believes the study shows strong evidence that survivors should avoid HRT.

Sloan-Kettering’s Dr. Dickler says few data, if any, support the safety of HRT in breast cancer survivors. But while safer treatments are available, such as statins for heart disease and bisphosphonates for bone health, not many options exist to treat hot flashes. While a class of antidepressants and vitamin E have shown modest benefit in alleviating hot flashes, nothing provides extensive relief.

For women who still have a uterus, some physicians have prescribed a low estrogen dose combined with an intrauterine device that releases a small amount of progestin directly into the uterus to prevent uterine cancer. This direct method of progestin delivery reduces the overall amount of hormone in the bloodstream, but the risk of cancer growth may still exist. Because estrogen-alone HRT hasn’t been linked to breast cancer—something doctors still find confusing and have few data to explain why—researchers point to progestin.

“I think the difference between estrogen and progestin versus estrogen alone in terms of breast cancer is still unclear,” Dr. Dickler says, though she acknowledges progestin may be a contributing factor. “I still don’t think it means estrogen is safe.”

Research and debate continue on the risks and benefits of HRT, even five years after the WHI study. Emerging data indicate HRT may actually be beneficial to the heart if taken by women in their 50s, but this new information has not persuaded physicians to recommend HRT to survivors. However, two ongoing studies are looking at whether using the natural hormone progesterone in place of synthetic progestin will eliminate the increased breast cancer risk.

The news of 14,000 fewer breast cancers in one year is huge, but few believe it will become a trend, including Dr. Ravdin. NCI data released this past April for 2004 breast cancer rates showed only a slight decrease compared with the 2003 data, indicating the rate may be leveling off. But the continued decline also shows those 14,000 fewer breast cancer cases in one year wasn’t a fluke.

