US breast cancer decrease tied to drop in hormone replacement therapy use

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A startling decrease in US breast cancer rates in 2003 may be attributable to the fact that millions of older women stopped using hormone replacement therapy (HRT) in 2002, according to researchers at the University of Texas M.D. Anderson Cancer Center.

Investigators reported a remarkable 7 percent relative decline in breast cancer incidence between 2002 and 2003, with a steeper decline of 12 percent in women between the ages of 50 and 69 diagnosed with estrogen receptor positive breast cancer, that is, breast cancer that is hormone-dependent for tumor growth. The findings were presented at the 29th annual San Antonio Breast Cancer Symposium.

"It is the largest single drop in breast cancer incidence within a single year I am aware of," said Dr. Peter Ravdin, a research professor at M.D. Anderson, in a press release. Ravdin added that the study can only indirectly infer the connection between the decline in breast cancer and stopping the use of HRT.

"But if it is true, the tumor growth effect of stopping use of HRT is very dramatic over a short period of time, making the difference between whether a tumor is detected on a mammogram in 2003 or not," asserted Ravdin. He added, however, that what it is not known is whether these tumors will regress and never become a problem or just take longer to show up.

The overall 7 percent decline represented, according to the researchers, some 14,000 fewer women who were diagnosed with breast cancer in 2003 than in 2002, a year in which some 203,500 new cases were diagnosed.

According to the M.D. Anderson analysis, the rate of breast cancer diagnoses increased steadily at 1.7 percent annually from 1990 to 1998, before decreasing to 1 percent a year from 1998 to 2002. By the end of 2003, the rate had dropped 7 percent when age adjustments were made.

"Incidence of breast cancer had been increasing in the 20 or so years prior to July 2002, and this increase was over and above the known role of screening mammography," said the study's senior investigator, Dr. Donald Berry of M.D. Anderson. "HRT had been proposed as a possible factor, although the magnitude of any HRT effect was not known. Now the possibility that the effect is much greater than originally thought all along is plausible, and that is a remarkable finding."

Consumption of hormone replacement drugs drastically fell after a groundbreaking study in 2002 by the Women's Health Initiative (WHI), which found that HRT—a combination of estrogen and sometimes progestin hormones—significantly increased the risk of developing invasive breast cancer.

Prescriptions for the estrogen-progestin pills plummeted from 22 million per quarter before the WHI study to 12.7 million in the last quarter of 2003. Millions of women were taking the pills in hope of relieving menopausal symptoms such as hot flashes and night sweats, believing them to be a protection as well against heart disease, osteoporosis and aging.

As a result, the menopausal drugs, particularly Prempro, manufactured by Wyeth, had become some of the most popular in history. Responding to the M.D. Anderson study, Wyeth issued a statement claiming that "the potential impact of hormone therapy on breast cancer has long been warned on product labels."

Dr. Ravdin said that some 30 percent of women older than 50 had been taking HRT in the early part of the decade, but that half of that group had stopped in late 2002 after the WHI findings were released. "Research has shown that ER-positive [estrogen receptor positive] tumors will stop growing if they are deprived of the hormones, so it is possible that a significant decrease can be seen if so many women stopped using HRT."

Added Berry: "It takes breast cancer a long time to develop, but here we are primarily talking about existing cancers that are fueled by hormones and that slow or stop their growing when a source of fuel is cut. These existing cancers are then more likely to make it under mammography's radar."

To conduct the study, Ravdin and Berry teamed up with researchers at the National Cancer Institute (NCI) and Harbor-UCLA Medical Center in Los Angeles. They analyzed data from nine regions across the US that contribute data to NCI's database, from which national cancer incidence statistics are derived.

The researchers warned that because the new study is based solely on population statistics, they cannot know for certain the reasons why incidence declines. "We have to sound a cautionary note because epidemiology can never prove causation," said Berry. While other effects, such as decreased

use of screening mammography and changes in the use of anti-inflammatory agents, SERM or statins, were considered, "only the potential impact of HRT was strong enough to explain the effect," according to Berry.

Besides the fact that the drop in breast cancer rates was seen in every cancer registry that reports information to the federal government, no big change occurred with any other major type of cancer, indicating that the breast cancer decline is not an error.

"It's a big deal," said another of the researchers, Dr. Rowan Chlebowski of Harbor-UCLA Medical Center. "It's better than a cure," he said, because these are cases that never occurred. Significantly, when researchers tracked month-to-month figures, they noticed an even stronger trend: cases dropped 6 percent in the first half of 2003 and 9 percent in the second half.

A separate study by the American Cancer Society also documented the plunge. In addition, presented to the San Antonio symposium were data through 2004 from the Northern California Cancer Center and Kaiser Permanente's Division of Research, showing reductions statewide in both the use of HRT and the incidence of breast cancer since the WHI 2002 study.

"Hormone therapy use dropped 68 percent between 2001 and 2003, and shortly thereafter, we saw breast cancer rates drop by 10 to 11 percent," said Dr. Christina A. Clarke of the Northern California Cancer Center. "This drop was sustained in 2004, which tells us that the decline wasn't a fluke."

Women in northern California's affluent Marin County were especially heavy users of hormone therapy before the 2002 WHI report and were being diagnosed with invasive breast cancer at a significantly higher rate than the officially recorded national average. Investigators found that California's overall drop of 11 percent in breast cancer rates in 2003, versus 7 percent nationally, was believed to be due to the fact that more women in California had been using HRT than in other states.

Dr. Marcia Stefanick of Stanford University, chairwoman of the steering committee for the Women's Health Initiative, said the cancer-hormone link helped clear up the mystery about Marin County's high cancer rates.

Renowned breast cancer specialist Dr. Susan Love, when asked during an interview on cable network CNN, December 18, if she believed that the significant drop in breast cancer rates was due to the fact that women had stopped taking hormone therapy, replied: "Absolutely. It's really the mirror image to the [WHI] study in 2002...so when women stopped, we now see the second half, which is the drop in breast cancer...there's a growing suggestion that having a dense mammogram, having a lot of density on your mammogram is a sign of a higher risk of breast cancer. And many women who go on HRT find their mammograms get more dense."

A spokeswoman for the National Breast Cancer Coalition, the nation's largest breast cancer advocacy group, urged caution about the M.D. Anderson study. Fran Visco, NBCC president, commented in a statement, "This report of a significant one-year decline in breast cancer incidence, particularly for post-menopausal women diagnosed with estrogen receptor positive breast cancer, is telling. However, one study of one-year data may not be enough to draw definitive conclusions on whether the decline is a trend or an anomaly. The next set of data, to be released by this research team in April, should help provide answers to that question."

Visco continued, "The analysis also suggests that during that year, this same demographic was also less likely to have taken hormone replacement therapy (HRT). The researchers involved with this study infer there may be a direct connection between a reduction in use of HRT and decreased incidence of breast cancer. We question whether enough time has passed to know if any decrease in incidence is related to HRT use."

The NBCC president noted that the findings underscored the importance of thoroughly testing all drug use to ensure that anticipated benefits were real and there were no unintended side effects. She observed that even if the relationship between the decline in HRT use and the decline in cancer was as the researchers described, the onset of breast cancers might simply be delayed. She pointed out that it also remained unclear whether the decrease would result in a decrease in breast cancer deaths.

Breast cancer is the leading major cancer and second major cause of death in American women. Some 275,000 new cases are expected to be discovered in the US in 2006 and more than 1 million worldwide. The American Cancer Society estimates that a woman in the US has a 1 in 8 chance of developing invasive breast cancer during her lifetime; the risk was about 1 in 11 in 1975.