

Does hormone replacement therapy (HRT) cause breast cancer? An application of causal principles to three studies

Part 5. Trends in breast cancer incidence in relation to the use of HRT

Samuel Shapiro,¹ Richard D T Farmer,² John C Stevenson,³ Henry G Burger,⁴ Alfred O Mueck,⁵ Anne Gompel⁶

For numbered affiliations see end of article.

Correspondence to

Professor Samuel Shapiro, Department of Public Health and Family Medicine, University of Cape Town Medical School, Anzio Road, Observatory, Cape Town, South Africa; samshap@mweb.co.za

Received 9 October 2012
Accepted 8 November 2012

ABSTRACT

Background Based principally on findings in three studies, the Collaborative Reanalysis (CR), the Women's Health Initiative (WHI), and the Million Women Study, it is claimed that hormone replacement therapy (HRT) is an established cause of breast cancer. The authors have previously reviewed those studies (Parts 1–4). The WHI findings were first published in 2002, following which the use of HRT rapidly declined. A correspondingly rapid decline in the incidence of breast cancer has been reported, and attributed to the drop in the use of HRT. The evidence, however, is conflicting.

Methods Using generally accepted causal criteria, in this article (Part 5) the authors evaluate reported trends in the incidence of breast cancer.

Results The evidence to suggest a correlated decline in the incidence of breast cancer following a decline in the use of HRT has not adequately satisfied the criteria of time order, detection bias, confounding, statistical stability and strength of association, internal consistency, and external consistency; biological plausibility is difficult to assess.

Conclusions Based on the observed trends in the incidence of breast cancer following the decline in HRT use, the ecological evidence is too limited either to support or refute the possibility that HRT causes breast cancer.

BACKGROUND

Based principally on evidence from three studies, the Collaborative Reanalysis¹ (CR), the Women's Health Initiative²

(WHI), and the Million Women Study³ (MWS), it is now claimed that hormone replacement therapy (HRT) with estrogen plus progestogen (E+P) is an established and major cause of breast cancer. The CR and MWS investigators have claimed that unopposed estrogen therapy (ET) also increases the risk, although to a lesser degree than does E+P. However, in the WHI study^{4–6} there was unbiased and statistically robust evidence to suggest that ET (conjugated estrogens) does not increase the risk; borderline evidence, still in need of independent confirmation, suggested that ET may even decrease it.

In Parts 1–4 of this series of articles we applied generally accepted epidemiological principles of causality to the evidence in the three studies.^{7–10} We concluded that HRT may or may not cause breast cancer, but the studies did not establish that it does.

The WHI findings for E+P were published in July 2002,² following which there was an immediate decline in the use of HRT,¹¹ and two initial studies reported a corresponding decline, in 2003, in the incidence of breast cancer in nine US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries,^{12 13} and in the Kaiser Permanente Northern California health plan.¹⁴ The SEER study was first published as a conference abstract¹² and then in full.¹³ The Kaiser Permanente findings were published in a letter to the editor.¹⁴

To cite: Shapiro S, Farmer RDT, Stevenson JC, et al. *Journal of Family Planning and Reproductive Health Care* 2013;**39**:80–88.

Subsequently, both in the USA and worldwide, the evidence has been conflicting:^{15 16} declines in incidence have been reported in some studies, but in other studies a decline has not been observed. Here, in Part 5 we focus on the two initial studies.^{12–14} The SEER study,^{12 13} in particular, has been cited as strong evidence to support the claim that HRT causes breast cancer.

First it is helpful to draw attention to some of the limitations of ecological evidence. In ecological studies trends over time (secular trends) in the prevalence of an exposure, followed by parallel trends in the incidence of a disease, may be invoked as evidence of causation. In circumstances in which changes (upwards or downwards) in the prevalence of a single exposure (e.g. cigarettes) are powerfully correlated with changes in the incidence of a disease (e.g. lung cancer), the evidence, some limitations notwithstanding, may indeed support causation.¹⁷ However, when a disease has a complex and multi-factorial aetiology (as is the case with breast cancer), and when the magnitude of an association is small [an overall relative risk (RR) of ≤ 1.5 for HRT users],^{1–3} parallel trends may be due to bias or confounding, the sources of which may or may not be identified; or seemingly correlated changes may simply be coincidental.

The limited capacity of ecological studies to deal with bias, confounding or coincidence is known as the ‘ecological fallacy’.¹⁸ To illustrate with an absurd hypothetical example: during much of the 20th century the number of household bathrooms increased, as did the incidence of breast cancer: bathrooms do not ‘cause’ breast cancer.

By contrast, consider a hypothetical analytical study (cohort or case-control study) in which each person is classified over time as exposed or non-exposed, and diseased or non-diseased. In a study of the bathroom/breast cancer relationship, allowance for the number of bathrooms would show that they do not ‘cause’ breast cancer; that demonstration would not be feasible in an ecological study. And, in a study of the cigarettes/lung cancer relationship, causation can further be supported by adjustment for confounding, evidence of a dose/duration-response effect, consistency within strata (e.g. occupation; socioeconomic status), and so on – all of which would not be feasible in an ecological study.

An additional difficulty is that in ecological research any causal inference based on correlated changes depends on the assumption that in the absence of the hypothesised cause, the incidence rates over time would otherwise remain more or less constant, which may or may not be the case. Despite this limitation, for a disease such as lung cancer, in which cigarettes are by far the most predominant cause, and in which a rise in incidence following a rise in use, and a fall following a decline in use, is massive and sustained, it is reasonable to infer that the correlation is indeed

causal. Even then, however, such evidence, unsupported by rigorous evidence from analytical studies, should be regarded as tentative. And when it comes to a multi-factorial disease such as breast cancer, coupled with smaller and less sustained changes, the evidence should be regarded as extremely tentative.

In short, in causal research ecological data collected at the population level are intrinsically less reliable than analytical data collected at the individual level.

THE INITIAL STUDIES

Ravdin et al. (2006 and 2007)^{12 13}

Age-adjusted incidence rates of breast cancer during 1975–2004 were estimated in nine cancer registries using the SEER database. Between 2002 and 2003 the incidence declined by 6.7%. Among women aged 50–69 years the decline from 2001 to 2004 was 11.8%, and 11.1% among women aged ≥ 70 years. The trend was evident in all nine registries. The decrease was more marked for estrogen-receptor-positive (ER+) than for estrogen-receptor-negative (ER–) tumours [14.7%, 95% confidence interval (CI) 11.6% to 17.4% vs 1.7% (95% CI 4.6% to 8.0%)]. The declines were similar for localised and advanced disease. Among women aged < 50 years the incidence rates did not change materially.

The investigators concluded that it was unlikely that changes in mammographic patterns, or a sudden decrease in incidence due to heavy screening, or a selective tendency to detect ER+ tumours on mammography, could explain the magnitude of the decline in 2003. They argued that “discontinuation of [HRT] could have caused a decreased incidence ... by direct hormonal effects on the growth of occult breast cancers”, and that “the rapidity of the change suggested that clinically occult breast cancers stopped growing or even regressed soon after discontinuation of the therapy”.

Clarke (2006)¹⁴

Automated pharmacy data from the Kaiser Permanente-Northern California (KPNC) health plan were used to determine the prevalence of HRT use during 1994–2004. Age-adjusted incidence rates of invasive breast cancer among women aged 50–74 years were determined from the KPNC source, as well as from the KPNC catchment area, and from the State of California cancer registry; the rates from each of these sources were similar.

“Between 2001 and 2003, the calendar years before and after the WHI announcement ... the rates of ET and [HRT] use declined 58% and 38%, respectively”, and in 2003 the incidence of breast cancer declined by 10–11%, depending on the source. The authors concluded that “incidence rates have been declining since 1999, but more substantial reductions in 2003 ... may reflect declines ... in the numbers of [HRT] users and, if so, could provide further evidence of a short latency

between [HRT] discontinuation and reduced risk". However, they cautioned that the ecological nature of the data "prohibited a causal interpretation".

EVALUATION OF THE TWO STUDIES

Below we apply causal principles^{18–21} to the evidence from the two studies. The principles are inter-related, and when appropriate we cross-refer.

TIME ORDER

It is likely that time order was violated. In both studies, among women aged ≥ 50 years the decline in breast cancer incidence commenced in 1999, 3 years before the major decline in HRT use commenced, in 2002. From 1999 to 2002 the decline in incidence was gradual, from 2002 to 2003 it was more marked, and in 2004 it tended to level off (Figure 1 in References 13 and 14).

From 1999 to 2002 the use of HRT declined by 1% per quarter,¹¹ whereas from 2002 to 2004 the corresponding decline was 18%. It has been suggested that the former decline may explain the drop in breast cancer incidence that commenced after 1999.²² However, under causal assumptions it has been shown that even a decline in HRT use of as much as 44% could only have explained about 43% of the decline in breast cancer incidence²³ (see: Statistical stability and strength of association). A decline in HRT use of only 1% per quarter cannot have had any perceptible effect on the incidence of breast cancer.

In the SEER study,^{12 13} from 2001 to 2004, among women aged ≥ 50 years the incidence of breast cancer declined by 11–12%, depending on decade of age, and for ER+ tumours the overall decline was 14.7%. The investigators suggested that these declines could be due to the withdrawal of HRT. It is perhaps possible that non-invasive cancers may sometimes regress, although there is no evidence to confirm that possibility (see: Biological plausibility). But in any event, the declines were similar for localised and advanced cancer.

It has been suggested that the effects of the withdrawal of HRT may resemble those of the estrogen-receptor-blocking effects of tamoxifen,²⁴ and bring about rapid shrinkage of advanced or metastatic cancers (see: Biological plausibility). However, it is unlikely that advanced or metastatic lesions could have ceased to be clinically diagnosable "soon after discontinuation of therapy".

The Kaiser Permanente investigators¹⁴ acknowledged that the decline in incidence commenced in 1999, but they stated that "more substantial reductions in 2003 and 2004 may reflect declines in the numbers of [HRT] users and, if so could provide evidence of short latency between [HRT] discontinuance and reduced risk".

That explanation is not credible: the WHI findings for E+P were published on 17 July 2002,² and it is

unlikely that breast cancers that were already advanced or metastatic can have regressed in less than 6 months (see: Biological plausibility).

DETECTION BIAS

Mammography gives rise to what is known as 'saturation screening'. Under the assumption of a relatively constant incidence of breast cancer over time, the introduction of screening first gives rise to a seeming increase in incidence as the pool of occult breast cancers is depleted, followed by a decrease once it is (more or less) depleted, and then by a plateau.

In correspondence following publication of the SEER report Cady and his colleagues²⁵ suggested that screening followed by surgical removal of pre-invasive ductal carcinoma *in situ* (DCIS) could explain the findings: "the decline in the incidence of breast cancer began 15 years after mammographic screening became widespread", and "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".

In response²⁶ the SEER investigators argued that "neither of these factors [saturation screening or surgical removal of DCIS] accounts for the sharp drop [in breast cancer incidence] within a single year". Figure 1 in their report¹³ demonstrates the fallacy of that argument: from 1986 to 1987 there was a *sharp and unexplained rise* in the incidence of breast cancer. Moreover, that rise was part of a *major, sustained, and unexplained rise* that extended from 1982 to 1987, a total rise that was much greater than was the decline from 2002 to 2003. As commonly occurs with ecological data, in the course of declining or rising incidence rates extending over a period of years it is not unusual for more marked changes to occur during a single year.

Changes in the prevalence of screening could also have explained the findings (see: Confounding). Women receiving HRT are advised to have regular mammograms, they could have stopped doing so in the year or two after they discontinued HRT, and a greater proportion of occult tumours may have gone undetected. In addition, the proportions of women who stopped having mammograms may have been different at different ages (see: Internal consistency).

The greater drop in the incidence of ER+ tumours than of ER– tumours has been invoked as evidence to support causality.¹³ However, ER+ tumours are selectively detected by mammography.^{27 28} In addition, "the number of patients with unknown [ER] status changed from 15% in 2001 to 8% in 2004".¹³ Thus a selective tendency to test cases of breast cancer for ER status in current users of HRT, and to report ER status to the SEER registries if they tested positive, could also have contributed to the drop.

In a subsequent study Kerlikowske *et al.*²⁹ made allowance for the effects of screening, based on data

from mammography registries in San Francisco, Vermont and New Hampshire. From 1997 to 2003, among 603 411 women aged 50–69 years who in the previous 9–30 months had had a mammogram, annual rates of breast cancer diagnosed within 12 months of having a follow-up mammogram, and identified in SEER or state tumour registries were assessed. Between 2000 and 2003 the incidence of invasive cancer declined by 5% ($p_{\text{trend}}=0.003$), and between 2001 and 2003 the incidence of ER+ tumours declined by 13% ($p_{\text{trend}}=0.002$). Incidence rates of *in situ* cancers were stable.

Kerlikowske *et al.* concluded that “a decline in screening mammography ... [was] unlikely to account for the ... decline in US breast cancer incidence”. Their study, however, could not rule out the possibility that HRT users who became aware of breast lumps or other abnormalities (e.g. a discharge or bleeding from the nipple) were selectively diagnosed with breast cancer, and hence did not attend for follow-up mammograms.

The study of Kerlikowske *et al.* was perhaps the most rigorous of all the ecological studies. Nonetheless, it serves to illustrate some of the intrinsic limitations of ecological data. In the absence of analytical epidemiological studies designed *ad hoc* to obtain detailed information on mammographic screening covering a period of years before July 2002, as well as years thereafter (see: Confounding; see: Duration-response), variable detection of occult breast cancers could have explained the findings, and it could not be ruled out.

CONFOUNDING

Major sources of potential confounding were not controlled. Some of the established determinants of breast cancer risk in menopausal women include age at menopause, type of menopause (natural or surgical with or without oophorectomy), obesity, socioeconomic status, family history, and age at first birth; suspected determinants include exercise and alcohol consumption. Changes in the distribution of such factors could possibly have explained all or part of the decline in the incidence of breast cancer from 1999 to 2004, as well as the rise from 1982 to 1986.³⁰ The SEER investigators argued that it was unlikely that confounding could have accounted for the sharp drop in breast cancer incidence in a single year, but as pointed out above (see: Time order), that decline was part of a more sustained decline over a longer time interval.

By far the most important confounder would have been secular changes in the prevalence of mammographic screening, and in the USA, between 1975 and 2004 screening first became more prevalent, and then declined.^{30–32} In addition, the trends could have been different in HRT users and non-users, different at different ages, different in different ethnic groups, and variable according to socioeconomic status. Following

discontinuation of HRT use, further changes could have occurred. Changes in the prevalence of mammography could also have contributed to the more marked drop in the incidence of ER+ than ER– tumours³² (see: Detection bias).

To sum up: in order to determine whether a drop in HRT use could have brought about a decline in the incidence of breast cancer, it was essential to make precise adjustment for the confounding effect of changes in mammographic screening, in particular, and also to adjust for changes in the distribution of other potential confounders. Such adjustment was not feasible.

STATISTICAL STABILITY AND STRENGTH OF ASSOCIATION

In ecological studies numbers are usually massive, and even a minor change in incidence can be ‘statistically significant’. Thus, although such studies can usually rule out chance, what matters is the magnitude of the change. If, in a reasonably well-conducted ecological study, a change is substantial (e.g. the large rise in lung cancer incidence over much of the 20th century as cigarette consumption increased,¹⁷ followed by the large fall as consumption decreased), it may be reasonable to judge that any distortion due to bias or confounding would be insufficient to eliminate the association. Thus a causal inference is tenable. But if a change is small, particularly given the limitations of ecological data, it may be impossible to discriminate among causation, bias and confounding.³³

In the SEER study relative to the incidence of breast cancer in 2002, by 2003 the incidence declined by 6.7%, to 93.3%; and for ER+ tumours the decline was 14.7%, to 85.3%. Put another way, the respective RRs were 0.93 (93.3/100) and 0.85 (85.3/100). In the Kaiser Permanente study, relative to the incidence in 2001, by 2003 the incidence declined by 10–11%, depending on the source, to 89–90%, and the RR was 0.89–0.90 (89–90/100).

In both studies the declines were represented as being substantial when in fact they were small, as indicated by the inverse of the RR estimates, which ranged from 1.08 (1.00/0.93) to 1.18 (1.00/0.85). In addition, those declines were overestimates: in statistical terms, Sprague *et al.*²³ have shown that based on assumptions of a 44% decline in HRT use, and a RR of ≤ 1.5 for current users,² only about 43% of the decline in incidence could be attributed to hormone use.

DOSE/DURATION-RESPONSE

Dose-response

Dose-response was not evaluated in the initial two studies. Subsequently,³⁴ however, based on HRT use ascertained from the California Health Interview Survey, and on data derived from the California Cancer Registry, from 2001 to 2004 changes in the

incidence of invasive breast cancer were estimated for counties with low, intermediate and high rates of HRT use. The rates of HRT use declined in all areas, and the respective incidence rates declined by 29.5 ($p=0.006$), 51.4 ($p<0.001$) and 89.2 ($p<0.001$) per 100 000 HRT users.

At first glance these changes may seem impressive, but in fact they were not. In the USA the incidence of breast cancer among menopausal women approximates 2 per 1000 per year,³⁵ and the respective changes in incidence were 0.07 (29.5/100/4), 0.13 (51.4/100/4) and 0.22 (89.4/100/4) per 1000 per year in areas of low, intermediate and high prevalence of HRT use; the corresponding RRs were 1.09, 1.12 and 1.29 (our calculations). Such small changes could readily have been explained by bias or confounding.

Duration-response

Duration of HRT use was not evaluated in the two initial studies. However, changes over time in the incidence of breast cancer after 2003 have subsequently been reported.³⁶ Under causal assumptions the decline in the incidence of breast cancer should have continued for several years (see: Biological plausibility). Yet from 2003 to 2007 it did not. Over that interval, among women aged 40–49 years there was a gradual increase in incidence; among women aged 50–59 years (the age group in which the use of HRT before 2002 was the highest) there was virtually no change; in the age groups 60–69 and ≥ 70 years there was no change from 2003 to 2006; from 2006 to 2007 the incidence increased.

INTERNAL CONSISTENCY

Under causal assumptions an association should be coherent in strata such as educational level, age at menopause, age at first birth, family history of breast cancer, and so on. However, beyond evaluation of trends within age strata, and in the SEER study within region, coherence in other strata was not assessed, mostly because the data were missing. Moreover, although it was possible to evaluate consistency according to ethnic group, this was not done. In SEER data reported subsequently,³⁶ among white women, from 2004 to 2007 the incidence of breast cancer did not change. Among Hispanic women, the decline from 2002 to 2003 was less marked than among white women, and among black women there was no decline at all; from 2004 to 2007 the incidence hardly changed in Hispanic women, and it increased among black women.

Valid evidence from the WHI suggests the use of ET without a progestogen does not increase the risk of breast cancer,^{4–6} and it might therefore have been expected that the incidence would not have declined in ET users. However, separate trends for women who used ET only, who would mostly have been hysterectomised (with or without oophorectomy), and for

naturally menopausal women who used ET combined with a progestogen (see: Confounding) could not be evaluated because the data were missing.

EXTERNAL CONSISTENCY

Following publication of the initial two studies, secular trends have been evaluated in several further studies carried out worldwide, and they have been reviewed.^{15–16} Gompel and Plu-Bureau¹⁵ concluded that “these ecological observations [were] not fully convincing” and they stressed “the importance of screening and variations in other risk factors” (see: Confounding).

Pelucchi *et al.*¹⁶ concluded that “the technical improvements and the increased effectiveness of breast cancer screening and detection during the 1990s led to a decreased number of pre-clinical cases found by screening in subsequent years [i.e. saturation screening]. Further, disentangling the effects of [HRT] use and screening is difficult, as women who stop using [HRT] may also undergo screening less frequently [see: Confounding]. Thus, the reasons for the fall in incidence remain open to discussion”.

Here the focus is on the consistency across studies of the evidence among menopausal women.

USA

In contrast to the initial SEER study,^{12–13} other studies based on SEER data have identified inconsistent patterns. Jemal *et al.*³⁷ reported that the decline in breast cancer incidence started in 1999, and that the incidence of ER– tumours also declined. They suggested that saturation screening in particular, and confounding by other factors, could have contributed to the changes (see: Confounding). However, they suggested that the decline in HRT use may also have contributed. Li and Daling³⁸ analysed 13 SEER registries, and reported a decline in the incidence of all types of breast cancer that started in 1998.

Inconsistent results have also been reported in the Kaiser Permanente data. Glass *et al.*³¹ reported a decline in incidence that started in 1998/1999 (see: Time order), both among pre- and post-menopausal women, as well as among ER+ and ER– cases. They also reported fluctuations in mammography rates (see: Confounding).

Canada

Kliwer *et al.*³⁹ reported that breast cancer rates “peaked in 1999 and since then have been declining among women of all ages”, and they suggested that factors other than the decline in HRT use “were also involved” (see: Time order; see: Detection bias). Gompel and Plu-Bureau¹⁵ observed declines that started in 1999 in all 10 provinces of Canada (see: Time order), and suggested that the changes in the prevalence of screening could have accounted for them (see: Confounding).

Australia

Based on data from the Australian Institute of Health and Welfare (AIHW), Canfell *et al.*^{40–41} reported a decline in breast cancer incidence from 2001 to 2003, much of which they attributed to the decline in the use of HRT. In the AIHW data there was an even greater decline from 1995 to 1996, as well as a number of equivalent fluctuations in incidence from 1982 onward.⁴² To attribute the decline from 2001 to 2003 to the fall in HRT use stretches credulity, and cannot reasonably be justified as supporting a causative role.

Germany

In Schleswig-Holstein, breast cancer incidence rates among women aged >50 years declined from 2001 to 2005.⁴³ By contrast, from 1999 to 2004, among women aged 50–64 years, Mueck and Wallweiner⁴⁴ reported no change in Schleswig-Holstein until 2004; in Saarland, from 2002 to 2003 the rate increased, and from 2003 to 2005 it declined. “In Germany mammographic screening remains mainly opportunistic, and it is difficult to know how many women benefit”¹⁵ (see: Confounding).

Switzerland

In Vaud (population ±616 000),⁴⁵ among women aged >50 years the incidence of breast cancer increased from 1986 to 1999. From 2000 to 2006, among women aged 50–69 years the rates hardly changed; in the ≥70-year age group the rates were unstable, presumably because of limited numbers. Other findings reported from Switzerland^{46–47} were based on small numbers, and the rates were unstable.

UK and Scotland

Among women aged 50–59 years the incidence of breast cancer did not change materially from 1999 to 2003,⁴⁸ and there was a small decline in 2004. In the age groups 60–69 and 70–79 years the incidence of breast cancer increased progressively from 1997 onward. However, it was difficult to interpret the findings: “In the UK mammographic screening for all women aged 50–64 years was introduced in 1988, and extended to include women aged 65–69 in 2002”¹⁵ (see: Confounding).

Norway

In four counties representing 40% of the Norwegian population, among women aged 50–59 years, Zahl and Maehlen reported no decrease in the incidence of breast cancer after 2002.⁴⁹ By contrast Kumle⁵⁰ observed a decline among women aged 50–69 years. However, the decline observed by Kumle could have been due to saturation screening¹⁵ (see: Detection bias).

France

Based on National Health Insurance data Allemand *et al.*⁵¹ (2008) and Seradour *et al.*⁵² reported declines

in breast cancer incidence from 2004 to 2006. National screening was introduced in France for women aged 50–74 years in 2004, which should have given rise to a seeming increase in the incidence. Instead, there was a decrease, and the authors suggested that this may have been due to a decline in the use of HRT. However, Gompel and Plu-Bureau¹⁵ have pointed out that opportunistic screening “most likely [covered] 60–70% of women of 50–65 years”. They added that “the situation in France is ... complex and cannot be interpreted simply by directly correlating the fluctuations in breast cancer incidence with much lower use of HRT” (see: Confounding).

The Netherlands

Among women aged 50–69 years, from 1992 to 2005 there were no material changes in the incidence of breast cancer.⁵³

Belgium

In the Limburg Cancer Registry, among women aged 50–69 years the incidence of breast cancer declined between 2003 and 2004, and increased in 2005.⁵⁴

Israel

In a health care population of women ranging from 118 724 in 2000 to 154 447 in 2007,⁵⁵ there was a “brief drop in breast cancer incidence in early 2003, followed by a rise in early 2004”. Intensive mammography screening began in 2004, and was followed by a rising incidence.

Finally, Gompel and Plu-Bureau¹⁵ have pointed out that the age-specific fluctuations in breast cancer incidence reported throughout Europe, fit well with “different levels of implementation of mammography screening in ... 1995”, as reported by Hemminki *et al.*⁵⁶ (see: Confounding).

To conclude: following publication of the WHI findings in 2002, under the assumption of an immediate risk reduction attributable to the withdrawal of HRT, a decline in breast cancer incidence should consistently have been observed in all or virtually all subsequent studies, and it has not been. The decline should also have continued for several years, and it did not (see: Dose/duration response; see: Biological plausibility).

Even within the USA, and sometimes even within the same databases (e.g. SEER and Kaiser Permanente) the findings have been inconsistent (e.g. variable findings for ER+ and ER– tumours). Analogous considerations apply to the findings in Canada, Australia and Europe. In some instances, contradictory results among studies in the same country have been reported (e.g. Germany, Norway).

One general pattern that has emerged is that in the majority of studies in which a decline in breast cancer incidence has been reported, it commenced before 2002, well before the major decline in HRT use

commenced (see: Time order). To get around that difficulty, some proponents have speculated that the observed declines in incidence may partly be attributable to factors other than the drop in HRT use (see: Confounding). With ecological data that speculation cannot be tested.

The most important factor that was not adequately allowed for in the various studies was the effect of variable levels of mammographic screening (see: Confounding). Again, with ecological data, such allowance was not feasible.

BIOLOGICAL PLAUSIBILITY

In Parts 1–4 of this series of articles^{7–10} we have referred to some mechanisms that are compatible with an increased risk of breast cancer,⁵⁷ and other mechanisms that are compatible with a decreased risk.⁵⁸

Briefly, the hypothesis is that the purported increased risk of breast cancer, observed in the CR,¹ WHI² and MWS,³ among users of estrogen combined with a progestogen is due to accelerated multiplication (promotion) of cells that have already been genetically damaged.⁵⁷ With regard to a possible decrease in the risk, there is some evidence that estrogen may accelerate apoptosis in genetically damaged malignant cells.⁵⁸

Here, the hypothesis is that as soon as HRT is stopped the promotional effect conferred by exposure ceases immediately, and may even be reversed. Some indirect evidence supports that possibility: the estrogen-blocking effects of tamoxifen can substantially slow the growth of even advanced or metastatic tumours.²⁴ It is possible that withdrawal of HRT may have analogous effects. However, the effect of withdrawal on cancer cells has not been tested *in vivo*.

Following the onset of genetic damage to breast tissue it has been estimated that, on average, at least a decade elapses before breast cancer becomes clinically detectable.⁵⁹ And correspondingly, under the same hypothesis it might be expected that reversal of a promotional effect following the withdrawal of HRT would confer a reduction in the incidence of breast cancer that would last for several years – which has not been the case.³⁶

CONCLUSIONS

We conclude that the ecological evidence to support the hypothesis that the incidence of breast cancer declines as soon as HRT is stopped does not adequately satisfy the principles of time order, bias, confounding, strength of association, dose/duration-response, internal consistency, or external consistency; biological plausibility cannot be assessed.

We have previously concluded that HRT, or certain forms of HRT, may or may not increase the risk of breast cancer,^{7–10} but that the CR,¹ WHI² and MWS³ did not establish that it does. We now add that the ecological evidence is too limited either to support or refute the hypothesis that HRT causes breast cancer.

Author affiliations

¹Visiting Professor of Epidemiology, Department of Epidemiology, University of Cape Town, Cape Town, South Africa

²Emeritus Professor of Epidemiology, Department of Epidemiology, University of Surrey, Guildford, UK

³Consultant Physician and Reader in Metabolic Medicine, National Heart and Lung Institute, Imperial College, London and Brompton Hospital, London, UK

⁴Emeritus Director, Prince Henry's Institute of Medical Research, Monash Medical Centre, Clayton and Consultant Endocrinologist, Jean Hailes Medical Centre for Women, Clayton, Victoria, Australia

⁵Professor of Clinical Pharmacology and Endocrinology, Department of Endocrinology, University Women's Hospital, Tübingen, Germany

⁶Professor of Gynaecology, Gynaecological Endocrinology Unit, Paris Descartes University, APHP, Port-Royal Hospital, Paris, France

Funding None.

Competing interests Samuel Shapiro, John Stevenson, Henry Burger, Alfred Mueck and Anne Gompel presently consult, and in the past have consulted, with manufacturers of products discussed in this article. Richard Farmer has consulted with manufacturers in the past.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997;350:1047–1059.
- 2 Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–333.
- 3 Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2003;362:419–427.
- 4 The Women's Health Initiative Steering Committee. Effect of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–1712.
- 5 Stefanick ML, Chlebowski RT, Manson JE, *et al.* Effects of conjugated equine estrogens on breast cancer and mammographic screening in postmenopausal women with hysterectomy. *JAMA* 2006;295:1647–1657.
- 6 LaCroix AZ, Chlebowski RT, Manson JE, *et al.* Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305–1314.
- 7 Shapiro S, Farmer RDT, Seaman H, *et al.* Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. Part 1. The Collaborative

- Reanalysis. *J Fam Plann Reprod Health Care* 2011; 37:103–109.
- 8 Shapiro S, Farmer RDT, Mueck AO, *et al.* Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. Part 2. The Women's Health Initiative: estrogen plus progestogen. *J Fam Plann Reprod Health Care* 2011;37:165–172.
 - 9 Shapiro S, Farmer RDT, Seaman H, *et al.* Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. Part 3. The Women's Health Initiative: unopposed estrogen. *J Fam Plann Reprod Health Care* 2011;37:225–230.
 - 10 Shapiro S, Farmer RDT, Seaman H, *et al.* Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. Part 4. The Million Women Study. *J Fam Plann Reprod Health Care* 2012;38:102–109.
 - 11 Haas JS, Kaplan CP, Greenberger MS, *et al.* Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann Int Med* 2007;140:184–188.
 - 12 Ravdin PM, Cronin KS, Howlader N, *et al.* Reduced hormone therapy use might be cause of steep decline in breast cancer cases. Abstract presented at the San Antonio Breast Cancer Symposium, San Antonio, TX, USA, 14 December 2006.
 - 13 Ravdin PM, Cronin KA, Howlader N, *et al.* The decrease in incidence of breast cancer in the United States. *N Engl J Med* 2007;356:16:1670–1674.
 - 14 Clarke C, Glaser SL, Uratsu CS, *et al.* Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population evidence. *J Clin Oncol* 2006;33:e49–e50.
 - 15 Gompel A, Plu-Bureau G. Is the decrease in breast cancer incidence related to a decrease in postmenopausal hormone therapy? *Ann NY Acad Sci* 2010;1205:268–276.
 - 16 Pelucchi C, Levi F, La Vecchia C. The rise and fall in menopausal therapy and breast cancer incidence. *Breast* 2010;19:198–201.
 - 17 International Agency for Research on Cancer (IARC). *Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking* (Volume 83). Lyon, France: IARC, 2004.
 - 18 Susser M. *Causal Thinking in the Health Sciences*. New York, NY: Oxford University Press, 1979.
 - 19 US Depart of Health, Education and Welfare: Public Health Service. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service* (Public Health Service Publication No. 11030). Washington, DC: US Government Printing Office, 1964.
 - 20 Hill AB. The environment and disease: association or causation? *Proc Royal Soc Med* 1965;58:295–300.
 - 21 Susser M. What is a cause and how do we know one? A grammar for pragmatic epidemiology. *Am J Epidemiol* 1991;133:635–648.
 - 22 Colditz GA. Decline in breast cancer incidence due to removal of promoter: combination estrogen plus progestin. *Breast Cancer Res* 2007;9:108–111.
 - 23 Sprague BL, Trentham-Dietz A, Remington PL. The contribution of postmenopausal hormone use cessation to the declining incidence of breast cancer. *Cancer Causes Control* 2011;22:125–134.
 - 24 Smith IE, Dowsett M, Ebbs Sr, *et al.*, IMPACT Trialists Group. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 2005;23:5108–5116.
 - 25 Cady B, Chung MA, Michaelson JS. A decline in breast cancer incidence. *New Engl J Med* 2007;357:511.
 - 26 Ravdin PM, Cronin KA, Chlebowski RT. The authors reply. *N Engl J Med* 2007;337:513.
 - 27 Greendale GA, Reboussin BA, Sie A, *et al.* Effect of estrogen and of estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. *Ann In Med* 1999;130:262–269.
 - 28 Porter PL, El-Basstawissi AY, Mandelson MT, *et al.* Breast cancer tumor characteristics as predictors of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 1999;91:2020–2028.
 - 29 Kerlikowske K, Miglioretti DL, Buist DS, *et al.* Declines in breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst* 2007;99:1–5.
 - 30 Breen N, Cronin KA, Meissner HI, *et al.* Reported drop in mammography. Is this cause for concern? *Cancer* 2007;109:2405–2409.
 - 31 Glass AG, Lacey JV, Carreon D, *et al.* Breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 2007;99:1152–1161.
 - 32 Caan B, Habel L, Quesenberry C, *et al.* Re: declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst* 2008;100:597–598.
 - 33 Shapiro S. Commentary: Bias in the evaluation of low-magnitude associations: an empirical perspective. *Am J Epidemiol* 2000;151:939–945.
 - 34 Robbins AS, Clarke CA. Regional changes in hormone therapy use and breast cancer incidence in California from 2001 to 2004. *J Clin Oncol* 2007;26:3437–3439.
 - 35 International Agency for Research on Cancer (IARC). *Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking* (Volume 72). Lyon, France: IARC, 1999.
 - 36 DeSantis C, Howlader N, Cronin K, *et al.* Breast cancer incidence rates in U.S. women are no longer declining. *Cancer Epidemiol Biomarkers Prev* 2102;20:733–739.
 - 37 Jemal A, Ward E, Thun M. Recent trends in breast cancer incidence rate by age and tumor characteristics in U.S. women. *Breast Cancer Res* 2007;9:R28.
 - 38 Li CI, Roger EM, Daling JR. Risk of mortality by histologic type of breast cancer among women aged 50 to 79 years. *Arch Int Med* 2003;163:2149–2153.
 - 39 Kliever EV, Demers AA, Nugent ZJ. A decline in breast cancer incidence. *N Engl J Med* 2007;357:509–510.
 - 40 Canfell K, Banks E, Moa AM, *et al.* Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *Med J Austral* 2008;188:641–644.
 - 41 Canfell K, Banks E, Clements M, *et al.* Sustained lower rates of HRT prescribing and breast cancer incidence in Australia since 2003. *Breast Cancer Res Treat* 2009;117:671–673.
 - 42 Australian Institute of Health and Welfare. *Cancer Incidence Projections: Australia 2011–2020* (Cancer Series No. 66). Canberra, Australia: Australian Institute of Health and Welfare, 2012;31–33.
 - 43 Katalinic A, Rawal R. Decline in breast cancer incidence after decrease in utilization of hormone replacement therapy. *Breast Cancer Res Treat* 2007;107:427–430.
 - 44 Mueck AO, Wallwiener D. Brustkrebsrate und HRT-verordnungen: differierende daten aus USA und Europa. *Frauenarzt* 2007;48:812–817.

- 45 Levi F, Randombison I, Choffat R. Cancer incidence in Vaud, Switzerland (1998–2002). In: Curado MB, Edwards B, Shin JMR, *et al.* (eds). *Cancer Incidence in Five Continents*. IARC Scientific Publications No. 160, Vol. DC. Lyon, France: IARC, 2007;369–377.
- 46 Verkooijen HM, Koot VC, Fioretta R, *et al.* Hormone replacement therapy, mammography screening and changing age-specific incidence rates of breast cancer: an ecological study comparing two European populations. *Breast Cancer Res Treat* 2008;120:519–523.
- 47 Bouchardy CM, Usel H, Verkooijen C, *et al.* Changing pattern of age-specific breast cancer incidence in the Swiss canton of Geneva. *Breast Cancer Res Treat* 2010;120:519–523.
- 48 Parkin DM. Is the recent fall in incidence of post-menopausal breast cancer in the UK related to changes in use of hormone replacement therapy? *Eur J Cancer* 2009;45:1649–1653.
- 49 Zahl BH, Maehlen J. A decline in breast cancer incidence. *N Engl J Med* 2007;357:510–511.
- 50 Kumle M. Declining breast cancer incidence and decreased HRT use. *Lancet* 2008;372:608–610.
- 51 Allemand H, Seradour B, Weill A, *et al.* Decline in breast cancer incidence in 2005 and 2006 in France: a paradoxical trend. *Bull Cancer* 2008;95:11–15.
- 52 Seradour B, Allemand H, Weill A. Changes by age in breast cancer incidence, mammography screening and hormone therapy use in France from 2000 to 2006. *Bull Cancer* 2009;96:E1–E66.
- 53 Soerjomataram I, Coebergh JW, Louwman MW, *et al.* Does the decrease in hormone replacement therapy also affect breast cancer risk in the Netherlands? *J Clin Oncol* 2007;25:5038–5039.
- 54 Vankrunkelsven P, Keilen E, Louisbergh D, *et al.* Reduction in hormone replacement therapy and declining breast cancer incidence the Belgian province of Limburg. *Breast Cancer Res Treat* 2009;118:425–432.
- 55 Silverman BG, Siegelmann-Danieli N, Braunstein R, *et al.* Trends in breast cancer incidence associated with reductions in the use of hormone replacement therapy. *Cancer Epidemiol* 2010;35:11–16.
- 56 Hemminki E, Kyronen P, Pukkala E. Postmenopausal hormone drugs and breast and colon cancer: Nordic countries 1995–2005. *Maturitas* 2008;61:299–304.
- 57 Seeger H, Wallwiener D, Kraemer E, *et al.* Comparison of possible carcinogenic estradiol metabolites: effects on proliferation, apoptosis and metastasis of human breast cancer cells. *Maturitas* 2006;54:72–77.
- 58 Mueck A, Seeger H. 2-Methoxyestradiol – biology and mechanism of action. *Steroids* 2010;75:625–631.
- 59 Dietel M, Lewis MA, Shapiro S. Hormone replacement therapy: pathobiological aspects of hormone-sensitive cancers in women relevant to epidemiological studies on HRT: a mini-review. *Hum Reprod* 2005;20:2052–2060.