

THEORY & METHODS

Hormone therapy and the rise and perhaps fall of US breast cancer incidence rates: critical reflections

Nancy Krieger

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Background Results of the Women's Health Initiative (WHI) study—which to many unexpectedly showed that hormone therapy (HT) did not decrease and may in fact have elevated risk of cardiovascular disease, while also finding expected links between HT and breast cancer—have spurred critical reflection chiefly regarding the cardiovascular results. Suggesting similar scrutiny of cancer epidemiology is warranted are new studies linking the post-WHI drop in HT use to a substantial decline in breast cancer incidence and the implications of these findings for prior explanations of the rising rates of US breast cancer incidence during the 1980s.

Methods Literature search for review and research articles on temporal trends in US breast cancer incidence during the past 25 years, starting in the mid-1980s, when extant epidemiologic evidence had already indicated that HT increased risk of breast cancer.

Results Among the 21 articles identified, spanning from 1987 to 2007, nine included no mention of HT as a possible factor contributing to the steep rise in breast cancer incidence in the 1980s, seven included a minor mention and only five (one published in 2003, the others in 2006 and 2007) provided any substantive discussion of this issue—but only in relation to current trends and not the 1980 rise in breast cancer incidence.

Conclusion A critical appraisal of the epidemiologic literature highlights important gaps in explanations for breast cancer incidence trends and also how current and changing population patterns of disease distribution are ultimately what put our aetiologic explanations to the test.

Keywords Breast cancer, confounding, epidemiology, hormone therapy, incidence rates, secular trends

Routine acceptance of use of hormone therapy (HT) was shattered in 2002 by the results of the largest randomized clinical trial of HT, the 'Women's Health Initiative' (WHI).¹ Conducted in a population of

mainly healthy women in the United States, this trial found that HT did not decrease, and may in fact have elevated, risk of cardiovascular disease, and it also observed expected links between HT and breast cancer.^{1–3} Publication of the results triggered a dramatic and enduring drop in prescriptions and marketing of HT in the United States, with the decline in HT use exceeding 50% compared with the period prior to the WHI results (Table 1).^{4–13}

Department of Society, Human Development and Health, Harvard School of Public Health, Kresge 717, 677 Huntington Avenue, Boston, MA 02115, USA.
E-mail: nkrieger@hsph.harvard.edu

Table 1 Data on hormone therapy use in the United States, 1966–2003

| Year | Dispensed retail hormonal prescriptions ^{13,77,78} | Type of hormonal prescription | US women aged 55 and older: N (thousands) ^{103,104} | Ratio: Rx per women age 55+ |
|------|---|--|--|-----------------------------|
| 1966 | 17.8 million | 16 million = estrogens 1.8 million = progestins | 19 778 | 0.90 |
| 1975 | 30.7 million | 28 million = estrogens 2.7 million = progestins | 24 060 | 1.28 |
| 1980 | 16.3 million | 14 million = estrogens 2.3 million = progestins | 26 796 | 0.61 |
| 1983 | 21.4 million | 14 million = estrogens 3.4 million = progestins | 28 140 | 0.76 |
| 1992 | 34.5 million | oral menopausal estrogens and combination estrogens + progestins | 30 254 | 1.14 |
| 2000 | 87.3 million | oral menopausal estrogens and combination estrogens + progestins | 32 852 | 2.66 |
| 2003 | 59.6 million | oral menopausal estrogens and combination estrogens + progestins | 33 892 | 1.76 |

The results of the WHI have led to much critical reflection and debate.^{2,3,14–22} At one level, controversies centre on the timing of HT administration for risk of coronary heart disease (CHD);^{16–22} none dispute the HT-breast cancer links. At another level, the WHI results have spurred discussion about problems of confounding in observational studies, complexities involved in the design and analysis of randomized clinical trials and the enormous difficulties in testing whether potentially plausible biological pathways elucidated by basic research actually do explain disease occurrence, let alone population distributions of disease.^{2,3,14–22} At issue is a core tension in scientific research: maintaining a deep humility and expansive curiosity about all that is unknown while simultaneously working to gain rigorously tested knowledge to acquire sufficient provisional certainty to guide action and interventions.^{2,23–26} Focusing on the cardiovascular findings, four key lessons proposed by Petitti¹⁴ are: ‘Lesson one: do not turn a blind eye to contradiction’ (i.e. allegedly different effects of estrogen in women vs men on risk of CHD); ‘Lesson two: do not be seduced by mechanism’ (since ‘we will never know all there is to mechanism. Mechanism is complex’); ‘Lesson three: suspend belief’ (i.e. a belief in the protective effects of HT led to ignoring the possible role of confounding) and ‘Lesson four: maintain skepticism’ (‘science doors that are closed have a way of reopening’, in this case about hypotheses regarding the cardiovascular protective effects of HT).

Is a critical reevaluation of cancer research likewise warranted in the aftermath of the WHI? New research linking the drop in HT use to a drop in breast cancer incidence^{27–33} suggests it is. Of relevance are not only the new debates about whether such a link might be causal^{27–34} but also—as important but thus far

unconsidered—the urgent need to re-evaluate prior explanations for the notable rise of US breast cancer incidence in the 1980s.

Keeping in mind Petitti’s caveats, the first point to note is that a link between HT and risk of breast cancer has been well-documented in the epidemiologic literature since the mid-1970s.^{2,35–44} Postulated mechanisms involve estrogen’s role as promoter (rather than initiator) of breast epithelial tissue cell growth, and especially that of tumours that are estrogen receptor positive (ER+).^{35–44} Evidence indicates that HT preferentially increases risk of breast cancer among: older women (>50 years of age, partly as linked to menopausal status and duration of use), women with a lower body mass index, women with ER+ compared with ER– tumours, and, in the case of HT including both progestins and estrogen, lobular and ductal-lobular carcinomas.^{35–44}

The WHI results prompted a new round of research on the implications of HT use for breast cancer risk, extending from beyond estimates of relative risk to the actual population burden of disease.^{2,27–33,45–49} Epidemiologic analyses published between 2002 and 2005, using data from the United States, Europe and Australia, estimated that HT might account for 10–25% of observed cases.^{45–48}

Predictions are one thing; changes in actual incidence rates are another. Notably, four new studies using post-WHI US cancer registry data have yielded findings compatible with the predicted estimates. In November 2006, Clarke *et al.*²⁷ reported that from 2001 to 2004, breast cancer incidence declined by 11% in California, including within Northern California, with use of HT among the Northern California population having declined by 68% during this same time period. Shortly thereafter, in December 2006, Ravdin *et al.*²⁸ presented a study at the San Antonio

Breast Cancer Conference, based on US Surveillance, Epidemiology and End Result (SEER) cancer registry data from nine different US SEER registries, showing that US breast cancer incidence declined by 7% in 2003 (compared with rates in 2002) and by 12% among women age 50 and older with estrogen receptor positive (ER+) tumours.

Subsequently, in a paper published in April 2007, Ravdin *et al.*²⁹ extended the analyses to include the 2004 breast cancer incidence data. They found 'little change in breast-cancer incidence between 2003 and 2004', and further reported that, comparing the 2004 with 2001 breast cancer incidence rates for women ages 50–69, 'the decrease was more evident in those with estrogen-receptor-positive tumours (14.7%; 95% CI 11.6–17.4) than in those with estrogen-receptor-negative tumours (1.7%; 95% CI –4.6 to 8.0)'.²⁹ Noting an absence of similar declines for other cancer sites, Ravdin *et al.*^{28,29} have speculated the breast cancer incidence decline was due to the drop in HT use subsequent to the release of the WHI results. Two subsequent US studies, one focused on the nine oldest SEER registries,³⁰ the other on US state cancer registries,³¹ have yielded comparable results. European studies have also begun to report similar findings.^{32,33} Building on these findings, in August 2007 a study on the population attributable impact of HT use on breast cancer incidence in the United States estimated that 'the number of breast cancers related to EP use (i.e. combined estrogen and progestin HT) could be on the order of hundreds of thousands, particularly given the elevated breast cancer risks and expanding prevalence of long-term users as time went on. For example, over the 7.5 year period between approval of Prempro and the WHI announcement (i.e. 1995 to mid-2002), over 127 000 breast cancer diagnoses could be related to EP, assuming a prevalence of EP use of 17.5% for women aged 50–79, and a relative risk of 2.0'.⁴⁹

The rapidity and magnitude of the reported breast cancer incidence decline not surprisingly invite scientific skepticism regarding a cause-effect relationship,^{27–34} especially given research indicating that breast tumours have an estimated doubling time of 50–100 days and require 30–35 doublings before attaining a clinically detectable size of 1 cm.⁵⁰ Alternative explanations, mentioned by Ravdin *et al.*,^{28,29} could include declines in mammography rates, leading to reduced detection, and also potential inaccuracies in the cancer registry data. Four testable arguments countering these concerns include:

- (1) The observed decline in the United States occurred uniquely for breast cancer across nine different geographic regions, implying that it was not an artefact due to errors in cancer registry reporting, as noted by Ravdin *et al.*^{28,29}
- (2) Women using or stopping use of HT, given their access to medical care, including mammography, and their greater health consciousness,^{51–56}

would be more, rather than less, likely to see a physician concerning their HT use and to have a tumour detected compared with non-HT users, implying that diagnostic bias (if extant) would result in higher, not lower, breast cancer incidence rates, the opposite of what was observed.

- (3) With regard to mammography, Ravdin *et al.*²⁹ cited evidence of a slight decline—by 3.2%, between 2000 and 2003—in US mammography rates, arguing that it was too small to explain the observed drop in overall breast cancer incidence and also incompatible with the drop occurring only among the estrogen-receptor positive and not estrogen-receptor negative tumours. New data from the US National Health Interview Survey, moreover, not only underscore that the 2000–05 decline in mammography was modest (from 80.8 to 79.5% among women age 40 and older)⁵⁷ but also indicate that among the reasons women age 50–69 gave for not getting a mammogram in the past 2 years, the one that exhibited the greatest increase was 'too expensive/no insurance/cost' (up from 9.4 to 12.0%). Since women with lower income typically have lower risk of breast cancer compared with higher income women,^{58,59} it follows that the disproportionate presence of this group among those not getting mammograms would further minimize the impact of reduced mammography rates on breast cancer incidence. The Clarke *et al.*²⁷ study, moreover, observed a sharp drop in breast cancer incidence in Marin county, one of the wealthiest counties in the United States.
- (4) The biological plausibility of the hypothesis: the posited mechanism, building on extant knowledge about hormonal tumour promoters,^{42–44,46,60,61} is that removal of exposure to HT among tumours whose growth was especially sensitive to HT would slow or stop their growth; whether these tumours are permanently stopped or simply growing more slowly (leading to diagnosis at a later date) remains unknown.^{29,34}

All of these arguments notably focus solely on the current observed drop in rates.

By implication, however, if the hypothesis that curtailing HT use could quickly lead to a marked reduction in breast cancer incidence is correct, then conceivably the reverse could be true: a substantive rise in HT use should result in higher breast cancer incidence rates. Here consideration of the recent historical record is useful.

Figure 1 shows well-known trends in the age-specific incidence of invasive breast cancer among US white women from 1937 to 1939 to 2003, drawing on data from the First, Second and Third National Cancer Surveys and the more recent SEER data.^{62–67} Results are shown only for the white women because they are the group most likely to exhibit HT-related changes in breast cancer incidence, given extensive

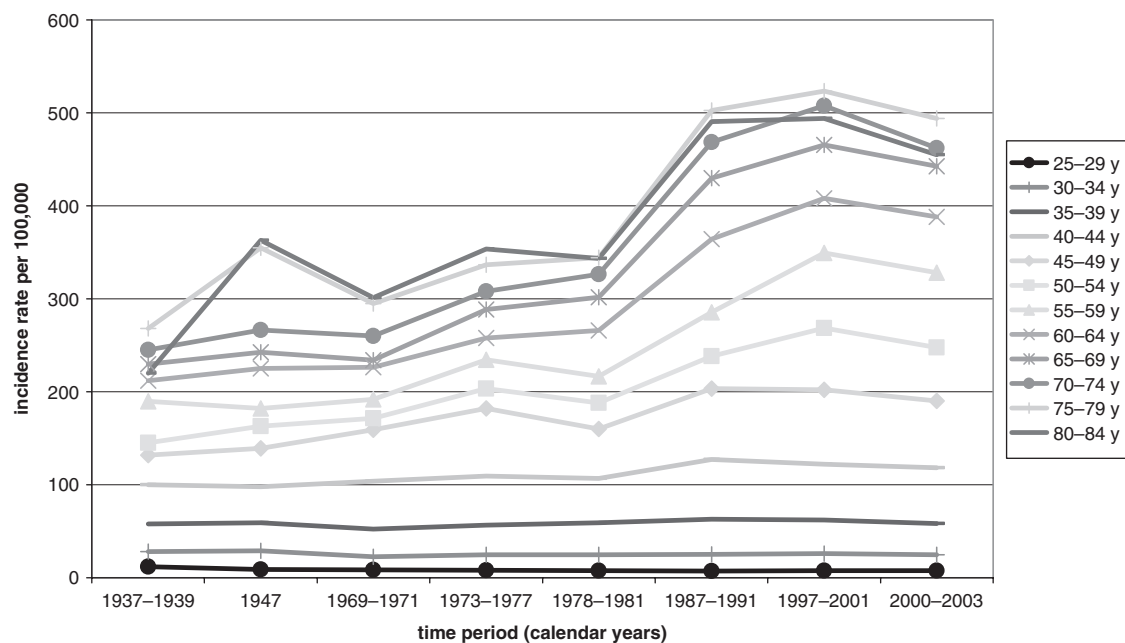


Figure 1 US breast cancer age-specific incidence rates (invasive):^{62–67} white women (age 25–84), 1937–39 to 2000–03

documentation that HT use in the United States, at least until 2002, was most common among more affluent, healthier and predominantly white women, i.e. women with access to medical care, who could afford HT, and who did not have contraindications against its use.^{2,51–56,68–72} The importance of presenting data solely on this group, rather than the total population, is indicated by Table 2, which shows the marked increase, between 1980 and 2005, and especially most recently, in the proportion of the SEER and US populations that were foreign-born (from 7.2 to 13.8% and from 6.2 to 12.4%, respectively) and of colour (from 19.9 to 30.1% and from 16.6 to 25.3%, respectively). Since breast cancer incidence rates are typically lower among both the US foreign-born population and populations of colour, compared with US-born white women,^{58,59} presenting data on the total population would potentially confound HT-related temporal trends in breast cancer incidence with demographic trends.

As Figure 1 shows, the age-specific incidence rates began rising especially quickly among women age 50 and older starting in the early 1980s. A new study has quantified the trends in the SEER data for 1975–2002 and reported that the largest increase among white women occurred between 1982 and 1987 among women aged 50 and older who had localized tumours, with the annual percent change equaling 9.9% (a magnitude significantly different from 0); in contrast, among this same group, the annual percent change for 1975–82 was only 0.9% (not significantly different from 0), for 1987–99 it was only 1.7% (significantly different from 0) and for 1999–2002 it was –1.9% (not significantly different from 0).⁷³ This 9.9% annual percent change in the 1980s is

noteworthy for two reasons. First, this annual percent increase is of the same order of magnitude as the currently observed drop in breast cancer incidence rates among women over age 50. Second, it occurred at a time when not only mammography rates were rising, as has been previously noted,^{74–76} but also when HT use was dramatically increasing, especially the combined estrogen-progestin formulations, following a period in the mid-1970s when use of HT dropped due to the growing evidence linking estrogen-only HT and endometrial cancer.^{2,9,19,77,78}

Keeping these data in mind, it is useful to review how numerous epidemiologic studies and review articles have explained the marked rise in US breast cancer incidence rates that occurred chiefly among women age 50 and older starting in the early 1980s. Table 3 presents a summary of articles published since the mid-1980s that have focused on temporal trends in US breast cancer incidence over the last 25 years,^{30,31,73–76,79–93} noting that by the start of this period epidemiologic evidence had already indicated that HT increased risk of breast cancer.^{2,35–44} Among the 21 articles identified, spanning from 1987 to 2007, nine included no mention of HT as a possible factor contributing to the steep rise in breast cancer incidence in the 1980s,^{74–76,80–82,85,90,91} seven included a minor mention^{79,83,84,86,87,89,93} and only five (one published in 2003, the others in 2006 and 2007) provided any substantive discussion of this issue^{30,31,73,88,92}—but only in relation to current trends and not the 1980 rise in breast cancer incidence. Moreover, among the 16 articles including either no or minor mention of HT, virtually all attributed the rapid rise in the 1980s chiefly if not solely to increased detection due to rising mammography

Table 2 Changing population composition of the core US SEER cancer registries and US total population: percentage white and percentage foreign-born, 1980–2005^{105,106}

| Population | 1980 | | | 1990 | | | 2000 | | | 2005 | | |
|--------------------------------------|-------------|-----------|------------------|-------------|-----------|------------------|-------------|-----------|------------------|-------------|-----------|------------------|
| | n | White (%) | Foreign-born (%) | n | White (%) | Foreign-born (%) | n | White (%) | Foreign-born (%) | n | White (%) | Foreign-born (%) |
| SEER registry | | | | | | | | | | | | |
| Connecticut | 3 107 576 | 90.0 | 8.6 | 3 287 116 | 86.9 | 8.5 | 3 405 565 | 81.6 | 10.9 | 3 394 751 | 74.7 | 12.5 |
| Hawaii | 964 691 | 33.0 | 14.2 | 1 108 229 | 33.4 | 14.7 | 1 211 537 | 24.3 | 17.5 | 1 238 158 | 24.9 | 17.2 |
| Iowa | 2 913 808 | 97.4 | 1.6 | 2 776 755 | 96.6 | 1.6 | 2 926 324 | 93.9 | 3.1 | 2 862 541 | 93.5 | 3.6 |
| New Mexico | 1 302 894 | 75.0 | 4.0 | 1 515 069 | 75.6 | 5.3 | 1 819 046 | 66.8 | 8.2 | 1 887 200 | 69.5 | 8.9 |
| Utah | 1 461 037 | 94.6 | 3.4 | 1 722 850 | 93.8 | 3.4 | 2 233 169 | 89.2 | 7.1 | 2 427 350 | 89.8 | 7.9 |
| Atlanta, GA ^a | 1 687 906 | 71.4 | 2.6 | 2 177 495 | 66.4 | 4.9 | 2 914 587 | 54.5 | 12.9 | 3 184 396 | 49.7 | 16.3 |
| Detroit, MI ^a | 4 044 284 | 76.0 | 6.7 | 3 912 679 | 73.5 | 1.3 | 4 043 467 | 67.5 | 8.1 | 3 988 039 | 67.9 | 9.4 |
| SF-Oakland, CA ^a | 3 250 630 | 71.8 | 15.7 | 3 686 592 | 65.9 | 21.1 | 4 123 740 | 56.7 | 27.4 | 4 071 751 | 55.3 | 29.5 |
| Seattle-Puget Sound, WA ^a | 2 752 364 | 90.5 | 6.6 | 3 366 824 | 87.8 | 7.2 | 4 045 707 | 80.4 | 11.1 | 4 094 995 | 78.5 | 13.7 |
| SEER registries: Total | 21 485 190 | 81.1 | 7.2 | 23 553 609 | 78.0 | 8.4 | 26 723 142 | 71.1 | 12.2 | 27 149 181 | 69.9 | 13.8 |
| US population | 226 545 805 | 83.4 | 6.2 | 248 709 873 | 80.3 | 7.9 | 281 421 906 | 75.1 | 11.0 | 288 378 137 | 74.7 | 12.4 |

^aSEER registry catchment area counties.^{64–67}

Atlanta, GA: Clayton, Cobb, DeKalb, Fulton and Gwinnett counties; Detroit, MI: Macomb, Oakland and Wayne counties; SF-Oakland, CA: Alameda, Contra Costa, Marin, San Francisco and San Mateo counties; Seattle-Puget Sound, WA: Clallum, Grays Harbor, Island, Jefferson, King, Kitsap, Pierce, San Juan, Skagit, Snohomish, Thurston and Whatcom counties.

rates, noting that the sharp rise was unlikely to be explained by the observed incremental rise of well-known risk factors (e.g. earlier age at menarche, later age at first childbirth).^{73–76,79,89,93}

Only starting in 2003, and especially in 2006, after publication of the WHI results, over 30 years after the first evidence linking HT use and breast cancer,^{2,35–44} and more than a decade after the epidemiologic evidence on these links were considered to be sufficiently robust to be a cause for serious concern, outweighing any then-presumed cardiovascular benefits,³⁸ did articles on US breast cancer trends begin to focus on HT use as a potentially important driver of population rates of breast cancer.^{30,31,73,88,92}

In other words, the lessons Petitti has drawn based on the cardiovascular-HT research apply equally to breast cancer. The point is not that the mammography explanation for the rapid rise in breast cancer incidence rates in the 1980s was ‘wrong’: part of the rise was shown to be due to increased rates of mammography and increased detection.^{73–75,81–93} Nor is the point that use of HT is more important than the other known risk factors for breast cancer. Rather, the problem is that since the mid-1980s, when extant knowledge linked HT use to risk of breast cancer, epidemiologic articles on trends in breast cancer incidence tended to offer scant or no mention of HT as a meaningful contributor to breast cancer incidence rates. Moreover, it was not until after the actual incidence of breast cancer fell, post-WHI, that connections between current drops in population rates of HT use and current declines in breast cancer incidence rates began to receive widespread attention, among epidemiologists, clinicians and the public at large³⁴—albeit without any parallel re-analysis of the 1980s rise in HT use and rise in breast cancer incidence.

At one level, the changing views in the breast cancer literature are not surprising: scientific research abounds with examples of old observations re-interpreted in the light of new hypotheses and new evidence^{23–26} (consider only the rethinking of ulcers and gastric cancer in relation to infection by *Helicobacter Pylori*²⁵ (pp.39–97)^{94,95}). More disturbing is the possibility that scientific hypotheses were influenced by deeply held beliefs in the benefits of science.^{2,23} Specifically, the expectation of greater detection hence higher incidence due to the intervention of mammography was more in keeping with the beliefs and values of cancer control (even taking into account concerns about false positives) than the alternative of iatrogenic harm. The implication is that it is essential to maintain a critical awareness of how interventions framed as ‘medical advances’ can damage, not just improve, population health, especially when economic interests are at play,² as recent concerns about the overhyping of benefits and minimization or suppression of risks of several major pharmaceutical products readily reveals.⁹⁶

Table 3 Epidemiologic analyses of and review articles about trends in US breast cancer incidence and their consideration of hormone therapy (HT) use as a possible explanation, 1987–2007

| Year | Authors | HT use discussed | | | Explanation of rising incidence of US breast cancer in 1980s |
|------|-------------------------------------|------------------|---------------|------------------------|--|
| | | No mention | Minor mention | Substantive discussion | |
| 1987 | Devesa <i>et al.</i> ⁷⁹ | | ✓ | | 'Declines in age at menarche, increases in age at first childbirth and perhaps increases in per capita fat consumption may contribute to increases in breast cancer rates', with the text also noting that links to HT use was a topic 'under active investigation' (p. 719, 721) |
| 1992 | Tarone and Chu ⁸⁰ | ✓ | | | Birth cohort pattern, in relation to changes in reproductive risk factors |
| 1993 | Miller <i>et al.</i> ⁸¹ | ✓ | | | '...descriptive data suggest that early detection may be playing a role in the recent increase in the incidence of breast cancer in women, although other risk factors cannot be ruled out' (p. 27), including 'age at menarche, age at menopause, oral contraceptive use, oophorectomy rates, and diet' (p. 38) |
| 1994 | Hankey <i>et al.</i> ⁷⁴ | ✓ | | | Increasing mammography rates, with data on rising rates of localized small tumours (<2 cm) providing 'indirect evidence that early detection played a major role in the increase of breast cancer incidence that occurred during the early 1980s' (p. 10) |
| 1994 | Sondik ⁸² | ✓ | | | 'increasing levels of screening' (p. 996) |
| 1995 | Devesa <i>et al.</i> ⁸³ | | ✓ | | To explain rise in breast cancer among white women from 1975–1979 to 1987–1991 (39.3% rise among women 55–74, 36.9% among women 75+), 'it appears that most of the rise in reported incidence is associated with earlier detection, although other factors may contribute; these factors may include changing prevalence of certain reproductive variables, diet, alcohol consumption, and long-term use of menopausal estrogens'. (p. 179), noting that 'the upward trend has been most pronounced for estrogen-receptor positive tumors, particularly those among older women, suggesting that some of the changes are related to hormonal factors' (p. 179) |
| 1995 | Wun <i>et al.</i> ⁷⁵ | ✓ | | | 'Breast cancer trends are seen to be generally consistent with the impact of increased use of mammography when its effect is superimposed upon the background of declining or slowing secular trends' (p. 135) |
| 1996 | King and Schottenfeld ⁸⁴ | | ✓ | | Increasing mammography rates and birth cohort changes in risk factors ('age at menarche, age at first birth, physical activity, obesity, diet, alcohol intake, estrogen therapy, and exposure to organochlorines'), noting that insufficient data existed to evaluate the HT hypothesis (p. 453) |
| 1996 | Chu <i>et al.</i> ⁷⁶ | ✓ | | | 'The large increases in breast cancer incidence rates in the 1980s have been tied to the dramatic increase in mammography use' (p. 1576) |
| 1998 | Wingo <i>et al.</i> ⁸⁵ | ✓ | | | Discussion focused on likely impact of increasing mammography on decreasing mortality, with no discussion of incidence trends |
| 2001 | Howe <i>et al.</i> ⁸⁶ | | ✓ | | Increasing rates 'may signify increased screening and early detection...It is not known whether any of the increase in incidence was due to age and birth cohort changes in reproductive patterns (delayed childbearing and having fewer children), recent hormone use, increases in obesity, or other, as yet unknown, risk factors' (p. 836) |

(continued)

Table 3 Continued

| Year Authors | HT use discussed | | | Explanation of rising incidence of US breast cancer in 1980s |
|--|------------------|---------------|------------------------|--|
| | No mention | Minor mention | Substantive discussion | |
| 2003 Weir <i>et al.</i> ⁸⁷ | | ✓ | | '...increasing breast cancer incidence rates reported during the 1990s have been attributed to, in part, increased mammography screening...The observed differences in breast cancer incidence rates among states may also reflect demographic differences and variations in modifiable risk factor, including alcohol consumption, sedentary lifestyle, obesity, and use of hormone replacement therapy' (p. 1293) |
| 2003 Li <i>et al.</i> ⁸⁸ | | | ✓ | '...the proportion of hormonally sensitive tumors being diagnosed seems to be rising, while the proportion of hormonally insensitive tumors is falling. Given that the incidence rates of ER- and PR-tumors remained relatively constant over the study period [1992–1998], it seems that the continued overall rise in breast cancer incidence in the United States is primarily a result of a rise in hormone receptor-positive cases...Interestingly, increases in the proportion of ER+ and decreases in the proportion of ER- tumors were limited to women with stage I cancer...These findings may be consistent with our hypothesis that the increases we observed are related to hormonal factors such as an increase in the use of HRT...' (p. 33) |
| 2003 Ghafoor <i>et al.</i> ⁸⁹ | | ✓ | | 'Reasons for the small increase in regional stage and larger tumors among white women during the most recent time period (1993–2000) are not fully understood. The increase may reflect the higher prevalence of some underlying risk factor such as postmenopausal obesity, HRT, or both.' (p. 346) |
| 2004 Nasser <i>et al.</i> ⁹⁰ | ✓ | | | '...results provide further support for the previously implied causal association between the use of screening mammography and the increased incidence of FBC (female breast cancer) in the United States' (p. 129) |
| 2005 Jatoi <i>et al.</i> ⁹¹ | ✓ | | | 'Incidence rates have increased gradually in Connecticut since the 1950s and in SEER since the 1980s, with sharper increases from the late 1970s to the early 1990s, reflecting the increased use of mammography screening' (p. 7837) |
| 2006 Holford <i>et al.</i> ⁹² | | | ✓ | Using age-period-cohort framework, conclude that 'the overall increase in breast cancer incidence is almost certainly due to multiple factors, including screening as well as etiological risk factors', accounting for divergence in trends for birth cohorts born before and after 1925 for women older and younger than age 50, noting that 'Among the breast cancer risk factor exposures that changed for these more recent birth cohorts are fewer children, increased age at first pregnancy, obesity, and increased use of hormone replacement therapy, all of which are qualitatively consistent with the post-menopausal increase in risk with birth cohort that is apparent from these analyses' (p. 24) |
| 2006 Smigal <i>et al.</i> ⁷³ | | | ✓ | 'The increase in the [female breast cancer] incidence rate through 1987 is thought to largely reflect the increased participation in mammography' (p. 170), coupled with: 'trends in risk factors that are most likely to effect recent incidence' are stated to include 'mammography use', 'obesity', and use of 'hormone replacement therapy (HRT)' (p. 172), coupled with the prediction that 'we should see a change in this trend in the near future because prescription rates for HRT fell rapidly following publication of Women's Health Initiative study results in 2002 that linked HRT use with breast cancer' (p. 172) and also that difference in HT use might explain the greater increase in incidence rates among White compared to African American women age 50 and older (p. 172). |

(continued)

Table 3 Continued

| Year | Authors | HT use discussed | | | Explanation of rising incidence of US breast cancer in 1980s |
|------|-------------------------------------|------------------|---------------|------------------------|---|
| | | No mention | Minor mention | Substantive discussion | |
| 2007 | Jemal <i>et al.</i> ⁹³ | | ✓ | | 'Female breast cancer incidence rates leveled off from 2001 to 2003 after increasing since 1980, which may reflect the saturation of mammography utilization and reduction in the use of hormone replacement therapy' (p. 48) |
| 2007 | Jemal <i>et al.</i> ³⁰ | | | ✓ | Analysed breast cancer data from the nine oldest SEER registries for 1975–2003; conclude that 'The sharp decrease in incidence from 2002 to 2003 that occurred in women 50 to 69 years old who predominantly, but not exclusively, had ER+ tumors may reflect the early benefit of reduced use of hormone replacement therapy' (p.1 of 6). |
| 2007 | Stewart <i>et al.</i> ³¹ | | | ✓ | Analysed breast cancer data for 1999–2003 from 41 state-level cancer registries included the Center for Disease Control and Prevention (CDC) National Program of Cancer Registries and SEER; noting that annual age-adjusted incidence rates for invasive breast cancer declined each year from 1999 to 2003, with the decline most steep between 2002 and 2003, the authors stated: 'Several factors might affect breast cancer incidence and contribute to differences in rates over time. One such factor is hormone replacement therapy (HRT)...Because the breast cancer incidence rate began decreasing before 2002 (i.e., before the decrease in HT use), other factors (e.g., differences in risk-factor prevalence, diet, and lifestyle) might be used to explain changes in breast cancer incidence rates. Mammography screening rates also might influence breast cancer incidence' (p. 3 of 7). |

Another key lesson concerns the value of population data, including cancer registry data.⁹⁷ Especially in this era of genomic research and increasingly molecularized epidemiology, the new data on breast cancer incidence trends underscore how current and changing population patterns of disease distribution are ultimately what put our aetiologic explanations to the test.^{26,98–102} Whether or not current knowledge and hypotheses about the biological mechanisms of breast cancer aetiology would predict a rapid and substantial drop in breast cancer incidence following marked reductions in HT use, we are confronted by the

observed recent sharp decline. This drop calls for explanation. Between the Scylla of too much scientific skepticism and the Charybdis of too much scientific certainty—whether about observed population data, postulated mechanisms or methods—it will be necessary to navigate a course of research and action moored to actual trends in breast cancer incidence and cognizant of, but not stranded by, the inevitable limitations of scientific knowledge.

Conflict of interest: None declared.

KEY MESSAGES

- Results of the WHI study have spurred critical reflection, chiefly regarding the cardiovascular results.
- Suggesting similar scrutiny of cancer epidemiology is warranted are new studies linking the post-WHI drop in HT use to a substantial decline in breast cancer incidence and the implications of these findings for prior explanations of rising rates of US breast cancer incidence during the 1980s.
- A review of 21 epidemiologic review and research articles on temporal trends in US breast cancer incidence, spanning from 1987 to 2007, found that nine included no mention of HT as a possible factor of the steeply rise in rates of breast cancer incidence in the 1980s, seven included a minor mention and only five (one published in 2003, the others in 2006 and 2007) provided any substantive discussion of this issue—but only in relation to current trends and not the 1980 rise in breast cancer incidence.
- These results reveal not only important gaps in explanations for breast cancer incidence trends but also highlight how current and changing population patterns of disease distribution are ultimately what put our aetiologic explanations to the test.

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