Hormone Replacement Therapy for Breast Cancer Survivors: An Answered Question?

This is part of an occasional series that recalls some of the stories reported 10 years ago in the News section of the Journal.

Ten years ago, there were a handful of observational studies that suggested that hormone replacement therapy (HRT) has a protective effect against recurrence in women who had had breast cancer—despite the general sense that HRT shouldn’t be given to these women for fear that the hormones would increase the likelihood of breast cancer recurrence. An article in a medical journal that called for clinical trials of HRT in breast cancer survivors set off months of debate in the scientific community and the public (see News, Vol. 87, No. 14, p. 1047, “ERT for Breast Cancer Survivors: A Hot Debate Runs On Little Data”).

Today, published results from three randomized trials confirm that caution is warranted, and most recommendations now advise against HRT use for these women.

Despite experimental evidence that hormones could make tumors grow in test tubes, at that time, a decade ago, “people thought that estrogen was good for you,” said JoAnne Zujewski, M.D., head of breast cancer therapeutics in the Clinical Investigations Branch at the National Cancer Institute. However, “there’s a danger in going from epidemiologic evidence to practice, no matter how strong,” she said.

A meta-analysis of studies of HRT use in breast cancer survivors, which appeared in the May issue of Breast Cancer Research, concluded that the data from the observational studies should be considered “essentially uninformative” with respect to the safety of HRT in breast cancer survivors and that only the randomized trials are likely to provide reliable estimates of safety.

Three randomized trials were started in the 1990s. A U.S. trial, headed by Rena Vassilopoulou-Sellin, M.D., of the University of Texas M. D. Anderson Cancer Center in Houston, had difficulty recruiting patients willing to take HRT. The data were eventually treated as an observational study, which found no increased risk of breast cancer recurrence among HRT users. Two randomized trials were begun in Sweden in 1997. The Hormonal Replacement Therapy After Breast Cancer—Is It Safe? (HABITS) trial randomly assigned women previously treated for breast cancer to be treated with HRT or best treatment without hormones. But in December 2003, with only 434 women recruited, the trial was stopped. After a median follow-up of 2.1 years, 26 women in the HRT group had a new breast cancer event compared with seven in the control group.

The second Swedish trial—the Stockholm trial, which was similar to HABITS but used an HRT regimen that differed in composition and timing—was stopped at the same time. The trial (see JNCI, Vol. 97, No. 7, p. 533) found no association between HRT use and breast cancer recurrence after a median follow-up of 4.1 years. Despite the mixed results, the important point is that none of the randomized trials supported the observational data that found that HRT protected against breast cancer recurrence, said Nananda Col, M.D., associate professor of medicine at Brown University Medical School and Rhode Island Hospital in Providence, and lead author on the recent meta-analysis. “I don’t think there’s any valid argument in persisting in doing any of these studies,” she said.

Combined with the negative results of the Women’s Health Initiative, most U.S. physicians and their patients have gotten the message that long-term HRT can be harmful, said Zujewski. “The things they were trying to treat with hormone replacement therapy we now have better measures for,” she said, such as bisphosphonates for the prevention of osteoporosis and aspirin or statins for cardiac health.

However, European women may be getting a different message, particularly from European menopause societies, said Col. “[These societies] really believe in the observational data,” and “they honestly don’t believe in the risk,” she said, calling it “very disturbing.”

And researchers continue to publish observational studies, Col pointed out. A consumer “is going to be grossly misled” by the volume of the data showing that HRT is safe for breast cancer survivors, but she will not be able to assess the quality of that data, she said.

—Sarah L. Zielinski