SPECIAL REPORT

The Decrease in Breast-Cancer Incidence in 2003 in the United States

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SUMMARY

An initial analysis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries shows that the age-adjusted incidence rate of breast cancer in women in the United States fell sharply (by 6.7%) in 2003, as compared with the rate in 2002. Data from 2004 showed a leveling off relative to the 2003 rate, with little additional decrease. Regression analysis showed that the decrease began in mid-2002 and had begun to level off by mid-2003. A comparison of incidence rates in 2001 with those in 2004 (omitting the years in which the incidence was changing) showed that the decrease in annual age-adjusted incidence was 8.6% (95% confidence interval [CI], 6.8 to 10.4). The decrease was evident only in women who were 50 years of age or older and was more evident in cancers that were estrogen-receptor–positive than in those that were estrogen-receptor–negative. The decrease in breast-cancer incidence seems to be temporally related to the first report of the Women's Health Initiative and the ensuing drop in the use of hormone-replacement therapy among postmenopausal women in the United States. The contributions of other causes to the change in incidence seem less likely to have played a major role but have not been excluded.

Major changes in cancer incidence and death rates, as detected in cancer-registry data, provide unique opportunities to examine questions related to the cause, prevention, detection, and treatment of cancer. In a preliminary report, we suggested that such a major change in breast-cancer incidence occurred in 2003 in the United States.[1] In contrast, the 1990s saw an increase in the annual age-adjusted incidence of breast cancer by an average of about 0.5% per year, a rise that was particularly evident among women who were 50 years of age or older[2] (Fig. 1). Changes in reproductive factors, in the use of menopausal hormone-replacement therapy, in mammographic screening, in environmental exposures, and in diet have all been proposed to explain the trend. Of these factors, only the use of hormone-replacement therapy changed substantially between 2002 and 2003.

In this report, we provide additional data from 2004 that show little change in breast-cancer incidence between 2003 and 2004. A comparison of incidence rates in 2001 with those in 2004 (omitting the years in which the incidence was in the process of changing) showed that the decrease in annual age-adjusted incidence was 8.6% (95% CI, 6.8 to 10.4).

The decrease in breast-cancer incidence began in mid-2002 and occurred shortly after the highly publicized series of reports from the randomized trial of the Women's Health Initiative, which reported a significant increase in the risks of coronary heart disease and breast cancer associated with the use of estrogen–progestin combination therapy.[3] By the end of 2002, the use of hormone-replacement therapy had decreased by 38% in the United States, with approximately 20 million fewer prescriptions written in 2003 than in 2002.[4,5]

The analyses we report here used information from the SEER Program of the National Cancer Institute (NCI) collected from nine cancer registries reporting on 9% of the U.S. population. Trends in the incidence of female breast cancer were age-adjusted to the standard population in the year 2000 and were adjusted for reporting delays. Joinpoint (version 3.0) statistical software (http://srab.cancer.gov/joinpoint/) was used for fit-

ting trends over time and to evaluate when changes in trends occurred. The number of patients with unknown estrogen-receptor status changed from 15% in 2001 to 8% in 2004; to adjust for this change, multiple imputation was used to generate estrogen-receptor values for missing data.

Comparison of incidence rates in 2001 with rates in 2004 (omitting the years in which the incidence was rapidly changing) showed that the decrease in annual age-adjusted incidence was evident only in women who were 50 years of age or more. During that period, there was an increase of 1.3% (95% CI, −3.1 to 5.8) in incidence for women below the age of 50 years, a decrease of 11.8% (95% CI, 9.2 to 14.5) for women between the ages of 50 and 69 years, and a decrease of 11.1% (95% CI, 7.9 to 14.2) for women 70 years of age or older.

For women between the ages of 50 and 69 years, the decrease was more evident in those with estrogen-receptor–positive tumors (14.7%; 95% CI, 11.6 to 17.4) than in those with estrogen-receptor–negative tumors (1.7%; 95% CI, −4.6 to 8.0). The decreases were similar for localized disease (11.3%; 95% CI, 8.0 to 14.6) and more advanced disease (13.6%; 95% CI, 9.2 to 17.9) and were evident in primary breast cancers (13.7%; 95% CI, 11.0 to 16.4) but not in contralateral second primary or later breast cancers, for which there was a nonsignificant increase (9.4%; 95% CI, −1.6 to 20.5).

Figure 2A shows the quarterly, age-adjusted incidence rates of breast cancer in women between the ages of 50 and 69 years, categorized according to estrogen-receptor status. The data for change in trend were examined with the use of Joinpoint statistical software. Changes in trend in mid-2002 and mid-2003 were evident for all patients and for patients with estrogen-receptor–positive tumors but not for those with estrogen-receptor–negative tumors. However, the low incidence of estrogen-receptor–negative tumors limited the statistical ability to detect a change in trend. For all patients, the quarterly changes in rate were an increase of 0.08% (95% CI, −0.60 to 0.77) in the first time interval, a decrease of 4.43% (95% CI, −12.66 to 4.75) in the next time interval defined by Joinpoint analysis, and a decrease of 0.04% (95% CI, −1.56 to 1.50) in the last time interval.

What might have been responsible for the sharp decline in breast-cancer incidence, followed by a relative stabilization at a lower incidence rate?

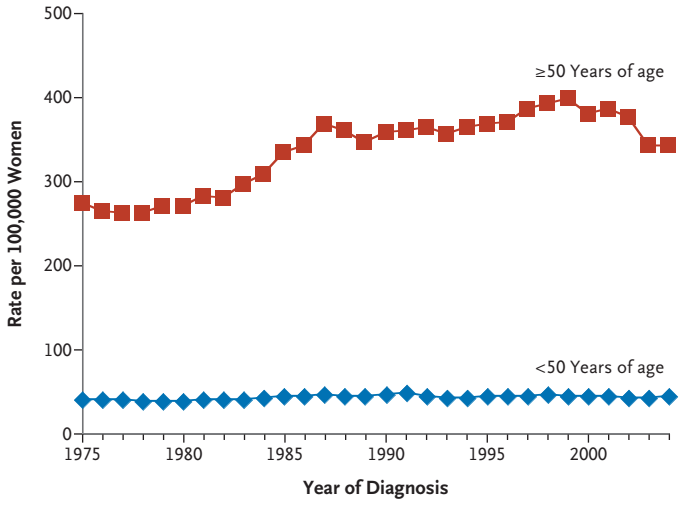

Figure 1. Annual Incidence of Female Breast Cancer (1975–2004).
Data are from nine of the NCI's SEER registries. SEER sites include San Francisco, Connecticut, Detroit (metropolitan area), Hawaii, Iowa, New Mexico, Seattle–Puget Sound, Utah, and Atlanta (metropolitan area).

One possibility is a SEER reporting flaw, which seems unlikely. The trend for a decrease in incidence in 2003 was evident in all nine SEER registries, there was no statistically significant change in the incidence of cancer other than breast cancer in women during this period, and the lower rates continued in 2004. Could the change have been related to a major decrease in the rate of screening mammography? Although a decrease of 3.2% in this rate was reported for women between the ages of 50 and 65 years for 2003, as compared with that for 2000,[6] such a change would seem insufficient to explain the observation. A change in screening patterns specific to women who formerly received hormone-replacement therapy is also a possibility. For example, if women who discontinued hormone-replacement therapy also stopped receiving mammograms, an apparent decrease in incidence could result. Although visits to physicians would probably decrease among women who discontinued hormone-replacement therapy, no published data are available showing a substantial decrease in mammographic screening in such women. Another possible explanation is that a decrease in incidence is expected in a heavily screened population, similar to that reported for prostate cancer. No sudden decrease has yet been reported for breast-cancer incidence in heavily screened populations.

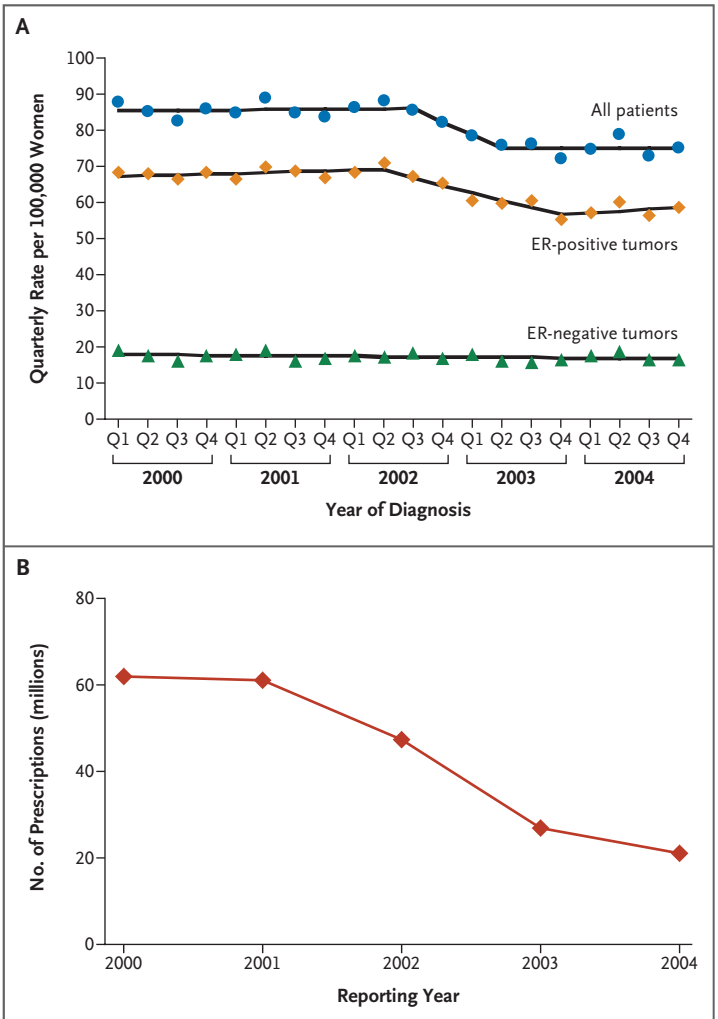

Figure 2. Quarterly Incidence of Breast Cancer in Women between the Ages of 50 and 69 Years, According to Estrogen-Receptor (ER) Status, and the Number of Prescriptions for Hormone-Replacement Therapy (2000–2004).

In Panel A, data are from nine of the NCI's SEER registries, with trends modeled with regression-analysis statistical software (Joinpoint). Trends were age-adjusted to the standard population in the year 2000 and were adjusted for reporting delays. Panel B shows the number of prescriptions reported in the United States for the combined estrogen–progestin preparation Prempro and the conjugated equine estrogen Premarin, according to year.

One of the arguments against changes in mammographic screening as a primary reason for the decline is that the effect was mainly on estrogen-receptor–positive tumors. Breast cancers that are detected on mammography are more likely to be estrogen-receptor–positive than are tumors not detected on mammography (80% vs. 70%),[7] but the difference in the percentages according to estrogen-receptor status is minor. Thus, a drop in screening would result in an approximately equal decrease in estrogen-receptor–positive and estrogen-receptor–negative tumors, an expectation that differed from our findings.

Discontinuation of hormone-replacement therapy could have caused a decreased incidence of breast cancer by direct hormonal effects on the growth of occult breast cancers, a change that would have been expected to affect predominantly estrogen-receptor–positive tumors. If the decrease in breast-cancer incidence had been associated with discontinuation of hormone-replacement therapy, the rapidity of change suggested that clinically occult breast cancers stopped progressing or even regressed soon after discontinuation of the therapy. The hypothesis that hormone withdrawal can rapidly influence the growth of breast cancer is supported by anecdotal reports of regression of breast cancer after discontinuation of hormone-replacement therapy.[8] A cessation of such therapy was associated with a reduction in the proliferative index of breast-cancer cells within 1 month in women with estrogen-receptor–positive tumors but not in those with estrogen-receptor–negative tumors in the same setting,[9] and responses within weeks after estrogen deprivation have been seen in clinical trials of neoadjuvant hormones. An early effect of tamoxifen was seen in the Breast Cancer Prevention Trial, in which the cumulative rates of invasive breast cancer in the tamoxifen group and the placebo group appeared to diverge within the first few months and differed statistically at the end of the first year.[10] An analysis of 51 epidemiologic studies showed that an elevated risk of breast cancer after the use of hormone-replacement therapy had largely if not wholly disappeared within 5 years after discontinuation of therapy, although a more detailed analysis of the time course of changes in risk within this period was not presented.[11]

Notably, the change in the use of hormone-replacement therapy also followed a time course that was similar to the decline in breast-cancer incidence, with a sharp decline followed by a relative stabilization at a new, lower level. The total number of prescriptions for the two most commonly prescribed forms of hormone-replacement therapy in the United States — Premarin and Prempro — had their steepest declines starting in 2002 and particularly in 2003 (62 million pre-

scriptions in 2000, 61 million in 2001, 47 million in 2002, 27 million in 2003, 21 million in 2004, and 18 million in 2005)[12] (Fig. 2B).

Other medications can influence the incidence of breast cancer. These drugs include tamoxifen and raloxifene, and there is some evidence for beneficial effects of nonsteroidal antiinflammatory drugs, statins, and calcium and vitamin D supplements. However, none of these agents were used by a substantial portion of postmenopausal women or showed substantial change in use during the period from 2000 to 2004.[12,13] Therefore, the drugs are unlikely candidates for causing the decrease in incidence.

When the results of the Women's Health Initiative hormone trial were announced, women were asked to discontinue their study medications (placebo or hormone) but were encouraged to continue undergoing annual mammography. These women continue to be followed for clinical outcome, and a report of follow-up of the combined estrogen-plus-progestin trial is anticipated later this year. This report will provide the highest level of evidence concerning the influence of cessation of hormone-replacement therapy on the incidence of breast cancer. Other observers have noted a decline in breast-cancer incidence after 2002. A report from a subgroup of California registries also showed a sharp decrease in breast-cancer incidence in 2003 and suggested that it extended into 2004.[14] A recent analysis of national cancer data by Jemal et al.[15] showed a decline in the incidence of breast cancer in 2003 but did not comment on its clinical relevance. The joinpoint in that study was done with annual (rather than quarterly) data. Annual rates obscure within-year trends, in this case within years 2002 and 2003. In addition, the statistical method used by Jemal et al. cannot select the final year in a range (in this case, 2003) as demonstrating a discontinuity.

It is possible that the ultimate understanding of the effect of cessation of hormone-replacement therapy will be complex; it will probably depend on more than one mechanism and will be affected in different ways by various forms of postmenopausal hormone-replacement therapy. The time course of the decrease in breast-cancer incidence is of both practical and theoretical interest. Our data suggest that much of the decrease in breast-cancer incidence that is attributable to changes in the use of hormone-replacement therapy has already occurred, but important questions remain. Can we expect only a delay in the appearance of clinically detectable tumors, with no reduction in long-term incidence, or will there be a long-term reduction? A change in the hormonal milieu may have slowed the growth of tumors slightly or temporarily. If this is the case, as the use of hormone-replacement therapy stabilizes, breast-cancer incidence should rise again. Alternatively, the change in hormonal milieu may have a more profound effect, similar to that of hormonal adjuvant therapy.[16]

We believe that the data are most consistent with a direct effect of hormone-replacement therapy on preclinical disease, but this conclusion does not rule out some contribution from changes in screening mammography. In any case, attempts to understand the rapid reduction in incidence using theoretical models of breast-cancer evolution and the effects of screening and treatment — such as those of the NCI's Cancer Intervention and Surveillance Modeling Network[17] — may lead to new insights into the development and prevention of breast cancer.

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