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Hormone replacement therapy and breast cancer: where are we now?

Jo Marsden

Background

Breast cancer generates considerable lay and health professional anxiety, regularly attracting media publicity with frequent, often sensationalist headlines. The development of this disease is complex, resulting from a combination of genetic, reproductive and lifestyle factors including long-term exposure to hormone replacement therapy (HRT). The recognised association with HRT, however, has attracted disproportionate attention following the publication of three studies between 2002 and 2004, namely the Women's Health Initiative (WHI), the Million Women Study (MWS) and the HABITS (hormonal replacement therapy after breast cancer – is it safe?) studies and their accompanying media publicity. Furthermore, confusing advice from regulatory authorities has not helped to maintain health professional confidence in HRT. Now that the initial furore surrounding these studies has settled, the question one needs to ask is whether the recent concern generated about breast cancer was justified? To answer this question it is worth considering what these recent studies have added to our previous knowledge and how the results of these studies have been disseminated.

Findings of recent studies

Prior to 2002, advice about the breast safety of HRT was based on observational trial evidence. In essence this encompassed the 1997 Collaborative Group for Hormonal Factors in Breast Cancer re-analysis of worldwide observational studies (predominantly these studies evaluated the effect of unopposed estrogen replacement) and subsequent observational studies specifically investigating the impact of combined HRT.[1,2] Overall, the degree of risk conferred by HRT was estimated to be equivalent to that of delaying the onset of the menopause, was found to be duration-dependent (emerging after 5 years' exposure) and greatest with combined therapy, suggesting that the addition of a progestogen was most relevant in conferring the observed risk increase. Following HRT cessation, risk falls; this supports a growth-promoting effect on pre-existing cells that have already undergone malignant transformation rather than initiation of malignant transformation itself. For women at an increased risk of developing breast cancer due to either a family history or biopsy-proven high-risk benign breast condition (i.e. atypical ductal or lobular hyperplasia) the effect of HRT does not appear to be additive. Such women have a higher baseline breast cancer risk compared with those women at population risk and therefore it follows that their absolute risk with HRT will be correspondingly greater.[3]

The WHI and MWS studies reported similar degrees and trends of risk as were already known, both studies concluding that breast cancer incidence was greatest with combined HRT.[4–6] The placebo-controlled WHI study (i.e. Grade I evidence) supported a duration effect; with continuous combined HRT, risk began to emerge after 3 years' use.[4] The premature closure of the unopposed estrogen component of the WHI study where incidence was not increased with a median duration of exposure of 4.6 years to conjugated equine estrogen (0.625 mg/day), prevents firm conclusions being drawn as to whether longer-term use may have an adverse impact.[5] In contrast to the WHI study and all other published evidence, the MWS investigators found risk to be elevated with as little as a few months' exposure.[6] The methodology and interpretation of this observational study has been subject to significant criticism, including the fact that total HRT duration was almost certainly underestimated, as this was based on duration of exposure at study entry and was not prospectively followed up.

HRT use in breast cancer survivors

The question of the safety of HRT for the management of estrogen deficiency symptoms in breast cancer survivors has also been subject to medical and media controversy. HRT use in this population of women has come about due to the fact that many women experience estrogen deficiency symptoms due to breast cancer therapy that either reduces endogenous estrogen production or antagonises oestrogen activity. No alternative to HRT has yet been found to be effective in symptom management. Hypotheses that HRT will not increase recurrence in women with estrogen receptor-negative (ER –ve) disease or women with estrogen receptor-positive (ER +ve) cancer in the presence of the anti-estrogenic effect of tamoxifen cannot be confirmed by observational studies that have failed to show an adverse effect on recurrence with short-term use (i.e. up to 2.5 years) due to potential bias.[3] Three randomised trials (i.e. the HABITS and Stockholm studies and a UK trial) established to answer this question have all been closed prematurely following the preliminary interim analysis of the HABITS study that showed an increase in recurrence.[7] HABITS received a great deal of publicity (publication was accompanied by a press release) but the Stockholm study interim analysis that failed to show an adverse effect on recurrence received no publicity whatsoever (there was no accompanying press release).[8] The contrasting preliminary outcomes have been attributed to less tamoxifen use and increased progestogen exposure (the predominant combined HRT used in HABITS was continuous combined whereas in the Stockholm trial long-cycle HRT was preferentially used). It is impossible now that all randomised trials have been closed to answer this question with any certainty.

Risk communication and publicity

One of the most significant factors contributing to the recent heightened anxiety about HRT is the language in which risk was communicated in medical press releases and ensuing media reports. As statistical innumeracy is high in both health professionals and the lay public it was essential that provision of public health information about HRT was clear. In the WHI and MWS press releases HRT-associated risk was described as a single-event probability (e.g. percentage increase), relative risk or hazard ratio and

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Table 1 Absolute risk of developing breast cancer with hormone replacement therapy with expression of risk as relative risk, percentage change and absolute number of events

Study	Relative risk/hazard ratio of breast cancer (percentage increase)	Number of extra breast cancers attributable to HRT with 5 years' use
Collaborative re-analysis (1997)[1]		
Predominantly unopposed estrogen	1.53 (53%)	+2/1000
Women's Health Initiative (2003, 2004)[4,5]		
Combined HRT	1.26 (26%)	+4/1000
Unopposed estrogen	0.73 (–27%)[a]	–4/1000
Million Women Study (2003)[6]		
Combined HRT	2.00 (100%)	+6/1000

[a]Percentage decrease in risk (not statistically significant). HRT, hormone replacement therapy.

absolute risk. In clinical practice, use of absolute risk with negative and positive framing is optimal as it removes ambiguity and is not open to the misinterpretation associated with percentage changes and relative risk, odds or hazard ratios.[9] There is a strong case arguing for the avoidance of these latter expressions of risk in any press release as they often suggest a greater degree of conferred risk than is the case in reality and hence are open to misinterpretation. This is exemplified in Table 1 where the relative risk, percentage change and corresponding absolute risk from the collaborative re-analysis, WHI and MWS studies are summarised. In the case of recent HRT studies, one could question whether use of absolute risk numbers alone would have attracted significant journalistic attention. Those who write and review research press releases must share responsibility with the media for the sensationalist, negative HRT headlines. No one wishes to underestimate the impact that a diagnosis of breast cancer will undoubtedly have, but there is an obligation to present research findings clearly.

Breast cancer and HRT is an emotive issue and it is not surprising that research on this topic attracts attention. So how do journals and medical charities determine which research should be issued with a press release and what purpose is served by doing so? In an era of the 'journal impact factor', press releases have been argued to be self-interested and governed by anticipated popular taste.[9] Certainly research concerning women's health issues and cancer is more likely to be selected. For reasons unknown, no press release was issued when the 'neutral', preliminary findings of the Stockholm study were published in 2005. Given all the worry surrounding HRT, this could have stimulated relevant media debate. Conversely, being 'good' news would a press release have generated any media coverage? Accusations of self-interest and popular taste can also be levelled at media coverage as press releases relating to breast cancer and negative outcomes are more likely to result in their attention.[10]

Role of the medicine regulatory authorities

The final nail in the coffin that undermined health professional confidence in the breast safety of HRT was the confusing advice issued by medicine regulatory bodies. Collectively they appear to have failed to comprehend that the WHI and MWS studies did not show a new breast safety issue or significant discrepancy in estimated risk when compared with previous evidence. With respect to breast cancer risk, the European Union's Heads of Agencies and Committee on Safety of Medicines have recommended that the balance of benefits and risks of HRT is favourable for the treatment of menopausal symptoms that adversely affect quality of life but is unfavourable for the use of HRT as first-line treatment for osteoporosis prevention. The recommendation that HRT should be used at the minimum effective dose for the shortest duration is oft repeated (and can be found in the National Institute for Clinical Excellence 2004 guidance on familial breast cancer)[11] but neither of these parameters has been defined and there is no evidence to support a dosage effect.

Conclusions

So given all the recent evidence, what should women be advised about HRT and breast cancer? With short-term use (i.e. up to 3 years' combined HRT or up to 5 years' unopposed estrogen) risk is not increased. For women who wish to continue HRT for a longer duration it is reasonable to review the perceived and real indications for doing so, but only if the women concerned are appraised of current uncertainty and the fact that absolute risk will be dependent on an individual's baseline risk. There is no indication for additional mammographic screening for women using HRT since this will only generate unnecessary additional concern. For breast cancer survivors the question of the safety of HRT is still unresolved and justifies further research. More responsible medical and media reporting could have prevented recent headlines and misinformation about HRT. There is, however, unfortunately no mechanism for accountability. How can this serve the public health interest?

Statements on funding and competing interests

Funding The author is the principal investigator on the national UK randomised trial of HRT in symptomatic women with early stage breast cancer and has been sponsored to attend conferences and received speaker's fees from Organon, Orion, Schering, Servier, Solvay Healthcare Ltd and Wyeth. The author has received consultancy fees from Wyeth and Organon, and fees for preparation of educational material from Novartis.

Competing interests The author is also on the council of the British Menopause Society and a member of the European Menopause Society.

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A BETTER WAY OF WORKING

A multidisciplinary, multi-agency approach to a young person's sexual health clinic

Margaret Kingston

Background to the service development

Manchester Centre for Sexual Health (MCSH) and Brook Manchester submitted a successful joint bid for genitourinary medicine (GUM) development pilot funding in 2004 to set up a dedicated young person's clinic (YPC) at MCSH and establish a nurse practitioner post developing sexual health services at Brook with support from MCSH.

How is the new service organised?

The YPC at MCSH commenced in April 2005. An upper age limit of 19 years was set; those under 16 years are assessed by a health advisor and senior doctor using a young person's proforma and in accordance with the Fraser Guidelines (a process agreed by the Trust child protection lead). The YPC runs from 3.30 pm to 6.30 pm as a drop-in service accepting patients up to 5.30 pm. A full sexually transmitted infection (STI) screening service is provided and contraception offered when required. The number of patients seen at the clinic has risen steadily since it opened, with 1018 visits (790 of these new episodes) in the year April 2005–April 2006. The majority of patients are female (74% of attendances) and the average age is 18.6 years. STIs are frequently diagnosed, with a diagnosis of chlamydial infection being made in 16% of cases and genital warts in 9%.

The full complement of clinic staff comprises a consultant, a staff grade doctor, four nurse practitioners [including one from Brook and one from the Manchester Public Health Development Service (PHDS)], one health advisor, one staff nurse, two health care assistants and two clerical staff. It was decided that in order to fully utilise the skills of each member of staff appropriately we would move away from a traditional way of running a GUM clinic to a more flexible system.

How does the new service work in practice?

On arrival patients complete a simple self-triage form indicating their reason for attending the clinic with brief details of any symptoms. This form is placed at the front of their case notes. Any patient aged under 16 years is seen by the health advisor who makes the initial assessment in line with Fraser Guidelines. Using the self-triage forms the doctors and nurses take patients appropriately, with the doctors focusing on those with symptoms such as pelvic pain or genital ulceration and the nurse practitioners those requesting asymptomatic screens or attending as contacts of infection. Both doctors and nurses see those with symptoms such as vaginal or urethral discharge or warts. Treatment is dispensed by all staff members in line with clinic guidelines and nurses administer treatment according to patient group directions. Very young patients or those who have been assaulted are seen by the health advisor and consultant.

What benefits does the new service offer?

This system requires flexibility in patient allocation and cross-referral between staff occurs regularly. We have found that bottlenecks in the system occur infrequently and that patient throughput with this system is efficient. The system also required most staff to be trained in family planning and GUM. This new way of working in our department and with our Brook and PHDS colleagues has proved a success that we hope to continue to build upon in the future.

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READERS' CONTRIBUTIONS INVITED ON 'A BETTER WAY OF WORKING'

Launching in this issue (see article above) is a new feature entitled 'A Better Way of Working', the purpose of which is to disseminate service delivery suggestions likely to be of interest and relevance to the Journal's readership.

Readers are invited to submit suggestions based on their own personal experience for consideration by the Journal Editor. Contributions should not exceed 250–500 words and should be written in a standardised format responding to the following four questions (or similar): Why was change needed? How did you go about implementing change? What advice would you give to others who might be considering a similar course of action? How did you show that the change had occurred?

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