Does hormone replacement therapy cause breast cancer? Commentary on Shapiro *et al.* papers, Parts 1–5

Nick Panay

Chairman, British Menopause Society; Consultant Gynaecologist, Queen Charlotte's & Chelsea Hospital, and Chelsea and Westminster Hospital; Honorary Senior Lecturer, Imperial College London, London, UK

Correspondence to

Mr Nick Panay,
Queen Charlotte's & Chelsea
Hospital, Du Cane Road,
London W12 0HS, UK;
nickpanay@msn.com

Received 1 January 2013

Revised 2 February 2013

Accepted 4 February 2013

INTRODUCTION

Menopause symptoms are often debilitating, affecting personal, social and professional quality of life. The majority of women use hormone replacement therapy (HRT) for valid reasons having carefully weighed up the pros and cons. Young women with premature menopause also require HRT for the primary prevention of osteoporosis, cardiovascular disease and dementia. Following the findings of three studies, the Collaborative Reanalysis (CR),¹ the Women's Health Initiative (WHI),² and the Million Women Study (MWS),³ it has been claimed that HRT is an established cause of breast cancer. As a result of this, and despite the many accepted benefits of HRT, a significant proportion of women who could benefit from HRT are not using it.

The WHI and MWS had a profound effect on the prescribing of HRT and therefore on the lives of millions of menopausal women. Prescribing declined by more than two-thirds in most countries, including the UK, particularly by primary health care professionals who qualified in the last decade. Women were left feeling confused and at times terrified by alarmist headlines. This was illustrated by a survey through the Menopause Matters website where 70% of women who came off their HRT were aged less than 50 years and given current knowledge, 45% would not have discontinued therapy.⁴ A series of critiques of these studies (Parts 1–4)^{5–8} have been published in previous issues of this Journal. The latest paper in this series (Part 5)⁹ examines the reported decline in the incidence of breast cancer and possible attribution to the fall in HRT usage post WHI and MWS.

IMPACT OF INITIAL TRIAL FINDINGS

The WHI set out to examine the effects of HRT in a much older (average age

63 years), largely asymptomatic population of women. The premature cessation of the WHI in 2002 was accompanied by reports that HRT led to increases in the incidence of coronary heart disease, stroke, dementia and breast cancer. The risks were alarmingly reported as percentages rather than absolute numbers, for example, a 26% increase in risk of breast cancer (rather than 1 extra case per 1000 women per year). The MWS was a questionnaire survey of women attending breast screening in the UK with subsequent follow-up of breast cancer cases from the national registry. This study also raised concerns over the long-term safety of HRT, suggesting that combined hormone therapy “doubled” breast cancer risk. The impact of these studies was further enhanced by strong statements from various regulatory authorities from around the world.

COLLABORATIVE REANALYSIS, WHI AND MWS CRITIQUE

The design and results of the WHI have been subject to intense criticism ever since publication in 2002. The validity of the results has recently been debated not only in the papers of Shapiro *et al.*^{5–9} but also in reviews in the ‘WHI issue’ of *Climacteric*.¹⁰ Breast cancer risks from the WHI study have been adjusted by investigators over the last decade, such that statistical significance has become borderline, with doubt cast over the association being causal.⁶ The significant reduction in risk of breast cancer in hysterectomised women using estrogen alone in the WHI trial has been given little publicity. Benefits related to bowel cancer, fracture incidence and overall mortality as well as risk stratification based on age, which demonstrated cardiovascular benefit in younger cohorts, also received little attention. A recent

To cite: Panay N. *Journal of Family Planning and Reproductive Health Care* 2013;**39**:72–74.

commentary called for an inquiry into the manner in which the initial results of WHI were reported, in view of the profound impact this had on the lives of women.¹¹

Shapiro and colleagues applied causal criteria, such as biases and biological plausibility, to also assess the CR⁵ and MWS⁸ findings. Their analysis highlighted several design flaws that would potentially have skewed the findings. They concluded that “HRT may or may not increase the risk of breast cancer, but the CR did not establish that it does”. In their subsequent critique of the MWS they went on to state that “the name ‘Million Women Study’ implies an authority beyond criticism or refutation”. “Yet it was an observational study, with attendant problems and uncertainties intrinsic to such studies. The evidence was unreliable and thus the only effect of its massive size was to confer spurious statistical authority to doubtful findings.”

FALLING BREAST CANCER RATES

The claim of falling breast cancer rates being linked to cessation of HRT mainly followed the publication of two ecological studies.^{12 13} In their latest critique, Shapiro *et al.*⁹ reasonably conclude that based on the observed trends in the incidence of breast cancer following the decline of HRT use, the ecological evidence is too limited either to support or refute the possibility that HRT causes breast cancer. For instance, breast cancer rates started to decline before publication of the WHI results. The data do not satisfy a number of key criteria including time order, detection bias, confounding, statistical stability, strength of association, internal consistency, and external consistency; biological plausibility was too difficult to assess. As with the WHI and MWS studies, further data are required to clarify the controversy.

THE WAY FORWARD WITH HRT

The WHI study was designed 20 years ago. HRT is discussed as if it were one entity with identical benefit and risk outcomes. Preparations in use nowadays are lower dose, often transdermal and identical to endogenous hormones, and as such could have completely different risk profiles. Recent observational data have suggested that the risk of breast cancer is neutral if natural progesterone is used; these findings require confirmation from prospective trials.¹⁴ New data from the Kronos Early Estrogen Prevention Study (KEEPS)^{15 16} and a Danish trial¹⁷ reaffirmed the belief of many health professionals in menopause medicine that early treatment with HRT during the ‘window of opportunity’ seems to confer many benefits and has few risks. However, the KEEPS trial was not large enough to study hard outcomes, reporting mainly on quality of life parameters and cardiovascular risk markers. The Danish trial reported a neutral impact on breast cancer risk after 16 years of follow-up, but due to a low event rate the cancer outcomes must be

interpreted with caution. Also, subjects in the Danish trial were randomised to “no treatment” rather than placebo. Ideally we need the definitive randomised prospective trial where women, given current knowledge, are treated with the correct hormones, for the correct indication, in the correct age group with sufficient power to study major benefits and risks.¹⁸

THE BRITISH MENOPAUSE SOCIETY POSITION

The British Menopause Society (BMS) has published observations and recommendations as part of the consultation process initiated by the Coalition Government to modernise the National Health Service.¹⁹ The recommendations of the BMS represent a substantial position statement on how menopausal women’s health should be optimised. These clear benchmarks should facilitate the development of locally applicable, high-quality, cost-effective standards for the care of menopausal women.

CONCLUSIONS

The arguments regarding the validity of the CR, WHI, MWS and breast cancer rate studies could rage on for years. We should learn what we can from previous trials and clarify their limitations, but we should not be distracted from the important task that lies ahead of us. Whilst epidemiologists argue whether small relative risks are valid, we must not forget the main point of the argument, which is how are we going to optimise the lives of millions of women going through the menopause transition in the ever-aging population of the 21st century? If there is a risk, the risk is small, and the benefits of HRT can be life altering; it is vital that we keep this in perspective when counselling our patients.

Competing interests The author is currently Chairman of the British Menopause Society. He has received honoraria and grants from pharmaceutical companies for lecturing, advisory board work and sponsored research.

Provenance and peer review 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 randomised controlled trial. *JAMA* 2002;288:321–333.
- 3 Million Women Study Collaborators. Breast cancer and HRT in the Million Women Study. *Lancet* 2003;362:419–427.
- 4 Cumming GR, Currie HD, Panay N, *et al.* Stopping hormone replacement therapy: were women ill advised? *Menopause Int* 2011;17:82–87.

- 5 Shapiro S, Farmer RD, Mueck AO, *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.
- 6 Shapiro S, Farmer RD, 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.
- 7 Shapiro S, Farmer RD, Mueck AO, *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.
- 8 Shapiro S, Farmer RD, Stevenson JC, *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.
- 9 Shapiro S, Farmer RD, Stevenson JC, *et al.* 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. *J Fam Plann Reprod Health Care* 2013;39:80–88.
- 10 Fenton A, Panay N. The Women's Health Initiative – a decade of progress. *Climacteric* 2012;15:205.
- 11 Utian WH. A decade post WHI, menopausal hormone therapy comes full circle – need for independent commission. *Climacteric* 2012;15:320–325.
- 12 Ravdin PM, Cronin KA, Howlader N, *et al.* The decrease in incidence of breast cancer in the United States. *N Engl J Med* 2007;356:1670–1674.
- 13 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.
- 14 Fournier A, Fabre A, Mesrine S, *et al.* Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. *J Clin Oncol* 2008;26:1260–1268.
- 15 Harman SM, Brinton EA, Cedars M, *et al.* KEEPS: the Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8:3–12.
- 16 Kronos Longevity Research Institute. Hormone therapy has many favorable effects in newly menopausal women: initial findings of the Kronos Early Estrogen Prevention Study (KEEPS). Press release dated 3 October 2012. <http://www.menopause.org/docs/agm/general-release.pdf?sfvrsn=0> [accessed 2 February 2013].
- 17 Schierbeck LL, Rejnmark L, Tofteng CL, *et al.* Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial. *BMJ* 2012;345:e6409.
- 18 Panay N, Fenton A. Has the time for the definitive, randomized, placebo-controlled HRT trial arrived? *Climacteric* 2011;14:195–196.
- 19 British Menopause Society Council. Modernizing the NHS: observations and recommendations from the British Menopause Society. *Menopause Int* 2011;17:41–43.

FACULTY AWARDS

The Faculty of Sexual and Reproductive Healthcare has available a number of annual awards for which applications are invited from Faculty members and non-members as listed below. Details of the individual awards, together with an application form and/or guidelines on how to apply and any eligibility criteria, may be found on the Faculty website at www.fsrh.org.

Margaret Jackson Prize Essay

Award: Three prizes awarded annually for the best essays on a topic related to contraceptive, reproductive and sexual health care. The first prize is £300, with £100 each for the two runners-up.

Eligibility: Individuals (undergraduate medical students)

Closing date: 24 March annually

The David Bromham Annual Memorial Award

Award: Prize awarded for a piece of work which, through inspiration, innovation or energy, has furthered the practice of sexual and reproductive health care in any way and any setting.

Eligibility: Individuals (Faculty members) or teams

Closing date: 7 April annually