Declines in Invasive Breast Cancer and Use of Postmenopausal Hormone Therapy in a Screening Mammography Population

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Whether a recent large decline in use of postmenopausal hormone therapy after the release of the Women's Health Initiative findings in July 2002 and/or a decline in screening mammography use is related to a recently reported decline in breast cancer incidence in the United States is controversial. We prospectively collected data from four screening mammography registries from January 1997 through December 2003 for 603 411 screening mammography examinations performed on women aged 50–69 years. Of these women, 3238 were diagnosed with breast cancer within 12 months of a screening examination. We calculated quarterly rates of self-reported current postmenopausal hormone therapy use and of invasive breast cancer, ductal carcinoma in situ (DCIS), and estrogen receptor (ER)–positive invasive breast cancer adjusted for age, registry, and time between screening examinations. All statistical tests were two-sided. Between 2000 and 2002 and between 2002 and 2003, annual rates of postmenopausal hormone therapy use declined by 7% and 34%, respectively (P_{trend}<.001 for both). Between 2000 and 2003, annual rates of invasive cancer declined by 5% (P_{trend} =.003). Between 2001 and 2003, annual rates of ER-positive invasive breast cancer declined by 13% (P_{trend} =.002). Rates of DCIS were stable during the study period. Our finding of a statistically significant decline in the rate of ER-positive invasive breast cancer in a screening mammography population after the start of a concomitant substantial decline in postmenopausal hormone therapy use suggests that a decline in screening mammography rates is unlikely to account for the recent decline in US breast cancer incidence.

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Release of the Women's Health Initiative findings in July 2002, which reported an increased risk of breast cancer in the estrogen plus progestin postmenopausal hormone therapy arm (1), has been followed by a rapid decline in the use of postmenopausal hormone therapy (2–4). During the same period, the US National Cancer Institute (NCI)–sponsored Breast Cancer Surveillance Consortium (BCSC) reported an increased risk of estrogen receptor (ER)–positive invasive tumors among long-term users of estrogen and progestin, but not of estrogen only, compared with nonusers (5). A recent report of data from the NCI Surveillance, Epidemiology, and End Results (SEER) program (6) demonstrated an 11.8% annual decline in breast cancer incidence and a 14.7% decline in ER-positive invasive breast cancer from 2001 to 2004 in women aged 50–69 years. However, this analysis did not account for differences in screening mammography use over time. Although it has been suggested that the decline in breast cancer incidence observed in the SEER data is due to the recent declines in use of postmenopausal hormone therapy (7), mammography screening rates among women aged 40 years and older have also decreased during the same time period (8). Women undergoing routine screening mammography have a two- to threefold higher breast cancer detection rate than those who are not screened (9–11). Thus, the proportion of women in the population undergoing routine screening mammography will influence population-based estimates of breast cancer incidence. No studies have examined breast cancer incidence and postmenopausal hormone therapy use in the same population of women while adequately taking into account surveillance with screening mammography.

This study was designed to examine whether parallel declines in postmenopausal hormone therapy use and rates of breast cancer are present among women undergoing routine screening mammography. We pooled data from four BCSC (http://breastscreening.cancer.gov) mammography registries: San Francisco Mammography Registry, Group Health's Breast Cancer Surveillance Project, Vermont Breast Cancer Surveillance System, and New Hampshire Mammography Network. These registries collect information on mammography examinations performed in their defined catchment areas and link women annually in their registry to a state tumor registry or to a regional SEER program to obtain population-based cancer data. Some registries also link to pathology databases. Each registry obtains annual Institutional Review Board approval for consenting processes or a waiver of consent to enroll participants and perform data linkages for research purposes. All registries have Federal Certificates of Confidentiality that protect research participants' identities.

The study included 603 411 screening examinations performed between January 1,

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CONTEXT AND CAVEATS

Prior knowledge

The incidence of breast cancer in the United States has dropped in the last few years, but whether the drop is related to a decline in the use of hormone therapy or to a decline in screening mammography has not been clear.

Study design

Data were collected prospectively from four registries on more than 600000 screening mammography examinations conducted from 1997 through 2003 on women aged 50–69 years. Trends in annual rates of breast cancer and postmenopausal hormone therapy use, calculated quarterly, were compared.

Contribution

Between 2000 and 2003, annual rates of postmenopausal hormone therapy use declined, as did annual rates of invasive breast cancer. Between 2001 and 2003, annual rates of estrogen receptor–positive invasive breast cancer also declined.

Implications

The observation of a decline in the rate of estrogen receptor–positive breast cancer in a population of women receiving screening mammography suggests that the recent decline in breast cancer incidence in the United States is unlikely to be due to a decline in screening mammography rates. The decline in use of postmenopausal hormone therapy use is a more likely contributor to the breast cancer decline.

Limitations

Statistical constraints imposed on the analysis of temporal changes could have caused errors in trend tests. Breast cancer rates were not determined separately among never and former users of hormone therapy.

1997, and December 31, 2003, on 232212 women aged 50–69 years who had had a prior mammography examination within the 9–30 months preceding their first screening examination in the study and who did not have a history of breast cancer or breast implants. We excluded screening examinations after December 2003 to ensure that cancer data would be complete for at least 12 months following all screening mammography examinations. All analyses were performed according to dates of mammography examinations.

We collected demographic information and a self-reported breast health history at the time of each screening examination using a questionnaire that included questions on history of hysterectomy and current postmenopausal hormone therapy use. Women were considered to be current users of postmenopausal hormone therapy at a screening examination if they reported using postmenopausal hormone therapy at that visit. For each screening examination, we examined for reported use of postmenopausal hormone therapy on the prior mammography examination and then classified pairs of examinations based on reported postmenopausal hormone therapy use at those two examinations. We classified pairs of examinations into four groups: nonusers did not use postmenopausal hormone therapy on either examination; discontinuers used postmenopausal hormone therapy on the first examination but stopped before the next examination; initiators did not use postmenopausal hormone therapy on the first examination but started before the next examination; and continuous users used postmenopausal hormone therapy on both examinations.

Women were considered to have breast cancer if invasive carcinoma or ductal carcinoma in situ (DCIS) was diagnosed within 12 months of a screening examination. Invasive cancers were categorized by ER status (positive, negative, unknown/not done), with 15.3% having unknown/not done ER status. Women with lobular carcinoma in situ only were not considered to have breast cancer.

We used marginal standardization (12,13) to estimate adjusted quarterly rates of current postmenopausal hormone therapy use, breast cancer (invasive cancer or DCIS), and ER-positive, ER-negative, and ER-missing invasive cancer per 1000 screening examinations. For each outcome, we fit a logistic regression model that included indicator variables denoting quarterly time intervals and that was adjusted for mammography registry, a quadratic effect of a woman's age, and time between screening examinations (9–18 months versus 19–30 months to stratify by annual versus biennial screeners, respectively). For each quarterly time interval, we calculated the weighted average of postmenopausal hormone therapy use and breast cancer rates estimated from the logistic regression models for each combination of age, registry, and time between screening examinations, weighted by the proportion of women in the study with the same combination of values in the year 2000 to ensure consistent age, registry, and screening distributions over time.

Table 1. Distribution of study population in 2000*

Characteristic	N (%)
Age, y	
50–54	31511 (35)
55–59	23769 (27)
60–64	18214 (20)
65–69	15632 (18)
Time between screening examinations, mo	
9–18	63501 (71)
19–30	25625 (29)

* Distributions of age and time between screening examinations in the year 2000 were used to standardize rates for all analyses.

To estimate trend lines, we modeled the quarterly rates of postmenopausal hormone therapy use and breast cancer using logistic regression with a piecewise linear time effect with two knots that define the locations of the changes in the regression line, adjusting for age, registry, and time between screening examinations. This approach results in a trend line with three different slopes for defining change in rates over time (on the log-odds scale). We selected knots for each rate by calculating the value of the likelihood function for all possible combinations of change points that satisfied the following conditions: the first knot was located at any quarter between January 1998 and January 2001, the second knot was located at any quarter between January 2001 and January 2003, and knots were at least a year apart, so that at least four points would be available to estimate each slope. We chose the two knots that maximized the likelihood function under these conditions. We then used marginal standardization, as described above, to estimate time trends on the original scale. We tested for linear time trends (on the logit scale) using likelihood ratio tests.

We calculated frequency and median time between screening examinations by type of postmenopausal hormone therapy use to determine screening patterns in all women aged 50–69 years undergoing screening mammography in the BCSC from 1997 through 2003 regardless of screening history. We used SAS 9.1 (Cary, NC) for statistical analyses. All statistical tests were two-sided.

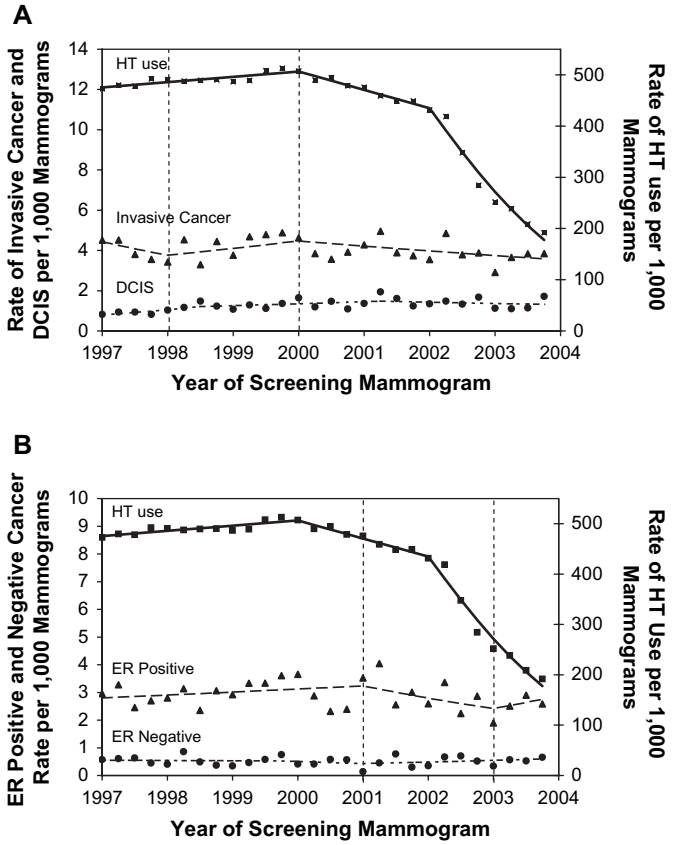

Fig. 1. Rates of current postmenopausal hormone therapy (HT) use and breast cancer in the Breast Cancer Surveillance Consortium. Rates are given per 1000 screening examinations and are standardized to the age, mammography registry, and time between screening examinations distribution of the study population in 2000. Breast cancer status was determined in the 12-month period following all screening examinations. Trend lines were estimated from piecewise linear logistic regression models with two knots. **A**) Rates of invasive cancer, ductal carcinoma in situ (DCIS), and postmenopausal HT use. **B**) Rates of estrogen receptor (ER)–positive and -negative cancer and postmenopausal HT use. **Vertical lines** indicate knot placement for invasive cancer in (**A**) and for ER-positive cancer in (**B**). Trends were determined across quarters. The *P* values from trend tests were as follows: *P*<.001 for decrease in HT use after 2000; *P* = .003 for decrease of invasive breast cancer between 2000 and 2003; *P* not statistically significant for rates of DCIS; *P* = .002 for decrease of ER-positive invasive breast cancer between 2001 and 2003.

Women aged 50–59 years accounted for 62% of the study population in 2000, with the majority having mammography examinations 9–18 months apart (Table 1). A total of 35% of the study population from 1997 through 2003 had one screening mammography examination, 22% had two examinations, and 43% had three or more examinations.

The BCSC population consisted of 51% nonusers of postmenopausal hormone therapy, 35% continuous users, 8% initiators, and 6% discontinuers. Median time between screening examinations did not differ by postmenopausal hormone therapy use (nonusers, 14.0 months; continuous users, 13.6 months; initiators, 14.3 months; discontinuers, 14.7 months).

Observational studies published in early 2000 (14,15) linked use of estrogen and progestin combinations to greater breast cancer risk than use of estrogen alone. We found that the prevalence of postmenopausal hormone therapy use started to decline at about the same time, with an annual decline of 7% from 2000 to 2002 (P_{trend}<.001, Fig. 1, A). An even larger decline was observed after release of the Women's Health Initiative study, with an annual 34% decline from 2002 to the last quarter of 2003 (P_{trend}<.001, Fig. 1, A). In women with a uterus, who were likely to be using estrogen plus progestin (5), postmenopausal hormone therapy use declined 38% annually from 2002 to the last quarter of 2003; among women without a uterus, who were likely to be using estrogen only (5), the decline was 25% annually over this period (both P_{trend}<.001, Fig. 2).

The rate of invasive breast cancer decreased from 1997 to 1998 (P_{trend} = .02), increased from 1998 to 2000 (P_{trend} = .03), and then started to decline again in 2000 at an annual rate of 5% between 2000 and 2003 (P_{trend} = .003) (Fig. 1, A). The rate of DCIS increased by 32% from 1997 to 1998 (P_{trend} = .09) but then stabilized (P_{trend} = .37; Fig. 1, A). The rate of ER-positive invasive cancer was stable until 2001 and then declined 13% annually from 2001 to 2003 (P_{trend} = .002; Fig. 1, B). A small but not statistically significant (P_{trend} = .31) increase in ER-positive disease after the first quarter of 2003 reflects only 9 months of data, which is too few data points to assess a meaningful trend. Rates of ER-negative invasive cancer from 2000 to 2003 and invasive breast cancer with missing ER status from 2001 to 2003 were stable and unchanged over the study period (P_{trend} = .18 and *P* = .19, respectively).

Use of estrogen and progestin therapy for 5 or more years is a relatively modest breast cancer risk factor that increases invasive breast cancer risk 24% (1) and ER-positive disease 72% (5) compared with non-use of postmenopausal hormone therapy (1). Thus, a decline in use of estrogen and progestin therapy would need to be large in a population to result in a sizeable decline in ER-positive invasive breast cancer. We observed a statistically significant 13% annual decline in the rate of ER-positive invasive breast cancer after the start of a large concomitant decline in postmenopausal hormone therapy use among women aged 50–69 years undergoing routine screening mammography, suggesting that the decline in postmenopausal therapy use has contributed to the decline in ER-positive invasive breast cancer.

A large decline in use of estrogen and progestin therapy could potentially result in either an increase or a decrease in breast cancer incidence. Postmenopausal estrogen and progestin therapies are associated with an increase in mammographic breast density, which decreases when therapy is discontinued (16–18). Increased mammographic breast density among women taking postmenopausal hormone therapy has been associated with decreases in the sensitivity and specificity of mammography

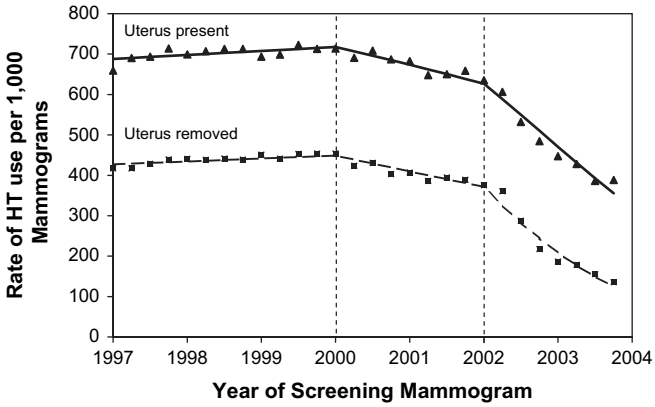

Fig. 2. Rates of current postmenopausal hormone therapy (HT) use among women with a uterus (surrogate for estrogen and progestin use) and without a uterus (surrogate for estrogen use) in the Breast Cancer Surveillance Consortium. Rates are given per 1000 screening examinations and are standardized to the age, mammography registry, and time between screening examinations distribution of the population in 2000. Trend lines were estimated from piecewise linear logistic regression models with two knots. **Vertical lines** indicate knot placement for HT use. $P<.001$ for trend across quarters in decrease of HT use among women with and without a uterus after 2000.

(5,19,20), with increases in minimal detectable tumor size (21) and with higher rates of stage II and higher breast cancer compared with those in nonusers (5). Cessation of postmenopausal hormone therapy could make existing tumors that were previously obscured by high breast density more visible and easier to detect by mammography, resulting in a short-term increase in breast cancer incidence. On the other hand, estrogen and progestin may act synergistically to promote tumorigenesis and more rapid tumor growth (22,23). Thus, the recent declines in postmenopausal hormone therapy use could result in a decrease in breast cancer incidence by halting or slowing hormone-related tumorigenesis such that, among former users of postmenopausal hormone therapy, some tumors may not grow to a sufficiently large size to be visible on mammography, some may regress completely, and some may grow so slowly that diagnosis is delayed for several years.

Another factor that could contribute to a decrease in breast cancer incidence is a decline in screening mammography. Mammography rates fell between 2000 and 2003, with the largest drop, 3.2%, occurring among women aged 50–69 years (24). These declines in mammography use have persisted, with a 6.8% decline observed between 2000 and 2005 for women aged 50–64 years (25). One would expect an immediate decline in early-stage invasive breast cancer with a decline in screening mammography because many nonpalpable cancers would go undetected. If women are less inclined to undergo routine screening mammography after they stop taking postmenopausal hormone therapy, the result could be a decrease in diagnoses of early-stage invasive breast cancer. We have no information on women who stopped postmenopausal hormone therapy and subsequently stopped undergoing mammography because BCSC registries capture postmenopausal hormone therapy use only in women undergoing mammography. However, a decline in mammography use is unlikely to account for the decline in breast cancer rates reported here because we restricted the study population to screened women. The fact that we did not observe a difference in DCIS rates or in median time between screening examinations by use of postmenopausal hormone therapy also suggests that changes in mammography utilization are unlikely to explain the decline in breast cancer rates. Moreover, one would expect a stable rate of breast cancer in routinely screened women unless risk of breast cancer decreased due to large changes in the prevalence of breast cancer risk factors, as use of postmenopausal hormone therapy did in our study population.

An increase in the use of tamoxifen for primary prevention of breast cancer could also contribute to a decrease in breast cancer incidence, particularly because there is ongoing benefit from treatment even after discontinuation of therapy (26). However, tamoxifen use is unlikely to have contributed much to the recent decline in breast cancer incidence because postmenopausal women seldom discuss or receive preventive therapy, even if they are at high risk for breast cancer (27,28). Reproductive factors are relatively weak risk factors, and there is no evidence that there have been large changes in the prevalence of these factors over time to account for the recent decline in breast cancer incidence. Finally, the finding that breast cancer rates declined after a decline in postmenopausal hormone therapy use could be a chance result, but this seems improbable given that the primary change we observed is a decline in ER-positive tumors, the type of tumor that is increased among users of postmenopausal estrogen and progestin therapy (5).

The observation that breast cancer risk among former users of postmenopausal hormone therapy does not become similar to that of never users of a similar age until 2–4 years after use has stopped (14,29) suggests that breast cancer risk decreases slowly among former postmenopausal hormone therapy users. Our results support this hypothesis in that the 13% annual decline in ER-positive invasive cancer that we observed in our surveillance population beginning in 2001 was more gradual than the decline in use of postmenopausal hormone therapy that occurred over the same period. One report of data from the SEER program results showed an annual decline of 14.7% in ER-positive invasive breast cancer incidence when comparing rates in 2001 with 2004 (6), and another reported a 9.1% decline between 2002 and 2003 (30), similar to our results.

We used an analytic approach that assumes that there are only two change points (knots) in rates over time, which is consistent with observed trends in use of postmenopausal hormone therapy and breast cancer over time. For trend tests, we picked knot locations that resulted in the best fit to the observed data. This may have increased the type I error rates for trend tests between change points because we did not account for possible uncertainty in knot location or number. We do not think this is a major concern, however, because the comparisons of primary interest are highly statistically significant and

consistent with published reports (6,30). We could not calculate breast cancer rates among never users and former users separately to investigate how quickly rates of breast cancer decline among former users.

Our results suggest that a decline in postmenopausal hormone therapy use has contributed to the decline in breast cancer incidence in the United States and that the small decline in screening mammography observed in the United States is unlikely to explain the national declines in breast cancer incidence. Based on an estimated 211 300 breast cancer cases in 2003—75% of these diagnosed in postmenopausal women, 85% of them ER-positive, and an annual decline of 13% in ER-positive disease—the impact of declining use of postmenopausal hormone therapy could account for an estimated 17 500 fewer ER-positive invasive breast cancer cases annually among women aged 50–69 years. Women aged 50–69 years who require estrogen and progestin to manage menopausal symptoms should be encouraged to use postmenopausal hormone therapy for the shortest time possible to minimize the chance of an increase in breast cancer risk. Measuring rates of early- and advanced-stage breast cancer and compliance with recommended screening mammography intervals in former, continuous, and never users of postmenopausal hormone therapy will be important to understanding the long-term influences of declines in postmenopausal hormone therapy use and mammography screening on breast cancer incidence.

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Notes

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