Breast Cancer Decline Mirrors Fall in Hormone Use, Spurs Both Debate and Research

By Caroline McNeil

A decline in breast cancer incidence from 2002 to 2003 may stem from the sudden fall in postmenopausal hormone use in the same period, according to a study presented at the San Antonio Breast Cancer Symposium in December.

The finding garnered massive media attention for several days, but that was just the beginning of its impact. In the research community, it has fueled plans for more studies—further analyses, modeling studies, and closer scrutiny of ongoing surveillance data—as statisticians, epidemiologists, and clinicians seek to confirm the association and sort out its long-term implications.

The analysis, presented in San Antonio by Peter Ravdin, M.D., of the University of Texas M.D. Anderson Cancer Center in Houston, used data from the Surveillance, Epidemiology, and End Results (SEER) database showing that breast cancer incidence dropped by 7% from 2002 to 2003. Ravdin and his colleagues looked at the rate in a subgroup of women, those age 50–69 with estrogen receptor–positive disease who were most likely to be affected by hormone use. There they found a dramatic 12% drop in incidence.

Moreover, the decline began in mid-2002, apparently mirroring the drop in hormone use that occurred after release of the Women’s Health Initiative (WHI) findings in June of that year. About 30% of postmenopausal women had been taking hormones—mostly an estrogen–progesterone combination—before the WHI finding that this combination increased the risk of breast cancer. About half of them quit.

The researchers stress that their analysis does not prove cause and effect. But the magnitude of the decline is certainly persuasive, said lead author Donald Berry, Ph.D., who heads the division of quantitative sciences at M. D. Anderson.

“It’s huge, and that’s the most compelling thing,” he said.

The month-by-month data, in particular, are startling, Berry said. From July 2002 to December 2003, breast cancer rates fell an average of 1% a month for women with estrogen receptor–positive disease in the 50–69 age group. The declines were seen in all nine SEER regions of the country.

The authors say that their findings raise several new questions: How long will the effect last? Have the tumors stopped or just slowed? And what are the characteristics of those tumors that are affected? Might the drop be due to something other than the decline in hormone therapy use?

Statistical issues accompany these questions. Most notably, will the association be as strong once the SEER data are more mature? Brenda Edwards, Ph.D., who heads the surveillance research program at the National Cancer Institute, noted that the most recent 2003 numbers were not final because of normal delays in receiving some cancer cases; SEER adjusts for this delay as much as possible in its annual report, but the final numbers could differ from the delay-adjusted figures. Some recent changes in the way data are coded and the statistics are reported by the SEER registries could also have affected the data, she said.

Duration of the Effect?

Especially anticipated is the SEER 2004 incidence rate for breast cancer, which will provide more evidence on trends for the crucial period after 2002.

At least 3 years’ worth of incidence figures are needed to show a trend, Edwards said, and at this point, the three data points available are 2001, 2002, and 2003. The decline over those years, although large, does not reach statistical significance. As a result, there is much interest in what the 2002–2003–2004 data will show. Edwards said that SEER analysts are poised to look at hormone receptor status and age as they go over the 2004 figures, due in April.

Another key question is what the apparent association means about the development of breast cancer. Is it biologically plausible that the effects of stopping hormone therapy could show up just 1 month later?

It is possible, Ravdin said in his presentation, if the early effect of hormone therapy is to slow the growth of existing tumors. Christine Berg, M.D., agreed, noting that clinicians can see the shrinkage of palpable tumors in some women almost immediately upon withdrawal of hormones. “I think that’s what happened in the first few months after the WHI findings,” said Berg, who heads the early-detection research group at NCI. “The cancer is there but below the threshold of detection. So the presentation of malignancy has been delayed.”

If tumor growth is only delayed and not stopped, the rates could go up again, Berry said. “Longer follow-up will be important for understanding whether tumors have been stopped or slowed. If their growth has only been slowed, then rates can be expected to bounce back at some point.”
There is also the possibility that tumors not detected in 2003 have particular characteristics, Berry noted. “Some of these tumors that are now going under the radar may turn out not to be aggressive. Or they may be the ones that are exquisitely sensitive to SERMs [selective estrogen receptor modulators],” drugs used to prevent breast cancer.

**Another Cause?**

In fact, one big remaining question is if not hormones what else might be driving, or contributing to, the decline in breast cancer incidence. The possibilities include a drop in mammography rates, the use of the SERMs raloxifene and tamoxifen, and the growing use of nonsteroidal anti-inflammatory agents and statins, which may also be preventive.

Mammography rates fell between 2000 and 2003 with the largest drop, 3.2%, occurring among women age 50–69. Also, about 5% of postmenopausal women are using SERMs to prevent breast cancer. Berry said that changes in these and other factors are not great enough, even taken together, to explain the magnitude of the decline in breast cancer incidence.

But others are not yet ready to say that hormone therapy use is the overwhelming reason for the drop in incidence. “I think there are probably several factors contributing to this decline,” Berg said.

“I also am not closing the door on any prevention effect of tamoxifen and raloxifene,” said Leslie Ford, M.D., associate director of NCI’s division of cancer prevention.

Modeling studies could help sort out the contributions of various factors. Berry said that plans are under way to include hormone therapy, mammography rates, SERM use, and other factors in a new model, now being planned by the Cancer Intervention and Surveillance Modeling Network (CISNET). The network is an NCI-funded consortium that uses computer models to evaluate the effect of various factors on cancer incidence and mortality. New treatments, such as trastuzumab, will also be plugged into the new model.

The San Antonio analysis also has heightened interest in long-term follow-up of the WHI participants who were originally randomized to either hormone therapy or placebo. Ford said that the investigators, who have funding for follow-up, are now developing proposals to specifically address the new data.

The flurry of new research related to hormone use and breast cancer incidence includes analyses of some state cancer registry data. One study in California, which predated the San Antonio presentation, found that breast cancer incidence fell 10% among Kaiser Permanente members in Northern California age 50–74 at the same time that prescriptions for estrogen–progesterone hormone therapy dropped 68%. This decline in incidence continued in 2004 in California as a whole, including the Kaiser catchment area, said lead author Christina Clarke, Ph.D., of the Northern California Cancer Center in Fremont. The study appeared in November in the *Journal of Clinical Oncology*.

At least one other state, Minnesota, is also beginning to look at its breast cancer incidence data in association with declines in hormone therapy use. Carin Perkins, Ph.D., of the Minnesota Cancer Registry, said that she is still trying to pin down hard data on hormone therapy use. But judging from the breast cancer incidence rates in the state, she does not think that hormone therapy use alone can account for the drop. Incidence in Minnesota began declining in 2000. And, although the decline accelerated between 2002 and 2003, preliminary data for 2004 show it leveling off. Perkins also pointed out that women age 70 and older in Minnesota showed no increase in risk during the 1990s but the same decrease in incidence from 2000 to 2003 as was seen in younger women.

Other states and groups will probably be asking questions about breast cancer incidence and hormone therapy use in the wake of the San Antonio news.

“I think there are any number of people now looking at their data,” NCI’s Edwards said.