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

The recent, sudden declines in breast cancer incidence in the United States (1,2) are unprecedented, and their origins are of great relevance to breast cancer prevention. To date, large population-based declines in breast cancer have been reported not only for the United States but also for Germany and New Zealand, although not for Norway, Sweden, and the Netherlands. Because hormone therapy (HT) use declined substantially in all of these areas after 2002, it has been suggested (3) that this variation in worldwide incidence trends weakens the conclusions of Kerlikowske et al. (2) and others that HT cessation was the major cause of the declines. We wish to note some relevant mathematical and biological considerations.

First, consider a change in the prevalence ($P_i$) from $P_1$ to $P_2$, of a risk factor with relative risk = RR. The percent change in incidence (PCI) that would be expected is

$$PCI = \frac{(P_2 - P_1)(RR - 1)}{P_1(RR - 1) + 1}.$$

Suppose that the change in $P$ is $-65\%$. It should be noted that the same $-65\%$ change could represent a change from 13% to 5% ($P_1 = 0.13, P_2 = 0.05$) or from 38% to 13% ($P_1 = 0.38, P_2 = 0.13$). Let us also suppose that RR = 1.25. Under these conditions, PCI = $-2\%$ if $P_1 = 0.13$, but PCI = $-6\%$ if $P_1 = 0.38$. Clearly, it is not the percent change in $P$ that drives changes in incidence but the absolute change in $P$.

Regarding the impact of changing relative risk, let us assume that $P$ changed from 38% to 13% but that in one scenario RR = 1.25 and in the other RR = 1.07. Here, PCI = $-2\%$ if RR = 1.07, but PCI = $-6\%$ if RR = 1.25. Again, it is clear that PCI is lower when the relative risk is lower.

In addition to duration of use, the relative risk associated with HT use may also depend on the specific HT formulation. These considerations of initial prevalence and relative risk may very well explain the very different changes in breast cancer incidence that have been observed in the United States, where the percent change in HT prevalence after 2002 was $-66\%$ (4), versus other countries that have also experienced substantial declines in HT use. For example, in the Netherlands the percent change in HT use from 2001 to 2005 was $-42\%$, and yet there has been no perceptible change in age-adjusted breast cancer incidence (5). HT use in the Netherlands appears to have peaked at approximately 13%, versus approximately 38% in the United States (6). Dutch women appear to have used HT for short durations (<5 years), whereas long-term use was the norm in the United States. Epidemiologic data suggest that the risk for breast cancer with short-term hormone use is much lower (RR = 1.07) (7).

For the Netherlands, the formula above would predict a PCI of close to zero, which agrees with the cancer surveillance data. Thus, these apparently counterfactual data from other countries with substantial declines in HT do not argue against the hypothesis that population-level changes in HT use in the United States and other countries may largely account for recent declines in breast cancer.

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References


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Notes

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Kerlikowske et al. (1) suggest that decreased use of hormone replacement therapy (HRT) led to decreased breast cancer incidence in a mammographically screened study population. Using sophisticated modeling techniques, the authors were able to show statistical significance in changing HRT and breast cancer diagnosis rates. However, the clinical conclusions reached...
by the authors are poorly justified if not contradicted by their findings.

As the authors note, HRT use plummeted in the study group population between 2002 and 2004, presumably due to the public announcement of the Women’s Health Initiative results in 2002 (2). Visual inspection of the study data (see their fig. 1, A and B) shows that this dramatic drop in HRT use occurred concomitantly with a drop in breast cancer incidence so small that it is virtually imperceptible to the naked eye. Although the rate of HRT use dropped from 50% in 2000 to less than 20% at the end of 2003, the actual rate of invasive breast cancer (solid triangles) hovered virtually unchanged at approximately 4 cases per 1000 mammograms between 1997 and 2004 (see their fig. 1, A). Had the dashed lines tracing the linear logistic regression model not been provided, the reader would be hard pressed to conclude that there was any relationship at all between the use of HRT and breast cancer incidence—the differences are simply too subtle and variable over time.

The data on estrogen receptor (ER)-positive invasive cancers are similarly problematic (see their fig. 1, B). The raw data (solid triangles) hover around 3 cases per 1000 mammograms during the entire study period, i.e., between 1997 and 2004. Although the authors describe a 13% decline in ER-positive cancers between 2001 and 2003 based on their model, visual inspection shows that this finding hinges on two high data points early in 2001 and a single low data point at the beginning of 2003 and is undermined by a subsequent rise in incidence later in 2003. The 13% rate would be lower and possibly statistically insignificant had a later time cutoff ("knot") been chosen. Although no difference in the incidence of ER-negative invasive cancers was found during this same period, ER-negative cancers represented less than 25% of the invasive breast cancers in the study population (<1 ER-negative case per 1000 mammograms). The number of ER-negative cases was therefore too small to show a change in incidence, even with sophisticated statistical modeling techniques.

Mammographically detected ER-positive cancers in postmenopausal women are, on average, clinically favorable cancers that change slowly over time, taking years to develop. The idea that a preexisting ER-positive cancer would rapidly disappear within a year of HRT discontinuation is biologically implausible. Were discontinuation of HRT to affect preexisting hormone-sensitive cancers, one would expect a corresponding change in incidence to take years to become demonstrable. Because no lag was observed between decreased HRT use and decreased breast cancer incidence in this study, other mechanisms to explain the findings should be considered.

If HRT causes hormone-sensitive cancers to “light up” and be more easily detected on mammograms, then discontinuation of HRT would reduce breast cancer detection at least for a period of time. This pattern is precisely what the authors observed. Did decreased HRT use simply delay the diagnoses of existing breast cancers in this mammographically screened population? Further follow-up needs to be performed. Until then, we should be cautious and circumspect before making sweeping clinical generalizations based on complex epidemiologic results that may be of negligible importance when considered at the level of the individual patient. Elimination of HRT would barely dent the current breast cancer epidemic but could have substantial adverse effects for women whose quality of life can really benefit from HRT.

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Response

The magnitude of decline in invasive breast cancer has been remarkably consistent across studies (1–4). Two of the main proposed causes for the decline are a decrease in screening mammography and a decline in use of postmenopausal hormone therapy (HT). We reported a decline in invasive cancer of 5% annually or 15% over a period of 3 years and a decline of estrogen receptor (ER)-positive invasive cancer of 13% annually or 26% over a period of 2 years in a population of women undergoing routine mammography in which the time between screening examinations was similar among current users of HT, former users of HT, and nonusers. The annual decline in ER-positive breast cancer remained comparable and statistically significant ($P_{\text{final}} = .01$) to what we reported even when we omit the first two data points in 2001 and last data point in 2003, despite Anderson’s suggestion that these data points drove our statistically significant findings. In summary, we have shown that a decline in screening mammography rates is unlikely to account for the recent decline in US breast cancer incidence.

Anderson suggests that, because the breast cancer rate we reported was virtually unchanged between 1997 and 2004 and the decline in breast cancer starting in 2000 was not proportional to the decline in HT use, it is hard to conclude that there is any relation between HT use and decline in invasive breast cancer. However, given that mammography use does not account for the decline in breast cancer rate that we observed, our results—particularly the corresponding changes in rates of HT use and breast cancer over time—do suggest that the precipitous decline in HT use likely played a part in the change in breast cancer rates. For example, we observed a statistically significant ($P_{\text{final}} < .001$) 2% annual increase in HT use from 1997 to 2000 and a concomitant statistically significant 9% annual increase in invasive cancer from 1998 to 2000 ($P_{\text{final}} = .03$). Likewise, as the rate of HT use started to decline in 2000, we

References


Notes

B. O. Anderson has served as a consultant and expert witness on behalf of Wyeth Pharmaceuticals in hormone therapy litigation.

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observed a statistically significant 5% annual decline in invasive cancer, as noted above.

Robbins and Clarke state that a percentage change in breast cancer incidence is dependent on the absolute change in prevalence of HT use and the relative increase in breast cancer risk among HT users compared with nonusers. We observed a 31.6% absolute decrease in HT prevalence from 2000 to 2004, but a lower 15% overall decline in breast cancer rate because invasive breast cancer risk is increased only 24% (95% confidence interval [CI] = 2% to 50%) in HT users relative to nonusers (5). We observed a greater decline in the rate of ER-positive breast cancer (26% over a period of 2 years) because ER-positive breast cancer risk is 72% (95% CI = 55% to 90%) higher in HT users than in nonusers (6).

Potential mechanisms that could result in a decline in breast cancer incidence are shown in Table 1. Of these potential mechanisms, we have shown that screening mammography use is not likely to account for a decline in breast cancer rates but that a decline in HT use likely plays a role. Measuring ER-positive breast cancer rates in continuous, former, and never users of postmenopausal HT may inform our understanding of the magnitude of the contribution of declines in postmenopausal HT use on breast cancer incidence.

**Table 1. Potential mechanisms to explain recent decline in breast cancer incidence**

<table>
<thead>
<tr>
<th>Potential mechanism</th>
<th>Short-term impact</th>
<th>Long-term impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in HT use†</td>
<td>Abrupt decrease in breast cancer rates</td>
<td>Possible increase in breast cancer rates in future years when slower-growing tumors become large enough to be detected by mammography</td>
</tr>
<tr>
<td>Decrease in initiation of new breast cancer events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in promotion of tumor growth</td>
<td>Abrupt decrease in breast cancer rates due to slowing of rate of tumor growth, to tumor regression, and/or to smaller tumors ceasing to grow, resulting in decreased detection of tumors</td>
<td>Possible increase in early-stage breast cancer rates and screen-detected cancers and decrease in interval cancer rates</td>
</tr>
<tr>
<td>Decrease in breast density</td>
<td>Increase breast cancer rates due to increased detection on mammography</td>
<td>Possible increase in early-stage breast cancer rates and screen-detected cancers and decrease in interval cancer rates</td>
</tr>
<tr>
<td>Disproportionate decline in screening mammography among former long-term HT users vs nonusers</td>
<td>Decrease in breast cancer rates</td>
<td>Possible increase in early-stage breast cancer rates and screen-detected cancers and decrease in interval cancer rates</td>
</tr>
<tr>
<td>Decline in screening mammography</td>
<td>Abrupt decrease in breast cancer rates because of decrease in detection of nonpalpable tumors</td>
<td>Increased breast cancer rates in future years, in particular increase in advanced stage</td>
</tr>
<tr>
<td>Increased use of chemoprevention therapies (e.g., tamoxifen)</td>
<td>Gradual decrease in breast cancer rates due to primary prevention</td>
<td>Possible increase in early-stage breast cancer rates in future years, in particular increase in advanced stage</td>
</tr>
<tr>
<td>Increased detection of DCIS over a period of 20 years</td>
<td>Gradual decrease in breast cancer rates if DCIS is a precursor for most invasive cancers</td>
<td>Possible further decrease in breast cancer rates in future years</td>
</tr>
<tr>
<td>Mammography saturation</td>
<td>Decrease in breast cancer rates because most prevalent cases identified</td>
<td>Possible further decrease in breast cancer rates in future years</td>
</tr>
</tbody>
</table>

* HT = postmenopausal hormone therapy; DCIS = ductal carcinoma in situ.
† Mechanisms not mutually exclusive.

**Notes**

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