

REVERSING TREND, BIG DROP IS SEEN IN BREAST CANCER

A COMMON TYPE FALLS 15%

Scientists Cite a Decrease in the
Use of Hormones
to Treat Menopause

By GINA KOLATA

Rates of the most common form of breast cancer dropped a startling 15 percent from August 2002 to December 2003, researchers reported yesterday.

The reason, they believe, may be because during that time, millions of women abandoned hormone treatment for the symptoms of menopause after a large national study concluded that the hormones slightly increased breast cancer risk.

The new analysis of breast cancer rates, by researchers from the M. D. Anderson Cancer Center in Houston and presented at a breast cancer conference in San Antonio, was based on a recent report by the National Cancer Institute on the cancer's incidence.

Investigators cautioned that they would like to see the findings confirmed in other studies, including, perhaps, in data from Canada and Europe, and they would like to see what happens in the next few years.

"Epidemiology can never prove causality," said Dr. Peter Ravdin, a medical oncologist at the M.D. Anderson center and one of the authors of the analysis.

But, he said, the hormone hypothesis seemed to perfectly explain the data and he and his colleagues could find no other explanation.

Donald Berry, head of the division of quantitative science at the cancer center and the senior investigator for the analysis, called the connection between the drop in

rates and hormone use "astounding."

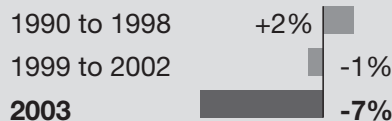
Over all, for women of all ages and all breast cancer types, the incidence of the cancer, the second leading killer of women, dropped by 7 percent in 2003, or about 14,000 cases, the researchers said. It was the first time that breast cancer rates had fallen significantly, something experts said was especially remarkable because the rates had slowly inched up, year by year, since 1945.

But the decrease was most striking for women with so-called estrogen-positive tumors, which account for 70 percent of all breast cancers.

In July 2002, the Women's Health Initiative, a large clinical trial looking at the use of one menopause drug, Prempro, made by Wyeth, found that women taking the drug had slightly higher breast cancer rates. The study's findings were a shock to many women and their doctors. Until then, many had assumed that Prempro simply replaced the lost hormones of youth. Within six months, the drug's sales had fallen by 50 percent.

Breast cancer rates dropped sharply in 2003, a year after many women stopped taking hormones. The sharpest drop occurred in tumors fueled by estrogen.

ANNUAL CHANGE IN BREAST CANCER INCIDENCE



Source: M.D. Anderson Cancer Center

Scientists knew that hormones could fuel the growth of estrogen-positive tumors, which carry receptors for estrogen on their cell surfaces. The hypothesis is that when women stopped taking menopausal hormones, tiny cancers already in their breasts were deprived of estrogen and stopped growing, never reaching a stage where they could have been seen on mammograms.

Other cancers may have regressed, making them undetectable. And, possi-

bly, without hormones, cancers that would have gotten started may never have grown at all.

"This could well be the study of the year in cancer," said Dr. Otis Brawley, director of the Georgia Cancer Center at Emory University. He added that it also might help explain why breast cancer rates were lower for black women than for white women — blacks, he said, were less likely to use hormones for menopause.

Dr. Brawley also said the findings might explain why cancer in black women was more lethal. Hormone-initiated cancers, he said, might be less deadly than those that arise on their own.

Candace Steele, a Wyeth spokeswoman, said in an e-mail message that "breast cancer is a complex disease and the causes are not known.

At this point, she said, "it is simply inappropriate to make any speculative statements" based on the analysis.

And, she added, "clearly, more studies are warranted."

Dr. Berry said that the biggest effect overall was seen in women ages 50 to 69. That, he added, is the group most likely to have been taking menopausal hormones. In them, the incidence of breast cancer, including the type that grows in response to estrogen and the one that does not, fell by 12 percent in 2003, the latest year for which data is available.

The findings of the new analysis were supported by a separate study in California. That study, published in the Nov. 20 issue of the Journal of Clinical Oncology, found an even bigger drop in rates in that state and a correspondingly bigger drop in hormone use starting in July 2002.

Other researchers, who saw Dr. Berry's analysis in advance of its presentation yesterday, said they found the hypothesis convincing.

Susan Ellenberg, a professor of biostatistics at the University of Pennsylvania, said the work was provocative. And, she added, "I certainly don't see any obvious thing that says, 'Oh, this can't be right,' or any obvious flaws."

Until 2002, as many as a third of American women over age 50 were

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taking menopausal hormones. The drugs could relieve symptoms like hot flashes, and were thought to protect against heart disease. Because the pills were known to slow bone loss, some women used them to prevent osteoporosis. Some women and doctors also believed, without any good evidence, that the pills could keep skin youthful, preserve memory and make women energetic.

Explaining the Decline

Overall, breast cancer rates fell by 7 percent in 2003. The steepest declines were for older women and for the kind of cancer that depends on hormones, consistent with a link between hormone therapy and cancer risk.

CHANGE IN BREAST CANCER INCIDENCE, 2000-2001 TO 2003

BY AGE

| | |
|----------|------|
| 40 to 49 | -1% |
| 50 to 59 | -11% |
| 60 to 69 | -11% |
| 70 to 79 | -7% |

BY TYPE OF TUMOR

| | |
|------------------------------------|-----|
| Growth depends on estrogen | -8% |
| Growth does not depend on estrogen | -4% |

Source: University of Texas M.D. Anderson Cancer Center

The use of estrogen to treat menopause took off in 1966, when a doctor, Robert Wilson, wrote the best-selling book "Feminine Forever" and flew across the country promoting it. He insisted that estrogen could keep women young, healthy and attractive. Women would be replacing a hormone they had lost at menopause just as diabetics replace the insulin their pancreas fails to make.

Before long, the menopause drugs, and in particular Prempro, from Wyeth, a combination of estrogen and progestins, became one of the most popular drugs in history.

The reversal of fortune came in July 2002 when the Women's Health Initiative was halted. Its accumulating data indicated that Prempro was associated with a slight increase in breast cancer and in

heart attacks, strokes and blood clots. The drug slightly decreased the risk of hip fractures and colon cancer, but those benefits were not enough to overcome its risks, the researchers said. Health authorities cautioned that similar pills must be regarded as having the same risks as Prempro until proven otherwise.

The very next year, 2003, the National Cancer Institute reported recently, there was a huge decline in breast cancer incidence. It was, Dr. Ravdin said, the largest decline for a single cancer in a single year that he was aware of. He and his colleagues wondered what was going on. The cancer kills an estimated 40,000 women a year and any decline in incidence can be important.

"We looked at all the possible explanations," Dr. Berry said. He ticked them off: less mammography screening. But there was no sign of that. Increased use of drugs like tamoxifen that can prevent breast cancer; no evidence of that.

"There was some notion that it might be statins, but that was essentially debunked," Dr. Berry said.

After July 2002, Dr. Berry said, the rate "dropped each month and it is exactly where you would expect it to be" if the declining use of menopausal hormones were the reason.

Dr. Barnett Kramer, the associate director for disease prevention at the National Institutes of Health, said that hormones were certainly the most plausible explanation for such an immediate effect on incidence. Most breast cancer is fueled by estrogen and studies have found that removing estrogen, with drugs like tamoxifen that block the hormone, sharply reduces breast cancer rates within a year.

'This could well be the study of the year in cancer,' a scientist says.

That was also the conclusion of Christina Clarke, an epidemiologist at the Northern California Cancer Center, and her colleagues, when they analyzed the cancer's rates in California. The investigators used data they had collected for a National Cancer Institute's

program and data from Kaiser Permanente, the health insurer.

Dr. Clarke said that they had data through 2004 and so could ask whether the decrease in cancer incidence in 2003 continued the next year. It did, she said, although it slowed somewhat, as might be expected.

The investigators found that the breast cancer incidence fell even more in California than in the rest of the country – the overall drop was 11 percent in 2003, compared with 7 percent nationally. And, Dr. Clarke said, more women in California also had been using hormone therapy than women in other states.

Kaiser Permanente's prescriptions for hormone combinations like Prempro fell by two-thirds in 2003 and prescriptions for estrogen alone dropped by one-third, Dr. Clarke and her colleagues reported. (Estrogen without progestin can cause cancer of the uterine lining so should only be used by women whose uteruses have been removed. While there is some question about whether estrogen alone increases breast cancer risk, the Women's Health Initiative did not find such an effect.)

'More studies are warranted,' cautions a drug company spokeswoman.

The heaviest users of hormone therapy were women in affluent places like Marin County, where high breast cancer rates had long troubled women and researchers. Women in those areas also largely abandoned the treatments after the 2002 report and their cancer rates declined accordingly, Dr. Clarke said.

Dr. Marcia Stefanick, a professor of medicine at Stanford University and chairwoman of the steering committee for the Women's Health Initiative, said she found the hormone argument persuasive and felt it helped clear up the mystery in Marin County.

"Everyone kept saying, What is it? What's in the environment?" she said. Now, she said, it is becoming clear. "The best explanation is hormone therapy."