EDITORIALS

Hormone replacement therapy: is it safe for breast cancer patients?

Probably in the short term, but results of ongoing trials are needed to determine longer-term safety

OESTROGENS PLAY AN IMPORTANT ROLE in the development of breast cancer. This is most evident in postmenopausal women: circulating levels of endogenous oestradiol are higher in those who develop breast cancer,[1] while use of hormone replacement therapy (HRT) increases breast cancer risk.[2] Recent results from the Women's Health Initiative randomised trial showed a 26% excess rate of breast cancer development in women who took combined continuous equine oestrogens and medroxyprogesterone acetate for a mean of 5.2 years compared with placebo.[3] This finding is consistent with results of earlier epidemiological studies that suggest breast cancer incidence is increased more by combined preparations than by oestrogen alone.[2] Further evidence that oestrogen is important in breast cancer development comes from a study of over 9300 postmenopausal women with early breast cancer.[4] This found that anastrozole (an aromatase inhibitor that dramatically reduces oestrogen production) significantly reduced the rate of new contralateral breast cancers compared with tamoxifen (hazard ratio, 0.42; 95% CI, 0.22–0.79; $P = 0.005$).[4]

Despite the increased incidence of breast cancer in women who use HRT, most studies have shown either no effect on mortality or a decrease.[5] The reason appears to be that breast cancers that develop in HRT users are smaller and clinically less advanced, with a lower rate of node positivity, better differentiation and more favourable histological type, than cancers that develop in women not using HRT.[2]

Menopausal symptoms are reported by two-thirds of postmenopausal women with breast cancer.[6] Can HRT be safely used by these women, or does it have the same impact on breast cancer recurrence as it appears to have on breast cancer development? A number of publications have addressed this issue. One systematic review documented 11 studies involving 214 women who took HRT after a diagnosis of breast cancer, and found that the risk of breast cancer recurrence was lower in HRT users (relative risk [RR], 0.64 (95% CI, 0.36–1.15) than in control women who did not use HRT.[5] Durna and colleagues report similar findings in this issue of the Journal (*page 347*).[7] They found significantly lower rates of recurrence (RR, 0.62; 95% CI, 0.43–0.87) and death from breast cancer (RR, 0.40; 95% CI, 0.22–0.72) in women who used HRT compared with non-users.[7] These are important data and are also consistent with those of a recently published United States case–control study of 174 women who chose to use HRT after breast cancer diagnosis and matched non-users.[8] These three studies reported a consistent reduction in recurrence and death from breast cancer in breast-cancer survivors who used HRT to treat menopausal symptoms, but all had potential confounding factors.[5,7,8] All studies to date have been observational and are thus subject to a variety of biases. In the Australian study, women who used HRT after treatment of breast cancer had smaller tumours and fewer involved nodes compared with non-users, and were more likely to have used HRT before diagnosis.[7] Although the final model adjusted for a number of prognostic factors, these did not include tumour grade, concurrent use of tamoxifen or oestrogen-receptor status. Concurrent tamoxifen is a particular confounding factor, as it was prescribed for almost 60% of women who used HRT, and would have limited the effects of oestrogen on normal and malignant breast epithelium.[9] Duration of HRT use after a diagnosis of breast cancer was short in all three studies — a median of only 1.75 years in the Australian study.

Socioeconomic factors could be part of the reason for the better outcome of women with breast cancer who take HRT

Surprisingly, in both the Australian[7] and American[8] studies there appeared to be a lower rate of breast cancer recurrence in patients taking progestogen alone, vaginal oestrogen alone, or a combination of the two. It is difficult to believe that the small amounts of oestrogen absorbed from vaginal preparations could have a positive influence on breast cancer recurrence and survival. This suggests that other characteristics of women who use HRT, whether vaginal or oral, may influence outcome. Socioeconomic status is an independent predictor of breast cancer recurrence and survival: women with more education and higher socioeconomic class have a lower recurrence rate and better survival.[10] Hot flushes are more commonly reported by educated women,[6] and these women are more likely to take HRT. Thus, socioeconomic factors could conceivably be part of the reason for the better outcome of women with breast cancer who take HRT.

What other possible reasons are there to explain why HRT use by women with breast cancer might improve survival? Most of the oestrogens used in HRT preparations are conjugated, a form that does not occur naturally in humans. They are termed "impeded oestrogens", as they interfere with the effect of more powerful, naturally occurring oestrogens, such as oestradiol, and their biological effect on breast cancer cells is unclear. In the pharmacological doses used, they are likely to have direct anti-oestrogenic effects and may also downregulate the oestrogen receptor. The progestogens used in combined HRT preparations may also have anti-oestrogenic effects and are weak aromatase inhibitors. This may be relevant in postmenopausal women, as much of the oestrogen present within their breast cancers is produced locally from androgens by aromatase.[11]

How should women with breast cancer who develop menopausal symptoms be treated? For vaginal dryness, water-based lubricating gels and vaginal moisturisers significantly improve symptoms. If these measures fail, then locally delivered oestrogens are effective.[12] For systemic symptoms, such as hot flushes, evening primrose oil, soya and black

cohosh are rarely effective, but low-dose megestrol acetate and the antidepressants venlafaxine and fluoxetine were shown to have benefits in randomised trials in breast-cancer survivors.[12,13] More recently, isoflavones from red clover were shown to reduce hot flush symptoms in postmenopausal women,[14] although there have been no studies in breast-cancer survivors. When these remedies fail, then HRT can be given in the knowledge that current data do not show any detriment in terms of recurrence or survival. Effective agents for osteoporosis in women with breast cancer include bisphosphonates, tamoxifen, raloxifene, diet and exercise.[12]

Ongoing randomised trials of HRT in breast-cancer survivors will determine whether longer-term HRT is safe. These trials will evaluate whether the increased incidence of breast cancer and reduced sensitivity of mammography in women using HRT[2] are important issues in women with breast cancer. Even if these trials show HRT to be safe, the problem in future will be how to treat menopausal symptoms in women taking one of the new aromatase inhibitors, which are already replacing tamoxifen in postmenopausal women with hormone-responsive breast cancer.[4] It makes no sense to give these women oestrogen. Ongoing studies are investigating the role of a variety of agents, including tibolone (a synthetic corticosteroid with oestrogenic, androgenic and progestational activity).

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Conference promotion in the media: serving whose interests?

Conference presentations are preliminary findings which should be interpreted with caution by the media, health professionals and the public

WHEN ORGANISERS BEGAN PLANNING the XXIXth International Congress of Ophthalmology, held in Sydney earlier this year, an early consideration was how to promote media coverage of the conference, with the aim of raising public awareness of the specialty of ophthalmology and eye health more generally. A company which specialises in media relations for medical conferences was retained to work with the conference scientific program committee to develop a media strategy. As a result of the press releases issued, there were more than 520 news reports in print, broadcast and online media in Australia and overseas, including substantial stories in major media outlets.

This is not an unusual scenario. Australian journalists are often approached to run stories arising out of conferences. In Europe and North America, where there is a larger market for such stories and a more established tradition of specialist medical and scientific reporting, media management of medical and scientific conferences is even bigger business. Such media management can have advantages for conference organisers, sponsors, participants, the media and the public:

- Conference organisers may wish to encourage media coverage as a way of promoting greater awareness of their profession or of particular health issues, and prefer to guide the media agenda so they are not left on the back foot, responding ad hoc to journalists' demands.
- Presenters may welcome media coverage to promote awareness of their work or professional interests. Corporate interests, conference funders and sponsors, and institutions such as universities, hospitals and research centres, often actively encourage such publicity. Indeed, both corporate and non-corporate interests have paid the expenses of Australian journalists to attend health and medical conferences, with the aim of promoting coverage.
- The media, driven by the community's thirst for health and medical news, finds conferences newsworthy on several grounds. Often they provide the first airing of research not yet formally published, and the timeliness of the presentation provides an additional "news hook". Also, conferences