

A Decline in Breast-Cancer Incidence

TO THE EDITOR: In their Special Report on the decrease in the incidence of breast cancer in the United States in 2003, Ravdin et al. (April 19 issue)¹ state that a 2002 report by the Women's Health Initiative (WHI)² noted a significant increase in the risk of breast cancer associated with the use of estrogen–progestin combination therapy by postmenopausal women. However, the increased risk of breast cancer in the WHI study did not reach statistical significance. The increased risk of breast cancer in the follow-up report³ barely achieved statistical significance, and no increased risk was found among WHI study subjects taking estrogen alone, as compared with those who did not receive hormone-replacement therapy.⁴

If the decreased incidence of breast cancer were due to a decrease in stimulation of subclinical estrogen-receptor–positive tumors, as proposed by Ravdin et al., the decreased incidence should have been confined to small, early breast cancers. It was not.

Moreover, the incidence of breast cancer increases with increasing age through menopause, and the majority of postmenopausal breast cancers are estrogen-receptor–positive. If the authors' postulate is correct, the incidence of breast cancer in this population of women, most of whom do not receive hormone-replacement therapy, should decrease with age. It does not.

Avrum Z. Bluming, M.D.

University of Southern California
Los Angeles, CA 90033
av@lafn.org

1. Ravdin PM, Cronin KA, Howlander N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007;356:1670-4.
2. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
3. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243-53.
4. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12.

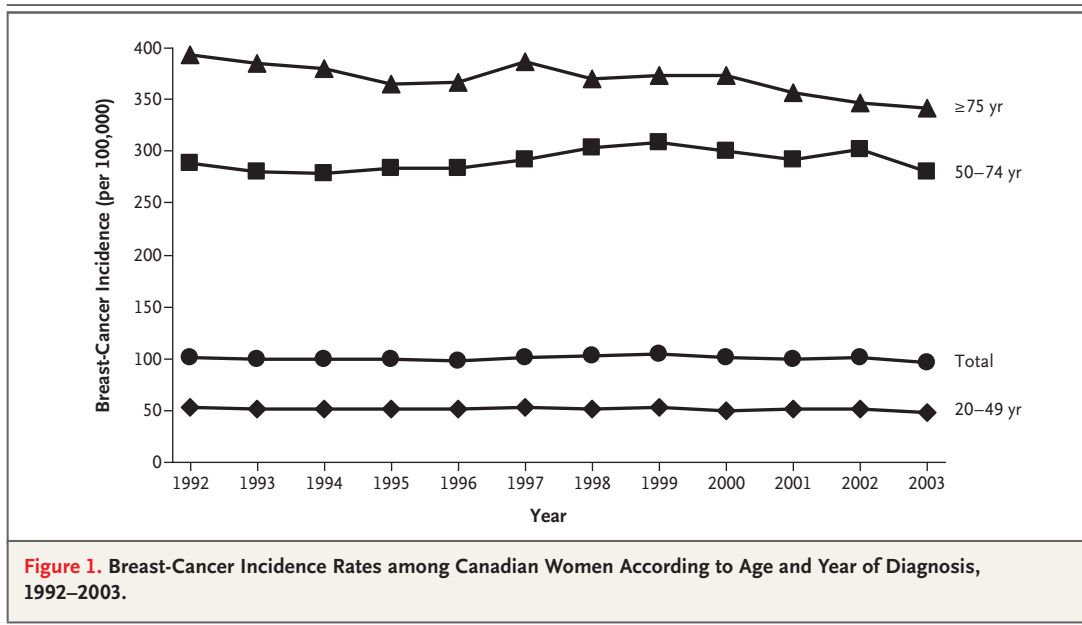
TO THE EDITOR: Recognizing that breast cancer is sensitive to both estrogen (stimulation) and anti-estrogen (inhibition) agents, Ravdin and colleagues believe that the data “are most consistent with a direct effect of hormone-replacement therapy on preclinical disease.” However, several factors argue against this conclusion. First, the incidence of estrogen-receptor–positive breast cancer appeared to peak in 1999, and a downward trend appeared to begin in 2000, not in 2002. Second, from 2002 to 2003, there was a 38% reduction in the use of hormone-replacement therapy but only a 15% reduction in the incidence of estrogen-receptor–positive breast cancer among women between the ages of 50 and 69 years. Third, all the women who had estrogen-receptor–positive breast cancer must have had occult disease before the cancer was detected. The establishment of cause and effect with epidemiologic data is difficult, at best. One might wonder whether hidden covariables were responsible for the changes in incidence seen in data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries.

Answers to three questions may be enlightening: What is the incidence of estrogen-receptor–positive breast cancer in women who never received hormone-replacement therapy, what is the incidence in those who have discontinued hormone-replacement therapy, and what is the incidence in those who continue to receive hormone-replacement therapy?

Gerald J. Elfenbein, M.D.

Boston University School of Medicine
Boston, MA 02118
gerald.elfenbein@verizon.net

TO THE EDITOR: Ravdin et al. report that between 2002 and 2003 there was a 6.7% decrease in the incidence of breast cancer in the United States. During the same period in Canada, prescription rates for hormone-replacement therapy decreased by 26.8%,¹ and the age-adjusted standardized incidence rate for breast cancer decreased by 5.6%.² In Canada, breast-cancer rates peaked in 1999 and



since then have been declining among women of all ages (Fig. 1). However, the decline was significant only for women 75 years of age or older; the annual change from 1999 to 2003 for all women was -1.8% ($P=0.06$); for women 20 to 49 years old, -1.5% ($P=0.19$); for those 50 to 74 years old, -1.7% ($P=0.13$); and for those 75 years of age or older, -2.6% ($P=0.01$). These results suggest that the use of hormone-replacement therapy may have had a role in the decrease in breast-cancer incidence rates. However, the fact that the rates for women in all three age groups started to decline before 2002 suggests that other factors were also involved.

Erich V. Kliewer, Ph.D.

Alain A. Demers, Ph.D.

Zoann J. Nugent, Ph.D.

CancerCare Manitoba
Winnipeg, MB R3E 0V9, Canada
erich.kliewer@cancercare.mb.ca

1. The ups and downs of HRT. Montreal: IMS Health, Canada, 2006. (Accessed July 12, 2007, at http://www.imshealth.com/vgn/images/portal/cit_40000873/6/1/79032750Insights01En061127.pdf.)

2. Public Health Agency of Canada. Cancer surveillance on-line.

(Accessed July 12, 2007, at http://dsol-smed.phac-aspc.gc.ca/dsol-smed/cancer/index_e.html.)

TO THE EDITOR: In contrast to the results reported by Ravdin et al., from 2002 to 2005, breast-cancer incidence rates were stable in Norway¹ and Sweden,² despite a sharp decline in the use of hormone-replacement therapy. Sales data for hormone-replacement therapy and the incidence of cancer during this period among women in four Norwegian counties who were between the ages of 50 and 69 years are shown in Figure 1 (next page). In this population, the breast-cancer incidence rate and the rate of mammographic screening have been stable since screening was introduced in 1996–1997.³ From 2002 to 2004, the decrease in the number of women receiving hormone-replacement therapy per 100,000 postmenopausal women was similar to the decrease in the United States. Our results do not support the suggestion by Ravdin et al. that a large reduction in the use of hormone-replacement therapy was associated with a rapid and large reduction in the breast-cancer incidence rate.

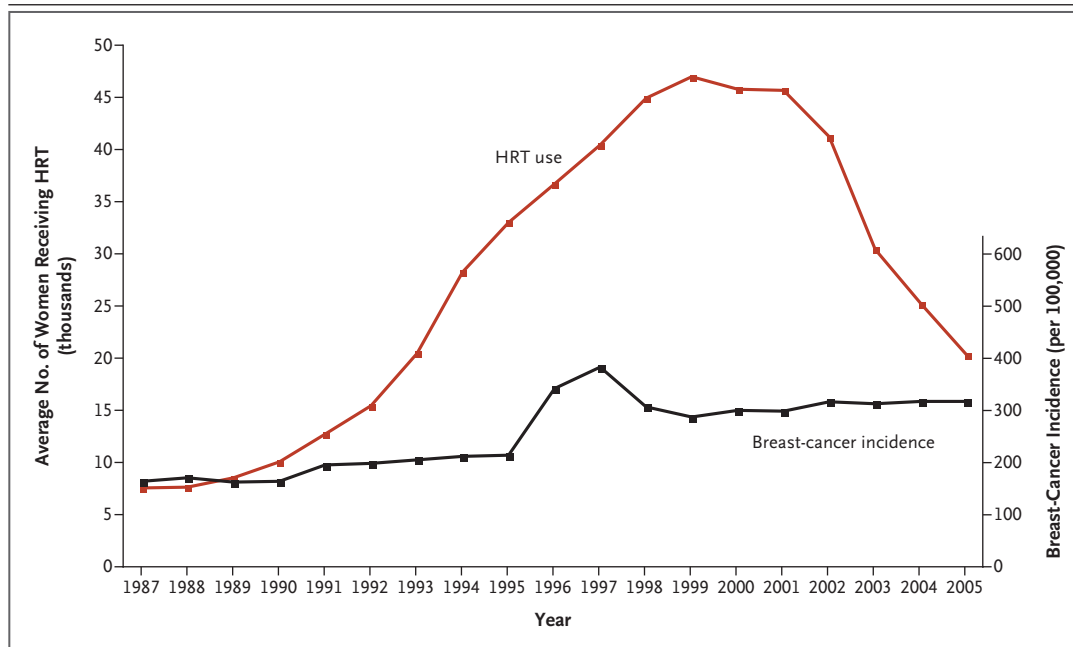


Figure 1. Hormone-Replacement Therapy (HRT) and Breast-Cancer Incidence among Women between the Ages of 50 and 69 Years in Four Norwegian Counties.

The population of the four counties represented in the graph constitutes 40% of the 4.6 million people living in Norway. The red curve indicates the average number of women receiving HRT per year, based on the sales of defined daily doses of HRT divided by 365 days. The black curve shows the breast-cancer incidence. Mammographic screening was introduced in 1996–1997 in this population.

Per-Henrik Zahl, M.D., Ph.D.

Norwegian Institute of Public Health
N-0403 Oslo, Norway
per-henrik.zahl@fhi.no

Jan Mæhlen, M.D., Ph.D.

Ullevål University Hospital
N-0407 Oslo, Norway

1. Cancer in Norway 2005. Oslo: Cancer Registry of Norway (Kreftregisteret), 2006.
2. Cancer incidence in Sweden 2005. Stockholm: National Board of Health and Welfare (Socialstyrelsen), 2007.
3. Zahl P-H, Strand BH, Mæhlen J. Breast cancer incidence in Norway and Sweden during introduction of nationwide screening: prospective cohort study. *BMJ* 2004;328:921-4.

TO THE EDITOR: Another explanation for the results reported by Ravdin et al. is surgical removal of preinvasive ductal carcinoma in situ (DCIS). Mammographic screening accelerated after 1985, with frequent detection of DCIS; the removal of this lesion usually prevents invasive breast cancer. Since the decline in the incidence of breast cancer began 15 years after mammographic screening became widespread, such a drop fits well, in both timing

and magnitude, with the presumed delay between the detection of DCIS and the subsequent appearance of invasive cancer. We believe that most of the decline in the incidence of breast cancer is the result of screening.

Blake Cady, M.D.

24 Walnut Pl.
Brookline, MA 02445
bcady123@comcast.net

Maureen A. Chung, M.D.

Rhode Island Hospital
Providence, RI 02903

James S. Michaelson, Ph.D.

Massachusetts General Hospital
Boston, MA 02114

TO THE EDITOR: Ravdin et al. did not examine whether regional changes in the incidence of breast cancer correlated with regional changes in the use of hormone-replacement therapy. If so, such a finding would strengthen the causal hypothesis that the use of hormone-replacement therapy is associated with an increased risk of breast cancer. Cal-

ifornia differs from most populations in that the population-based cancer incidence and data regarding risk factors are collected for individual counties. We recently analyzed data from all 58 counties in California to see whether regional changes in the incidence of breast cancer between 2001 and 2004 correlated with regional changes in the use of hormone-replacement therapy.¹

We obtained data on rates of invasive female breast cancer that were specific for age, race or ethnic group, and county from the population-based California Cancer Registry, and we obtained population estimates from the National Center for Health Statistics. Data on the use of hormone-replacement therapy were obtained from the 2001 and 2003 California Health Interview Surveys.² We limited the study to non-Hispanic white women between the ages of 45 and 74 years because the incidence of breast cancer varies widely according to race or ethnic group and because this age group had the highest prevalence of use of hormone-replacement therapy. For all California counties, we obtained estimates of the prevalence of the use of hormone-replacement therapy in 2001 and 2003 and the age-adjusted incidence of breast cancer per 100,000 women in 2001 and in 2004 (the most recent year for which data were available). To measure the correlation between a change in breast-cancer incidence (ΔI) and a change in the prevalence of the use of hormone-replacement therapy (ΔP), we used weighted linear regression, with weights that were proportional to the inverse of the variance of ΔI .

Regression results suggested that each 1% decrease in the prevalence of the use of hormone-replacement therapy was associated with a decrease in breast-cancer incidence of 3.1 cases per 100,000 women ($P < 0.001$). The correlation coefficient between ΔP and ΔI was 0.75, and it indicated that 57% of the variation in ΔI was explained by variation in ΔP .

Although other, unmeasured changes in the population may explain the observed changes in the incidence of breast cancer, these data provide further evidence that population-level changes in the use of hormone-replacement therapy between 2001 and 2003, when media attention surrounding the WHI results was widespread, may be responsible for a substantial population-level decline in the incidence of breast cancer between 2001 and 2004.

Anthony S. Robbins, M.D., Ph.D.

California Cancer Registry
Sacramento, CA 95815
arobbins@ccr.ca.gov

Christina A. Clarke, Ph.D.

Northern California Cancer Center
Fremont, CA 94538

Dr. Clarke reports receiving consulting fees from attorneys preparing litigation regarding hormone therapy. No other potential conflict of interest relevant to this letter was reported.

1. Robbins AS, Clarke CA. Regional changes in hormone therapy use and breast cancer incidence, California, 2001–2004. *J Clin Oncol* (in press).
2. California Health Interview Survey. (Accessed July 12, 2007, at <http://www.chis.ucla.edu>.)

TO THE EDITOR: Ravdin et al. do not mention that the recent decrease in the incidence of breast cancer was not observed in black women. Between 2001 and 2004, the delay-adjusted breast-cancer incidence rate for women 50 years of age or older increased from 313.8 to 327.0 per 100,000 person-years among black women, as compared with a decrease from 408.8 to 358.8 per 100,000 person-years among white women. Among U.S. women who became menopausal between 1970 and 1992, 33% of black women and 51% of white women reported the use of hormone-replacement therapy; the duration of use was at least 10 years for 11% of black women and 20% of white women.¹ Among 14,468 black and 5793 white postmenopausal women enrolled in the Southern Community Cohort Study² from community health centers from 2002 to 2007, 31% of blacks and 51% of whites reported ever receiving hormone-replacement therapy; 12% of blacks and 18% of whites reported current use. Similar reductions in the use of hormone-replacement therapy after July 2002 were reported for both black women and white women.^{3,4} The breast-cancer trend since 2001 among black women does not appear to support a role of reduced use of hormone-replacement therapy in the recent decrease in breast cancer among women in the United States.

Lisa B. Signorello, Sc.D.

Robert E. Tarone, Ph.D.

International Epidemiology Institute
Rockville, MD 20850
bob@iei.ws

1. Brett KM, Madans JH. Use of postmenopausal hormone replacement therapy: estimates from a nationally representative cohort study. *Am J Epidemiol* 1997;145:536-45.
2. Signorello LB, Hargreaves MK, Steinwandel MD, et al.

Southern Community Cohort Study: establishing a cohort to investigate health disparities. *J Natl Med Assoc* 2005;97:972-9.

3. Wei F, Miglioretti DL, Connelly MT, et al. Changes in women's use of hormones after the Women's Health Initiative estrogen and progestin trial by race, education, and income. In: Vogt TM, Wagner EH, eds. *Health care systems as research platforms: the cancer research network*. Journal of the National Cancer Institute monographs. No. 35. Bethesda, MD: Oxford University Press, 2005:106-12.

4. Hillman JJ, Zuckerman IH, Lee E. The impact of the Women's Health Initiative on hormone replacement therapy in a Medicaid program. *J Womens Health (Larchmt)* 2004;13:986-92.

THE AUTHORS REPLY: Multiple factors affect the incidence of breast cancer: mammographic screening, demographic and lifestyle changes, and the use of exogenous hormones. Understanding the interplay among these influences is a challenge. The WHI study¹ shows that even a single factor can be complex — for example, both the type of hormone-replacement therapy and its duration of use are important. Given this complexity, various trends in the incidence of breast cancer within population subgroups is not surprising. These differences — essentially natural experiments — may provide insights into how to use hormone-replacement therapy in the safest and most beneficial fashion.

Recent data such as those from California (reported by Robbins and Clarke²), Canada (noted by Kliewer et al.), and Germany (reported by Katalinic and Rawal³) provide additional support for our hypothesized connection between the use of hormone-replacement therapy and the incidence of breast cancer. Modeling of intracounty changes in breast-cancer incidence and the prevalence of the use of hormone-replacement therapy in California suggest that 57% of the variation in incidence is explained by variation in the use of hormone-replacement therapy. This analysis provides an answer to Elfenbein's statement about nonproportionality between the use of hormone-replacement therapy and the incidence of breast cancer.

We are not surprised by the absence of an effect on breast-cancer incidence among black women, an issue raised by Signorello and Tarone, since the prevalence of use of hormone-replacement therapy in this group was lower than that among white women. Moreover, the statistical power to identify an effect is lower among blacks because they are a subgroup of the population. Bluming suggests that older postmenopausal women are less likely to receive hormone-replacement therapy than are younger postmenopausal women and that its

discontinuation in older women might therefore be expected to have less of an effect. On the other hand, since these women have received hormone-replacement therapy for a longer period than have younger women, the effect of discontinuation could still be substantial.

We cannot fully explain the absence of a change in breast-cancer incidence in Norway. One possibility is that there are only 170,000 women between the ages of 50 and 69 years in the Norwegian database, so statistical power is an issue. Also, in Norway, the major forms of hormone-replacement therapy are based on estradiol rather than conjugated estrogens. The effects on breast cancer and the effect of the discontinuation of hormone-replacement therapy may well differ for these preparations.

Several writers mention that the decrease in the incidence of breast cancer began in 1999. Cady et al. propose that early detection of DCIS may eventually lower the overall incidence, thus explaining at least part of the decrease, and that this decrease may have started in 1999. In a similar vein, Jemal et al.⁴ propose that the modest decrease beginning in 1999 is consistent with saturation of mammographic screening. However, neither of these factors accounts for the sharp drop within a single year. Although there is no conclusive proof of a causal link between coincident sharp declines in the use of hormone-replacement therapy and the incidence of estrogen-receptor-positive breast cancer, we have yet to see a credible alternative explanation.

Peter M. Ravdin, M.D., Ph.D.

M.D. Anderson Cancer Center
Houston, TX 77030

Kathleen A. Cronin, Ph.D.

National Cancer Institute
Bethesda, MD 20892

Rowan T. Chlebowski, M.D., Ph.D.

Harbor-UCLA Medical Center
Los Angeles, CA 90502

1. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243-53.

2. Robbins AS, Clarke CA. Regional changes in hormone therapy use and breast cancer incidence, California, 2001-2004. *J Clin Oncol* (in press).

3. Katalinic A, Rawal R. Decline in breast cancer incidence after decrease in utilization of hormone replacement therapy. *Breast Cancer Res Treat* (in press).

4. Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Res* 2007;9:R28.