Commentary: Hormone therapy and breast cancer incidence: did epidemiologists miss an effect on national trends?

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Publication of the Women's Health Initiative trial of post-menopausal hormone therapy caused re-thinking and heart-searching in epidemiology, although the scale of the upset at that time can be exaggerated. As Krieger and colleagues have pointed out elsewhere, biological, clinical and epidemiological evidence questioning the purported benefits of hormone therapy on heart disease and counting the harms had been available well before 2002.

Krieger in this volume has turned to the effects of hormone therapy on breast cancer risk and asks an important question: if the effect of hormone therapy on breast cancer was established from the 1970s, why was so little attention paid to the effects of hormone therapy on national breast cancer rates? Breast cancer incidence rose markedly in the United States during the 1980s, especially among women aged 50 and older. This question, she notes, is highly pertinent given the recent decline in breast cancer incidence—after a persistent rise—and the coincidence of this fall with declines in hormone therapy use.

It is plausible that the recent decline in breast cancer incidence is real and is related to the decline in use of hormone therapy, although there are uncertainties—not least of which are SEER-wide cancer site specific reporting delays. Let us assume, as Krieger does, that the decline is real and related to stopping hormone therapy.

Given there is so much interest now in examining the effect of stopping hormone therapy on breast cancer incidence rates, why was there so little interest in the past in exploring the effects of increases in hormone therapy on increases in incidence rates? Krieger has considered 21 articles, which examined trends in US breast cancer incidence. She shows that, except for papers published since 2003, the reviews of temporal trends from the 1980s either ignored a possible effect of hormone therapy or mentioned it only in passing as a possibility among others.

To assess this apparent failing, we need to consider the quality of the evidence available from the late 1980s when the trends were first assessed. Krieger is particularly interested in increases in incidence during the 1980s, at a time when hormone therapy use was rapidly increasing (after a fall from 1975 to 1980). The first meta-analysis published in 1988 concluded ‘unequivocally’ that ever-use of oestrogen did not alter risk by any measurable amount and that apparently elevated risks in subsets of women should be treated with great caution. Two further meta-analyses published in the early 1990s concluded that risk was confined to women who used either high doses or who took hormones for more than 5 years. After 15 years of use the relative risk was 1.3 (95% confidence interval (CI) 1.2–1.6). There was also significant heterogeneity in the results—probably because of inadequate control of confounding, especially for age at menopause, in some studies.

Although Krieger gives the commentary by Rosenberg in 1993 as the final date when the evidence was sufficiently robust for serious concern, it was not until 1997 that the problems of heterogeneity and sub-group analyses were solved by bringing together and re-analysing individual data from 51 studies. This showed that the main effect was confined to current and recent use, and within that group, risk was related to duration of use. The relative risk was 1.35 (95% CI 1.21–1.49) for women who had used hormone therapy for 5 years or longer (average 11 years). Even then, the authors cautioned that the observed effect might not be causal and that earlier diagnosis of breast cancer among women using hormone therapy could not entirely be ruled out as an explanation.

Thus, through most of the 1990s an association between hormone therapy and breast cancer appeared to be confined to users of long duration and causality was uncertain. Hence, it is unsurprising that hormone therapy did not feature strongly in the interpretation of temporal trends. Moreover, it clearly would have been difficult to test the causal hypothesis by examining temporal trends in the 1980s—when any effect would have had a lag period to accumulate five or
more years of use, the increase in use was gradual (compared with the steeper decrease in use), the relative risk was modest, and breast cancer incidence was already increasing because of known effects, especially of mammographic screening. Indeed the ‘sharp rise’ observed from 1982 to 1987 occurred before hormone therapy use reached the level it had been in 1975 and is still unlikely to be clearly attributable to the increased use of hormone therapy. It should also be noted that Figure 1 of Krieger’s paper uses a variable scale on the x-axis, having the effect of exaggerating the incidence rise in the 1980s.

With hindsight there is an extra problem. The increase in hormone therapy use in the 1970s and the subsequent decline in use once the effect on endometrial cancer was publicized, should have been evidenced in an immediate decline in breast cancer incidence. (There was a 50% decline in prescriptions evidenced in an immediate decline in breast cancer endometrial cancer was publicized, should have been the subsequent decline in use once the effect on

In 1989 evidence emerged suggesting that oestrogen plus progestogen might be worse. There is now compelling evidence that the risk of breast cancer is raised further by the addition of a progestogen. The UK Million Women’s Study has put the relative risk for current users of oestrogen alone at 1.30 (95% CI 1.22–1.38) and oestrogen plus progestogen at 2.00 (95% CI 1.91–2.09). The Women’s Health Initiative trial results are consistent with such a difference. What lessons can be drawn? Krieger worries that deeply held beliefs in the benefits of science can blind investigators to the possibility of iatrogenic harm. Although there are such examples, it is more usual for cancer epidemiologists to be accused of looking for trouble about the adverse effects of medicines than of turning a blind eye to iatrogenic harm. In this case, I doubt that attention to the effects of hormone therapy on rising breast cancer incidence rates in the 1980s would have been useful in gaining evidence to assess causality. More pertinent would have been attention to the decline in breast cancer incidence in the 1970s that appears to have followed the rapid decline in hormone therapy use. Only in strictly limited circumstances will changes in national incidence trends provide the evidence of a natural experiment.

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References
