CLIMACTERIC 2004;7:284–291

# Breast cancer in premenopausal women: recurrence and survival rates and relationship to hormone replacement therapy

*E. M. Durna, G. Z. Heller*, L. R. Leader, P. Sjoblom, J. A. Eden and B. G. Wren*[†]

School of Women's and Children's Health, University of New South Wales, Sydney; *Department of Statistics, Macquarie University, Sydney; [†]Barbara Gross Research Unit, Sydney Menopause Centre, Royal Hospital for Women, Sydney, Australia

Key words: MENOPAUSE, HORMONE REPLACEMENT THERAPY, BREAST CANCER, ESTROGEN PLUS PROGESTIN

## ABSTRACT

*Objectives* To determine any association between hormonal replacement therapy (HRT) usage and breast cancer recurrence and survival rates in women who were premenopausal at the time of diagnosis of breast cancer.

*Methods* The study group comprised 524 women who were diagnosed with breast cancer when they were premenopausal. Of these, 277 women reached menopause before recurrence of the disease, being lost to follow-up, or reaching the end of the study. In this group, 119 women took HRT to control menopausal symptoms. The majority took combined continuous estrogen–progestin treatment. Times from diagnosis to cancer recurrence or new breast cancer, to death from all causes, and to death from primary tumor were compared between HRT users and non-users.

*Results* Women who used HRT after their menopause had an adjusted relative risk of recurrence or new breast cancer of 0.75 (95% confidence interval (CI), 0.29–1.95) compared to that of non-users. The relative risk of death from all causes was 0.36 (95% CI, 0.11–1.16) and that of death from primary tumor was 0.24 (95% CI, 0.05–1.14).

*Conclusion* HRT use in women who were premenopausal at the diagnosis of primary invasive breast cancer is not associated with worse outcomes in terms of breast cancer recurrence or mortality.

## INTRODUCTION

Current epidemiological data on healthy women indicate that current users of postmenopausal hormone replacement therapy (HRT) have an increased risk of breast cancer. Controversy still exists whether hormonal therapy causes breast cancer or promotes growth of pre-existing tumors[1,2].

Breast cancer has been viewed as an absolute or relative contraindication to HRT in symptomatic women[3,4]. Concerns about promoting growth and/or disseminating occult malignant cells have been the primary considerations, despite there being no direct evidence to indicate that HRT worsens prognosis. To the best of our knowledge,

Correspondence: Professor J. A. Eden, School of Women's and Children's Health, Royal Hospital for Women, Barker St, Randwick, NSW 2034, Australia

ORIGINAL ARTICLE

DOI: 10.1080/13697130400001380

Received 13-10-03
Revised 27-01-04
Accepted 29-01-04

no studies of breast cancer patients who have been prescribed HRT have shown an increased risk of tumor recurrence or death from progressive disease[5–16]. Since it has been suggested that breast cancer in young women is more aggressive than in women who are postmenopausal at diagnosis[17], we believed it would be important to conduct a study of women who were premenopausal when diagnosed, some of whom would go on to use HRT. We have previously published a study using the same methodology, looking at the same outcomes in women who were postmenopausal when diagnosed with breast cancer[16]. The purpose of the present study was to determine whether HRT usage was associated with any negative outcomes with regard to recurrence and survival rates in women who were premenopausal when diagnosed with breast cancer.

## METHODS

### Study design

This study was a retrospective analysis of medical records with regard to recurrence and mortality among premenopausal women with histopathologically confirmed breast cancer. This research team did not deem it necessary to seek approval from a human research ethics committee, as the study was a retrospective audit.

The inclusion criterion for the study was histopathologically confirmed, primary invasive breast cancer, diagnosed before menopause. The women in this study were patients of three surgeons and two gynecologists in three tertiary hospitals in Sydney, Australia, treated either at the hospital menopause clinic or the doctor's private rooms. All women meeting the inclusion criterion, i.e. being treated by these doctors, were included in the database. For the present study, all women who were premenopausal, i.e. menstruating, at the time of diagnosis were included. All patients in the study were reviewed clinically 6–12 monthly to determine their response to the HRT treatment and for signs of cancer recurrence. The information about the age at menopause was obtained from patients during their annual follow-up visits. Data were collected from medical records of the subjects and, in case of incomplete information, complementary information was requested from the patient's general practitioner. If no response had been received by the end of 1999, the patient was contacted by letter or telephone.

The study population consisted of 524 premenopausal women of whom 277 reached menopause before recurrence, death, loss to follow-up, or the end of the study. Seventy-six women were lost to follow-up; their observation was censored at the date of the last specialist visit. Hormone replacement therapy was commenced at the time of menopause. Of the 277 women, 119 used HRT to control menopausal symptoms. The majority of women ($n = 75$ (63%)) took combined continuous estrogen–progestin therapy, because it seemed to be most effective in treating symptoms and had the best risk profile with regard to endometrial and bowel cancers[1,18,19]. All women were reassessed at 3 months after the initiation of HRT and, if the response was unsatisfactory, their HRT regimen was altered.

Nineteen women (15.9%) used continuous oral progestin for menopausal symptoms. Only a small number of women ($n = 5$ (4.2%)) took continuous oral estrogen. Ten women (8.4%) used vaginal estrogen cream in combination with continuous oral progestins. Vaginal estrogen only was taken by ten women (8.4%). Women who took progestins for advanced disease were excluded from the analysis.

Comparisons were made between non-users and users of all HRT types, and between non-users and users of continuous combined HRT. Because of the small number of subjects, comparisons between the different types of HRT could not be made.

The median daily dose of estrogen used by women taking continuous combined HRT was 0.625 mg conjugated equine estrogens (CEE) (range, 0.3–0.625 mg), or 1.25 mg estrone sulfate, or 2 mg estradiol valerate. The median daily dose of progestin in combined HRT was 50 mg medroxyprogesterone acetate (MPA, range 10–500 mg), or 5 mg norethisterone (range 1–5 mg). Women who took either estrogen or progestin only used similar doses. Vaginal estriol cream (0.5 g) and estradiol vaginal tablets (25 $\mu$g) were used twice weekly, either alone or combined with oral progestins, in doses similar to those in combined HRT.

Ages at diagnosis of breast cancer and menarche were entered as completed years. Other characteristics entered were parity, gravidity, menstrual status at diagnosis, tumor size ($< 2$ cm, 2–5 cm or $> 5$ cm), number of positive axillary lymph nodes, stage of the disease, and receptor status. HRT type and duration of use were recorded at the annual or biannual reviews. Data on tumor grade were incompletely recorded and therefore not analyzed. Women were followed up to the end of 1999 for cancer recurrence or new breast

cancer, death from primary tumor, or death from other cause. Observations were censored for cancer recurrence or new breast cancer at the time of death or last specialist visit, and for death from all causes at the last visit.

## Statistical analysis

The study population was divided into three groups:

(1) Patients who either experienced cancer recurrence or death before menopause, or dropped out of the study, or reached end of the study, before menopause;

(2) Patients who reached menopause before recurrence, death, drop-out, or study end, and did not take HRT;

(3) Patients who reached menopause before recurrence, death, drop-out, or study end and took HRT.

When analyzing the effect of HRT usage on recurrence and survival, only groups (2) and (3) were compared, since group (1) had not had the opportunity to take HRT and its inclusion would have severely biased the analysis. HRT usage was classified as all HRT types or combined estrogen–progestin. Cox regression analysis was carried out for the following outcomes: time from diagnosis to recurrence or new breast cancer, survival time (time from diagnosis to death from all causes), and survival time (time from diagnosis to death from primary tumor); the analysis was adjusted for the following covariates: stage of disease, tumor size, number of positive axillary nodes, age at diagnosis, age at menarche, age at menopause, parity, gravidity, and calendar year of diagnosis. The latter was considered to be a covariate because of the long time-span of this study, and was classified as: 1970–1979; 1980–1989; and 1990–1999. Only covariates significant at the 5% level were retained in the final regression models. Women who used HRT were compared with non-users, and comparison was also made between non-users and users of continuous combined estrogen–progestins. HRT usage was entered into the models as a (binary) time-dependent covariate.

One-way analysis of variance was used to compare continuous covariates across groups for normally distributed covariates, and the Mann–Whitney $U$ test was used for non-normally distributed covariates. The $\chi^2$ test for independence was used for categorical variables. Time-to-event variables were compared across groups using the log-rank test. All analyses were performed at a 5% level of significance.

## RESULTS

Five hundred and twenty-four premenopausal women who met the inclusion criterion were followed up for a median of 6.33 years (range, 0–27 years). The mean ($\pm$ standard error) age at diagnosis was 42.1 ($\pm$ 0.26) years. The characteristics of the patients are shown in Table 1.

As would be expected, patients who reached menopause were older at diagnosis ($p < 0.001$) than those who did not. A larger proportion of them had Stage I breast cancer ($p = 0.002$), had fewer axillary nodes that were positive ($p = 0.012$), and had smaller tumors, although this difference was not statistically significant ($p = 0.066$). Their parity was greater than that of those patients who did not reach menopause ($p = 0.009$).

Of the patients who reached menopause (groups 2 and 3), those who took HRT were significantly younger at diagnosis ($p = 0.001$), and experienced a longer time from diagnosis to menopause ($p < 0.001$) and a longer duration of follow-up ($p < 0.001$). In other respects, they were not statistically different from the group who did not take HRT. It appears from Table 1 that the difference between group 2 and group 3 with regard to distribution of disease stages was marginally significant ($p = 0.058$) in that women who took HRT were at an earlier stage of disease.

Table 2 shows that women who were younger at diagnosis tended to be at a more advanced stage of the disease ($p = 0.023$). Seventeen percent of patients aged 35 years or younger were at Stage III or IV, compared with 12% of patients aged 36–45 years, and 10% of those aged 46 years and older.

There were no statistically significant differences between recurrence and survival of HRT users compared with non-users, as seen in Table 3.

Stage of disease was the only covariate found to be significant in all of the Cox regressions. Other, non-significant covariates were excluded from the final regression models. In particular, age at diagnosis was not a significant determinant of recurrence or new breast cancer ($p = 0.10$), survival time (all cause mortality, $p = 0.56$), or survival time (death due to primary tumor, $p = 0.64$). Tamoxifen was not considered as a predictor in this model, because of its association with the stage of the disease and the tumor size. We also did not have knowledge as

**Table 1** Characteristics of the study population. Data are given as means ± standard errors or ranges, as appropriate

| | *Group 1* ($n = 247$) | *Group 2* ($n = 158$) | *Group 3* ($n = 119$) | $p_1$ | $p_2$ |
|---|---|---|---|---|---|
| *Age* (years) | | | | | |
| At diagnosis | 39.3 ± 0.4 $n = 247$ | 45.5 ± 0.3 $n = 156$ | 43.6 ± 0.5 $n = 119$ | < 0.001 | 0.001 |
| At menarche | 12.9 ± 0.1 $n = 158$ | 12.8 ± 0.1 $n = 109$ | 12.8 ± 0.1 $n = 117$ | 0.894 | 0.736 |
| At menopause | 47.9 ± 0.9 $n = 26$ | 48.5 ± 0.5 $n = 90$ | 48.7 ± 0.4 $n = 102$ | 0.695 | 0.765 |
| Parity | 1.8 ± 0.1 $n = 218$ | 2.2 ± 0.1 $n = 142$ | 2.1 ± 0.1 $n = 115$ | 0.009 | 0.285 |
| Gravidity | 2.4 ± 0.1 $n = 196$ | 2.8 ± 0.1 $n = 132$ | 2.5 ± 0.1 $n = 118$ | 0.074 | 0.123 |
| *Years from diagnosis* | | | | | |
| To menopause | | 3 (0–18) $n = 156$ | 4 (1–24) $n = 119$ | | < 0.001 |
| To HRT start | | | 6.3 (0–25) $n = 111$ | | |
| *Duration* (median) | | | | | |
| Of HRT after diagnosis | — | — | 2.5 (0–21) $n = 113$ | — | — |
| Of follow-up | 4.2 (0–23) $n = 246$ | 7.0 (1–24), $n = 158$ | 11.6 (2–27) $n = 117$ | < 0.001 | < 0.001 |
| Size of tumor (cm) | 2.3 ± 0.1 $n = 230$ | 2.2 ± 0.1 $n = 147$ | 1.8 ± 0.2 $n = 84$ | 0.066 | 0.076 |
| Positive axillary nodes | 0.6 ± 0.1 $n = 234$ | 0.5 ± 0.1 $n = 153$ | 0.4 ± 0.1 $n = 105$ | 0.012 | 0.127 |
| *Disease stage* ($n$ (%)) | | | | 0.002 | 0.058 |
| I | 150 (63%) | 100 (66%) | 86 (78%) | | |
| II | 48 (20%) | 36 (24%) | 20 (18%) | | |
| III/IV | 42 (17%) | 15 (10%) | 4 (4%) | | |
| *Treatment* (number of patients) | | | | | |
| Partial mastectomies | 124 | 67 | 41 | | |
| Mastectomies | 120 | 90 | 78 | | |
| Radiotherapy | 143 | 80 | 56 | | |
| Chemotherapy | 89 | 45 | 23 | | |
| Tamoxifen | 67 | 37 | 34 | | |

* Groups 1–3 are defined in the text

to whether the tamoxifen medication overlapped with HRT.

Figures 1–3 show the adjusted baseline survival functions for recurrence or new breast cancer, all-cause mortality, and mortality due to primary tumor, respectively. These demonstrate that the survival curves for the HRT and non-HRT groups are initially similar, and start diverging after about 3 years from diagnosis. This corresponds approximately to the median time for the onset of menopause from diagnosis, which is 3 years for the non-HRT group, and 4 years for the HRT group.

## DISCUSSION

To the best of our knowledge, no other study on HRT in women with breast cancer has analyzed

**Table 2** Number and percentage of patients at each stage of disease, by age group

| | *Stage of disease* | | |
|---|---|---|---|
| *Age at diagnosis* (years) | *I* | *II* | *III/IV* |
| ⩽ 35 | 46 (61%) | 17 (22%) | 13 (17%) |
| 36–45 | 154 (63%) | 61 (25%) | 30 (12%) |
| ⩾ 46 | 135 (76%) | 25 (14%) | 18 (10%) |
| Overall | 335 (67%) | 103 (21%) | 61 (12%) |

**Table 3** Recurrence and death rates, and adjusted relative risks

| | *Number of patients* | *Number of events* | *Rate per 1000 person-years* | *Adjusted relative risk (95% confidence interval)* |
|---|---|---|---|---|
| *Recurrence or new breast cancer* | | | | |
| No HRT | 158 | 26 | 20.8 | 1 (referent) |
| HRT (all types) | 119 | 18 | 12.8 | 0.75 (0.29–1.95) |
| Combined | 75 | 9 | 9.2 | 0.50 (0.22–1.13) |
| *Death from all causes* | | | | |
| No HRT | 157 | 12 | 9.1 | 1 (referent) |
| HRT | 115 | 4 | 2.8 | 0.36 (0.11–1.16) |
| Combined | 72 | 1 | 1.0 | 0.16 (0.02–1.25) |
| *Death from primary tumor* | | | | |
| No HRT | 157 | 9 | 6.8 | 1 (referent) |
| HRT | 115 | 2 | 1.4 | 0.24 (0.05–1.14) |
| Combined | 72 | 0 | 0.0 | 0.00 (0.00–∞) |

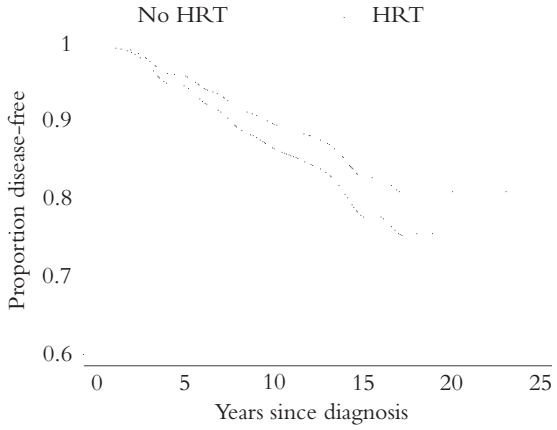


**Figure 1** Adjusted survival curve for disease-free interval

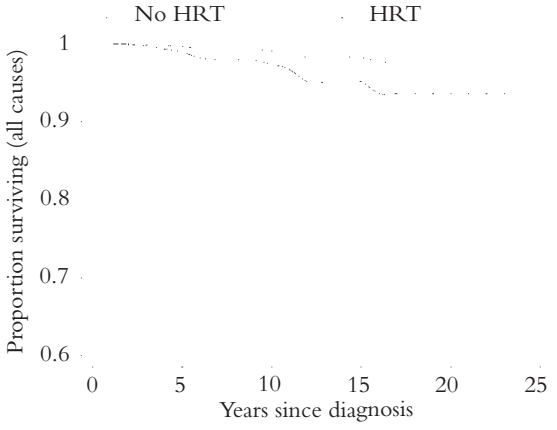


**Figure 2** Adjusted survival curve for all cause-mortality

premenopausal women as a separate group. Other studies on the use of HRT after breast cancer include both premenopausal and postmenopausal women.

In this study of women who were premenopausal at the diagnosis of breast cancer, the relative risk (RR) of recurrence or new breast cancer in users compared to that with non-users was 0.75 (CI, 0.29–1.95). The relative risk of death from all causes for users was 0.36 (CI, 0.11–1.16), and that of death from primary tumor for users was 0.24 (CI, 0.05–1.14). Thus, the relative risks for

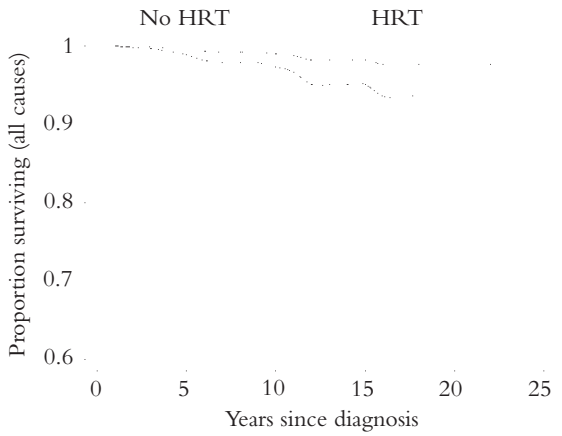


**Figure 3** Adjusted survival curve for mortality due to primary tumor

adverse events for women taking HRT compared with women not taking HRT were not significantly different from 1.0.

Our findings are in accord with the limited data available (all from observational studies) on the effect of HRT use on breast cancer survivors, which suggest that HRT use after breast cancer has no adverse impact on breast cancer recurrence and mortality[5–16].

We are unable to explain the difference in median length of follow-up between those who took HRT (11.6 years) and those who did not (7 years), or why women who took HRT attended their doctor on a more regular basis. The most likely explanation for the difference in the median lengths of follow-up is that women who took HRT attended their doctors on more regular bases to obtain supplies of HRT. It is unlikely that their doctors would continue to prescribe HRT to them regularly without follow-up examination. If anything, however, this longer follow-up should have disadvantaged the HRT users, if they had been at a greater risk of adverse events, since there were more opportunities for adverse events to occur in this group. Consequently, it is unlikely that this difference in follow-up affects our interpretation of the results.

In addition, other studies on HRT have generally shown that HRT users are healthier, take better care of themselves and doctors are more likely to discuss HRT with them[20,21].

Data were not available to study the association of weight with the risk of recurrence. Also, estrogen levels were not recorded, so we are unable to determine whether the symptomatic women (i.e. those that received HRT) had lower endogenous estrogens, and possibly a lower risk of recurrence than those not receiving HRT.

The HRT users were at an earlier stage of disease than the non-users (marginally, $p = 0.058$): the effect of this would have been to benefit HRT users in a comparison with the non-users. Consequently, we corrected for stage of disease in the Cox regressions. HRT users were also younger at diagnosis than non-users ($p = 0.001$). This potential confounder might have benefited HRT non-users, since previous studies[17,22] suggest a poorer prognosis for younger women. In the present study, however, age at diagnosis was not a significant determinant of adverse outcomes, so we conclude that our analysis would also not be biased by this factor.

The use of HRT has been listed as contra-indicated with a previous diagnosis of breast cancer[3,4]. There is a reluctance to prescribe HRT to them and many of them are wary of taking it. Studies of the menopause and breast cancer have reported that only 8–18% of women take HRT after breast cancer treatment[23,24]. At our clinic, women presenting with severe menopausal symptoms are offered HRT with caution and with full participation of the patient in the decision-making. Non-hormonal alternatives to HRT are available and are routinely offered to these women as a first line of treatment; however, these approaches are less than ideal as these treatments are known to be less effective than HRT. For example, treatment with clonidine induces headaches, depression and nausea[25], and may decrease overall quality of life[23,25]. Selective estrogen receptor modulators have been effective for prevention of osteoporosis but these may aggravate the menopausal symptoms[26].

Because the comparison between users and non-users of HRT could only be made amongst those women who had reached the menopause before experiencing a recurrence, death or drop-out, the numbers in the comparison are fairly small and the study is consequently underpowered to demonstrate a statistically significant difference in risk of adverse outcomes; this is reflected in the wide confidence intervals for the relative risks. Even if statistical significance had been reached, the present data, being obtained in a retrospective study, would not allow the conclusion that HRT reduces the risk of adverse events in premenopausal women diagnosed with breast cancer. Such a conclusion could only be based on results of prospective trials. However, the present study has clinical relevance as data from this and other

studies do not suggest that HRT increases the risk of recurrence of breast cancer. Nevertheless, HRT should be offered to women previously treated for breast cancer with caution and with their full participation in the decision-making process.

## ACKNOWLEDGEMENTS

We thank Dr C. Magarey (St. George Hospital, Sydney, NSW), Dr P. Crea (St. Vincent's Hospital Clinic, Sydney, NSW) and Dr P. Schwartz (St. George Hospital, Sydney, NSW) for providing access to medical records for this study.

*Conflict of interest* Nil.

*Source of funding* No financial or other support was received for this study.

## References

1. 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. *J Am Med Assoc* 2002;288:321–33
2. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419–27
3. Roy JA, Sawka CA, Pritchard KI. Hormone replacement therapy in women with breast cancer: do the risks outweigh the benefits? *J Clin Oncol* 1996;14:997–1006
4. Rostom AY. The management of menopausal sequelae in patients with breast cancer. *Clin Oncol* 2001;13:174–80
5. Beckman MW, Jap D, Djahansouzi S, *et al*. Hormone replacement therapy after treatment of breast cancer: effects on postmenopausal symptoms, bone mineral density and recurrence rates. *Oncology* 2001;60:199–206
6. Eden JA, Bush T, Nand S, *et al*. A case-control study of combined continuous estrogen–progestin replacement therapy among women with personal history of breast cancer. *Menopause* 1995;2:67–72
7. Eden JA, Wren BG. Hormone replacement therapy after breast cancer: a review. *Cancer Treat Rev* 1996;22:335–43
8. Dew J, Eden J, Beller E, *et al*. A cohort study of hormone replacement therapy given to women previously treated for breast cancer. *Climacteric* 1998;1:137–42
9. Marsden J, Baum M, Sacks NPM. Hormone replacement therapy in women with previous breast cancer. *Trends Endocrinol Metab* 1998;9:32–8
10. Vassilopolou-Sellin R, Asmar L, Hortobagyi GN, *et al*. Estrogen replacement therapy after localised breast cancer: clinical outcome of 319 women followed prospectively. *J Clin Oncol* 1999;17:1482–7
11. Natrajan PK, Soumakis K, Gambrell RD. Estrogen replacement therapy in women with previous breast cancer. *Am J Obstet Gynecol* 1999;181:288–95
12. Natrajan PK, Puthugramam K, Gambrell RD. Estrogen replacement therapy in patients with early breast cancer. *Am J Obstet Gynecol* 2002;187:289–95
13. Uršis-Vrščaj M, Bebar S. A case-control study of hormone replacement therapy after primary surgical breast cancer treatment. *Eur J Surg Oncol* 1999;25:146–51
14. O'Meara ES, Rossing MA, Daling JR, *et al*. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst* 2001;93:754–62
15. Col NF, Hirota LK, Orr RK, *et al*. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol* 2001;19:2357–63
16. Peters GN, Fodera T, Sabol J, *et al*. Estrogen replacement therapy after breast cancer: a 12-year follow-up. *Ann Surg Oncol* 2001;8:828–32
17. Durna EM, Wren BG, Heller GZ, *et al*. Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. *Med J Aust* 2002;177:347–51
18. De La Rochefordiere A, Asselain B, Campana F, *et al*. Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 1993;341:1039–43

19. Lethaby A, Farquhar C, Sarkis A, Roberts H, Jepson R, Barlow D. Hormonal replacement therapy in menopausal women: endometrial hypoplasia and irregular bleeding. *Cochrane Database Syst Rev* 2000;2:CD000402
20. Loprinzi CL, Kugler JW, Sloan JA, *et al*. Venlafaxine in management of hot flushes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356:2059–63
21. Norman SG, Studd JW. A survey of views on hormone replacement therapy. *Br J Obstet Gynaecol* 1994;101:879–87
22. Dennerstein L, Shelley J, Smith AM, Ryan M. Hysterectomy experience among mid-aged Australian women. *Med J Aust* 1994;161:311–13
23. Lee CG, McCormick B, Mazumdar M, *et al*. Infiltrating breast carcinoma in patients age 30 years and younger: long term outcome for life, relapse and second primary tumors. *Int J Radiat Oncol Biol Phys* 1992;23:969–75
24. Durna EM, Crowe SM, Leader LR, *et al*. Quality of life of breast cancer survivors: the impact of hormonal replacement therapy. *Climacteric* 2002;5:266–76
25. Vassilopoulou-Selin R, Zolinski C. Estrogen replacement therapy in women with breast cancer: a survey of patient attitudes. *Am J Med Sci* 1992;304:145–9
26. Clayden JR, Bell JW, Pollard P. Menopausal flushing: double-blind trial of a non-hormonal medication. *Br Med J* 1974;1:409–12
27. Clemons M, Danson S, Howell A. Tamoxifen ('Nolvadex'): a review. *Cancer Treat Rev* 2002;28:165–80