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Special Issue Released December 20, 2006

This e-newsletter presents reviews of important, recently published scientific articles selected by members of The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS. Disclosures are available on request. Oversight for this e-newsletter is by Robert A. Wild, MD, PhD, MPH, Chair-Elect, 2006-2007 NAMS Professional Education Committee. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Late-breaking news with comments by Leon Speroff, MD, Francine Grodstein, ScD, and Margery Gass, MD

Reduced hormone therapy use might be cause of steep decline in breast cancer cases

Ravdin PM, Cronin KS, Howlader N, Chlebowski RT, DA Berry DA. News release from the University of Texas M.D. Anderson Cancer Center. December 14, 2006.

A report presented December 14, 2006, at the 29th San Antonio Breast Cancer Symposium in Houston shows a 7% drop in US breast cancer rates. The analysis suggests a link between the decline in breast cancer and hormone therapy (HT) use.

In 2003, breast cancer incidence in the United States dropped sharply, and this decline may be due to the fact that millions of older women stopped using HT in 2002. Investigators from the M.D. Anderson Cancer Center, National Cancer Institute (NCI), and Harbor UCLA Medical Center report that the steepest decline was 12%, occurring in women aged 50 to 69 years diagnosed with estrogen receptor-positive breast cancer. The researchers therefore concluded that as many as 14,000 fewer women were diagnosed with breast cancer in 2003 than in 2002 (when

an estimated 203,500 new cases of breast cancer were diagnosed according to the American Cancer Society).

Researchers analyzed data from 9 regions across the country that contribute to the NCI's Surveillance Epidemiology and End Results (SEER) database, the source of national cancer incidence statistics.

But the report stresses that because the analysis was based solely on population statistics, the reasons why incidence declined is not certain.

Comment. The recent, well-publicized reports highlight the currently most important unanswered question: Does postmenopausal HT cause an increase in breast cancer or do the epidemiologic data reflect an impact of HT on preexisting tumors? A short latent period between discontinuation of HT and a reduction in prevalence is a striking feature of these reports. This agrees with the uniform findings in case-control and cohort studies of an increase in breast cancer risk only in current users, with a rapid reduction after cessation of treatment. The current reports are consistent with breast cancer statistics derived from the area around Geneva, Switzerland, from another point of view. Beginning in 1997, the peak of breast cancer incidence in the Geneva area increased in a

younger group of women (60–64 years), and the increase occurred only in stage I and stage II disease with estrogen receptor–positive tumors in hormone users.¹

These effects of HT are also in harmony with the multiple reports of better outcomes in hormone users diagnosed with breast cancer because of better-differentiated tumors,^{2, 3} an effect that can be interpreted as a beneficial consequence.

Another finding that is consistent with an effect on preexisting tumors is the fact that not a single study thus far has reported a risk increase for noninvasive disease. If HT were initiating (causing) new tumor formation, one would expect to see an increase in in situ disease.

Even the M.D. Anderson Cancer Center authors pointed out that their data most likely primarily reflect existing cancers just below the detection limit in 2002 that slowed or stopped their growing. Thus, a serious question is raised: What will the statistical data show in the coming years? Will some of the preexisting tumors be overcome by body defenses and disappear? If tumors emerge later, will they be advanced in stage and grade with poorer outcomes? At this point in time, we must recognize that HT could be having a favorable effect on breast cancers.

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Comment. This and other reports¹ indicate that breast cancer incidence rates have declined noticeably in recent years. During the same period, use of postmenopausal HT also decreased markedly, due largely to the findings of the Women’s Health Initiative (WHI) that the benefits of HT do not outweigh the risks.² These parallel trends may or may not be related—such descriptive data cannot establish causes and effects, and it is not possible to discern whether the breast cancer trends may be the result of reduced hormone use or some other, unidentified factor.

Regardless of the true cause of the changes in breast cancer rates in the United States, it is not news that HT increases the risk of breast cancer. Almost a decade ago, the Collaborative Group on Hormonal Factors in Breast Cancer³ collected data from virtually every existing observational epidemiologic study of HT and breast cancer. Based on over 52,000 breast cancer cases in 51 investigations, they found that each year of HT use elevated breast cancer rates by 2.3% (95% confidence interval [CI], 2.1%-3.4%), with a relative risk of 1.35 after 5 years of use (95% CI, 1.21-1.49). However, after stopping HT, there was no significant difference in the rate of breast cancer for those who had taken versus those who had not taken hormones. Then, 3 years ago, the WHI randomized controlled study confirmed that combined use of estrogen with progestin increased breast cancer risk by 24% ($P < 0.001$).⁴ Together, these are convincing data, with or without noticeable national trends in either HT or breast cancer rates.

The best, and only real news here is that breast cancer incidence can be changed in a favorable direction. All of our research efforts now should focus on identifying clear, modifiable, and completely safe means of further decreasing breast cancer rates.

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Comment. The astounding news that a 7% overall decline in invasive breast cancer may be related to a decline in hormone therapy prescriptions deserves our attention and scrutiny. It hardly seems plausible that a marked decline in HT prescriptions starting precipitously in July 2002¹ would effect a reduction in breast cancer incidence 1.5 years later. Many of us remember learning it takes years for breast cancer to develop to the stage where it is detectable by mammogram or palpation. Key questions include:

Is the source reliable? Data and analyses were derived from 9 registry sites of the SEER program of the NCI that first started collecting data during 1973-1975. SEER has a strict quality-control component and is considered a gold standard for cancer registries worldwide. The effect was seen in all 9 registries. Other sources of data included the National Center for Health Statistics and the HMO Research Network, a consortium of 15 HMO with established health-research capabilities.

Are there other substantiating data? In November 2006, the *Journal of Clinical Oncology* published a letter to the editor from the Research Division of Kaiser Permanente that reported an 11% reduction in breast cancer in the catchment area of northern California between the years 2001 and 2003.² For 2004, the

incidence rates were even lower than in 2003. During the same time frame, estrogen therapy (ET) and estrogen-progestogen therapy (EPT) were discontinued by 36% and 68% of users, respectively. Within this catchment, Marin County has been noted to have had a higher than average use of HT as well as a higher than average rate of breast cancer, especially ER+/PR+ breast cancers.³ Other factors besides use of HT that may be associated with urban, affluent lifestyle and the increased risk for ER+/PR+ breast cancer include delayed childbearing, fewer children, and alcohol consumption.⁴ There has been no known reported change in these behaviors over the last few years.

In a presentation at the 2006 NAMS Annual Meeting, it was reported that the greatest decrease in breast cancer was in the number of ER+/PR+ breast cancers. There was little change in other breast cancers. The greatest decrease also occurred in the women aged 50 to 69, those most likely to be using HT.

Is the finding biologically possible? Cancer theory has long held that there can be cancerous cells in the body throughout life and that the body has numerous ways of eliminating them. There is still ongoing discussion about the fate of carcinoma in situ of the breast. It may be that the body can rid itself of many cancerous cells until the growth rate of the cells outstrips the body's various defense mechanisms. Recent reports have included both initiation and promotion mechanisms of estrogen with regard to breast cancer.^{5,6} Removal of the growth promoter could result in an immediate stagnation, if not apoptosis, of tumor cells.

Do other related models add plausibility? The natural decline in estrogen at menopause decreases the rate of increase in breast cancer with an obvious change in the slope of the graph occurring around age 50 on a semilog graph. The increased rate of breast cancer among HT users in the *Lancet* meta-analysis was very similar to that seen with a delay in menopause of one year.⁷ The decrease in invasive breast cancers in the National Surgical Adjuvant Breast and Bowel Project P-1 Study evaluating tamoxifen for

prevention of breast cancer was seen in the first year.⁸ Annual rates of reduction beginning with the first year of the study were 33%, 55%, 39%, 49%, 69%, and 55%. These results were presumably achieved by competitive blockade of the estrogen receptors, effectively a rapid decline in estrogen resulting in a rapid decline in breast cancer within the first year.

Are there other potential hypotheses that would explain the findings? Various hypotheses could explain the results. A decline in screening mammograms and breast examinations in the office may have resulted in missed diagnoses, although reported declines in office visits may not translate into a decline in annual examinations. The fact that the greatest decline in mammograms occurred in the women aged 50 to 64 (3.2% vs. 1.0% in all women over age 40) raises the concern that it may have been the women who discontinued HT who thought they could also discontinue or skip a year of mammograms once they had stopped their hormones.

In 1998, raloxifene was introduced to the market. The tamoxifen prevention trial was published in 1998. Combined calcium and vitamin D use was being promoted for bone health and has been reported to be associated with a decline in breast cancer.^{9,10} Nonsteroidal anti-inflammatory drugs were increasingly used during this period of time. They also appear to be associated with a reduction in breast cancer in some reports.¹¹ Did the gradual increase in use of these products converge in 2003 to produce an abrupt effect? One might expect a more gradual effect as most increases in product sales occurred over a 2- to 3-year interval. A major weight loss epidemic or a marked decline in alcohol consumption could have had a beneficial effect on breast cancer incidence, but there seems to be little evidence to support these behaviors as the explanation.

Future directions. Ravdin et al have presented an intriguing observation that deserves further exploration. They cautioned that studies of this nature cannot prove causality. Prior to accepting their hypothesis as the most credible, more data are needed to demonstrate that alternative

hypotheses, or a combination thereof, are not viable. It is good news to see a decline in breast cancer. Understanding why it occurred would advance the science and potentially give women a way to reduce their personal risk. The 2004 SEER data could strengthen or weaken the case, as would data from other countries. In the future we will have the analysis of the breast cancer data from the participants in the WHI EPT arm who discontinued their study drug in July 2002.

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