RESEARCH

Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality

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ABSTRACT

Objective: To determine whether hormone replacement therapy (HRT) after treatment for breast cancer is associated with increased risk of recurrence and mortality.

Design: Retrospective observational study.

Participants and setting: Postmenopausal women diagnosed with breast cancer and treated by five Sydney doctors between 1964 and 1999.

Outcome measures: Times from diagnosis to cancer recurrence or new breast cancer, to death from all causes and to death from primary tumour were compared between women who used HRT for menopausal symptoms after diagnosis and those who did not. Relative risks (RRs) were determined from Cox regression analyses, adjusted for patient and tumour characteristics.

Results: 1122 women were followed up for 0–36 years (median, 6.08 years); 154 were lost to follow-up. 286 women used HRT for menopausal symptoms for up to 26 years (median, 1.75 years). Compared with non-users, HRT users had reduced risk of cancer recurrence (adjusted relative risk [RR], 0.62; 95% CI, 0.43–0.87), all-cause mortality (RR, 0.34; 95% CI, 0.19–0.59) and death from primary tumour (RR, 0.40; 95% CI, 0.22–0.72). Continuous combined HRT was associated with a reduced risk of death from primary tumour (RR, 0.32; 95% CI, 0.12–0.88) and all-cause mortality (RR, 0.27; 95% CI, 0.10–0.73).

Conclusion: HRT use for menopausal symptoms by women treated for primary invasive breast cancer is not associated with an increased risk of breast cancer recurrence or shortened life expectancy.

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AROUND 11 000 WOMEN are diagnosed with breast cancer in Australia each year.[1] About three-quarters are aged over 50 years, and many have menopausal symptoms. In addition, most chemotherapies for breast cancer can cause ovarian dysfunction or premature menopause. For example, tamoxifen promotes vasomotor symptoms, despite oestrogen-like effects on the uterus and vagina.[2] Indeed, 60% of premenopausal women who receive adjuvant therapy for breast cancer subsequently have oestrogen deficiency.[3,4]

A significant reduction in menopausal symptoms and improvement in bone mineral density have been reported in women taking hormone replacement therapy (HRT) after breast cancer diagnosis.[5] However, few women use HRT after treatment for this disease,[6] possibly because of concern about the effect on disease progression. Nevertheless, none of the previous studies of breast cancer survivors prescribed HRT have found an increased risk of tumour recurrence or death from progressive disease.[5,7-16]

We previously conducted an audit of women treated for breast cancer and their use of HRT.[7-9] The current study extends this audit to 1999 and further analyses the data, focusing on postmenopausal women. It examines the association between HRT taken after diagnosis and breast cancer recurrence and death.

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METHODS

This was a retrospective observational study of breast cancer recurrence and mortality among postmenopausal women with histopathologically confirmed breast cancer. As the study was a retropective audit, approval from a human research ethics committee was not deemed necessary.

Study population

We analysed records of women who were diagnosed with breast cancer between 1964 and 1999 and were patients of three surgeons and two gynaecologists at three tertiary hospitals in Sydney, New South Wales. Women attended either public hospital clinics or the doctors' private rooms. The entry criterion for the study was histopathologically confirmed primary invasive breast cancer diagnosed after menopause. All women were reviewed clinically at six- to 12-monthly intervals and had annual mammograms.

Data collection

Information was collected from the medical records of both the treating doctors and the hospitals and entered into a database. Ages at diagnosis of breast cancer, menarche and menopause were entered as completed years. If age at menopause was missing, it was deemed to be 50 years. Other characteristics entered were parity, gravidity, menstrual status at diagnosis, tumour size (<2 cm, 2–5 cm or >5 cm), number of positive axillary lymph nodes, and stage of disease. Tumour grade was not recorded. Oestrogen-receptor status was obtained from records of the treating doctors, or, if not available, from the pathology laboratory. We also recorded HRT type and duration of use before and after diagnosis, and any changes in HRT use at annual follow-up visits.

Women were followed up to the end of 1999 for cancer recurrence or new breast cancer, death from primary tumour or other cause. Observations were censored for cancer recurrence or new breast cancer at the time of death or last specialist visit, for death from primary tumour at the time of death from another cause or last visit, and for death from all causes at the last visit.

If case notes were lost, a letter was sent to the patient's general practitioner asking for the information. If no response had been received from the GP by the end of 1999, the patient was contacted by letter or telephone with the same questions.

1: Characteristics of study subjects, by use of hormone replacement therapy (HRT) after diagnosis

	*n**	No HRT	*n**	HRT	*P*
Age in years (mean, 95% CI)					
At diagnosis	832	63.7 (63.0–64.4)	285	55.8 (54.8–56.8)	<0.001
At menarche	536	13.1 (13.0–13.2)	273	13.0 (12.8–13.2)	0.36
At menopause	579	48.2 (47.8–48.6)	269	47.4 (46.8–48.0)	0.07
Parity (mean, 95% CI)	733	2.2 (2.1–2.3)	279	2.2 (2.0–2.4)	0.87
Gravidity (mean, 95% CI)	651	2.7 (2.6–2.8)	281	2.9 (2.7–3.1)	0.18
HRT use before diagnosis					
Number of women	683	127 (19%)	240	161 (67%)	<0.001
Years of use (median, range)	683	3.0 (0.05–29)	240	6.5 (0.17–34)	0.008
HRT use after diagnosis					
Years from diagnosis to HRT start (median, range)			258	1.0 (0–23)	
Years of use (median, range)			267	1.75 (0–26)	
Years of follow-up (median, range)	835	5.1 (0–36)	286	5.8 (0–29)	<0.001
Tumour size (cm) (mean, 95% CI)	790	2.4 (2.3–2.5)	262	1.8 (1.6–2.0)	<0.001
Number of positive axillary nodes (mean, 95% CI)	731	2.3 (1.9–2.7)	262	1.5 (1.0–2.0)	0.006
Treatment (number of patients)					
Partial mastectomy		339		138	
Mastectomy		457		146	
Radiotherapy		346		150	
Chemotherapy		103		49	
Tamoxifen		505		167	

*Number of subjects with data available.

Statistical analysis

Characteristics were compared between patients who used HRT after diagnosis and those who did not by one-way analysis of variance (for normally distributed continuous variables), Mann–Whitney U test (for non-normally distributed continuous variables), χ^2 test for independence (categorical variables) and the log-rank test (time-to-event variables).

The effect on risk of HRT use after diagnosis was determined by Cox regression analysis. Analyses were carried out for the outcomes time from diagnosis to cancer recurrence or new breast cancer, time to death from primary tumour, and time to death from all causes. The analyses were stratified by stage of breast cancer disease and adjusted for the covariates tumour size; number of positive axillary nodes; HRT use before diagnosis; ages at diagnosis, menarche and menopause; parity; gravidity; and calendar year of diagnosis. The latter was considered a covariate because of the long time-span of the study and was classified as 1964–1979, 1980–1989 or 1990–1999. Non-significant covariates were progressively eliminated from the regression models, leaving only covariates significant at the 5% level in the final models.

HRT use after diagnosis was included as a factor to enable comparison of women who used HRT with non-users. Comparisons were also made between those who used different HRT types (continuous combined oestrogen and progestins, oral or transdermal oestrogen alone, progestin alone, vaginal oestrogen alone, and vaginal oestrogen plus oral progestin) and non-users. The final models were reanalysed with stage of disease as a covariate rather than stratification variables to assess the prognostic effect of HRT use over the stages of disease.

All analyses were performed at a 5% level of significance.

RESULTS

A total of 1122 women met the entry criteria and were followed up for a median of 6.08 years (range, 0 to 36 years). One hundred and fifty-four of the 1122 women were lost to follow-up; their observations were censored at the date of the last specialist visit.

Of the 1122 women in the study, 286 used HRT after breast cancer diagnosis to treat menopausal symptoms. A further 60 women with advanced breast

2: Covariates significantly associated with outcomes (values are relative risks and 95% CIs)

	Recurrence or new breast cancer		Death from all causes		Death from primary tumour	
Covariate and level	Any HRT*	HRT by type†	Any HRT*	HRT by type†	Any HRT*	HRT by type†
Number of complete cases (% of total)	993 (89%)	993 (89%)	965 (86%)	945 (84%)	960 (86%)	944 (84%)
Tumour size						
<2 cm	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
2–5 cm	1.90 (1.40–2.57)	1.93 (1.42–2.61)	1.74 (1.19–2.55)	0.58 (0.31–1.08)	2.11 (1.30–3.42)	0.38 (0.19–0.77)
>5 cm	2.81 (1.73–4.56)	2.79 (1.71–4.53)	1.74 (0.96–3.16)	0.96 (0.57–1.61)	2.73 (1.37–5.45)	0.79 (0.45–1.39)
Age at diagnosis	NS	NS	1.03 (1.02–1.05)	1.03 (1.02–1.05)	NS	NS
Year of surgery	NS	NS				
1964–1979			0.14 (0.04–0.52)	0.16 (0.04–0.60)	0.06 (.01–0.54)	0.06 (0.01–0.54)
1980–1989			0.96 (0.69–1.33)	0.99 (0.70–1.40)	0.89 (0.59–1.34)	0.86 (0.57–1.31)
1990–1999			1 (referent)	1 (referent)	1 (referent)	1 (referent)

NS = Not significant (covariate not significantly associated with outcome and therefore eliminated from the final regression model).
*For the regression model that compared any HRT with no HRT use. †For the regression model that compared individual HRT types with no HRT use.

cancer disease took oral progestins to control tumour recurrence and were classified as not having used HRT.

The women in the study were aged 35 to 96 years at diagnosis. Their characteristics are shown in Box 1 by HRT use. Those who used HRT after diagnosis were significantly younger when diagnosed with breast cancer than non-users ($P < 0.001$). They were also significantly more likely to have used HRT before diagnosis ($P < 0.001$), had smaller tumours ($P < 0.001$) and fewer positive axillary lymph nodes ($P = 0.006$) and were followed up for longer ($P < 0.001$). There were no significant differences between the two groups in ages at menarche and menopause, parity and gravidity. Oestrogen-receptor status of the tumour was known in only 282 patients and was not included in the analysis. Most women in both groups took tamoxifen (58% and 60%, respectively).

Women who used HRT after diagnosis comprised 180 of 650 with Stage I disease (28%) and 64 of 255 with Stage II disease (25%), compared with 22 of 142 with Stage III or IV disease (15%; $P = 0.01$). (Stage was unknown for 75 women.)

Types of HRT used

Types of HRT used after breast cancer diagnosis were continuous combined oestrogen plus progestin (138; 48%), oral progestin alone (78; 27%), vaginal oestrogen alone (32; 11%), vaginal oestrogen plus oral progestin (21; 7%), and oral or transdermal oestrogen alone (17; 6%).

Median daily dose of oestrogen used by women taking continuous combined HRT was 0.625 mg conjugated equine oestrogen (range, 0.3–0.625 mg) or equivalent (1.25 mg oestrone sulfate, 2 mg oestradiol valerate or 50 μg transdermal oestradiol). Median daily dose of progestin in combined HRT was 50 mg medroxyprogesterone acetate (range, 10–500 mg) or 5 mg norethisterone (range, 1–5 mg). Similar doses of oestrogen and progestin, respectively, were used by women who took oestrogen or progestin alone. Vaginal oestrogens included oestriol cream (0.5 g) and oestradiol vaginal tablets (25 μg) used twice weekly, either alone or combined with oral progestins in similar doses to those in combined HRT.

Variables included in final models

Covariates found to be significantly associated with outcomes are shown in Box 2 with their relative risks [RRs]. Tumour size was significant to all outcomes, with larger tumours associated with higher risk of recurrence and death. For example, a woman with a tumour 2–5 cm in diameter had a risk of recurrence or new breast cancer 1.90 times that of a woman with a tumour <2 cm when analysed by the model that included any HRT use as a covariate. RR rose to 1.93 for the model that included individual HRT types as covariates. We note the anomaly that women with 2–5-cm tumours had significantly lower risk of death from primary tumour than those with smaller tumours when analysed using the latter model.

Age at diagnosis was significant only for death from all causes. Year of surgery was significant for death both from all causes and from the primary tumour, with surgery between 1964 and 1979 being associated with longer survival times than later surgery. HRT use before diagnosis, ages at diagnosis, menarche and menopause, parity and gravidity and number of positive axillary nodes were not significant determinants of recurrence or survival, and therefore not included in the final regression models.

HRT versus no HRT

Adjusted RRs of each outcome in HRT users versus non-users are shown in Box 3. After adjustment for significant covariates, the group that used HRT after diagnosis had a significantly lower risk of recurrence or new breast cancer compared with the no-HRT group (adjusted relative risk [RR], 0.62; 95% CI, 0.43–0.87). The HRT group also had significantly lower risks of death from all causes (adjusted RR, 0.34; 95% CI, 0.19–0.59) and from the primary tumour (adjusted RR, 0.40; 95% CI, 0.22–0.72).

3: Rates of recurrence and death and adjusted relative risks in women who used hormone replacement therapy (HRT) after diagnosis versus non-users

	Recurrence or new breast cancer			Death from all causes			Death from primary tumour		
Type of HRT	Number of events	Rate per 1000 person-years	Adjusted relative risk (95% CI)	Number of events	Rate per 1000 person-years	Adjusted relative risk (95% CI)	Number of events	Rate per 1000 person-years	Adjusted relative risk (95% CI)
No HRT (n=836)	247	58.2	1 (referent)	199	29.4	1 (referent)	122	18.0	1 (referent)
HRT (all types) (n=286)	44	24.0	0.62 (0.43–0.87)	16	8.3	0.34 (0.19–0.59)	13	6.7	0.40 (0.22–0.72)
Combined HRT* (n=138)	23	23.6	0.81 (0.52–1.27)	5	4.9	0.27 (0.10–0.73)	4	3.9	0.32 (0.12–0.88)
Progestin alone (n=78)	12	32.5	0.59 (0.32–1.09)	4	9.6	0.34 (0.12–0.93)	4	9.6	0.33 (0.12–0.91)
Vaginal oestrogen (n=32)	4	14.9	0.18 (0.04–0.75)	4	14.3	0.30 (0.07–1.30)	2	7.1	0.35 (0.07–1.68)
Vaginal oestrogen plus progestin (n=21)	1	8.6	0.00 (0.00–∞)	0	0.0	0.00 (0.00–∞)	0	0.0	0.00 (0.00–∞)
Oestrogen alone (n=17)	4	39.2	0.81 (0.30–2.21)	3	28.8	0.85 (0.26–2.75)	3	28.8	1.11 (0.35–3.60)

*Combined = continuous combined oestrogen plus progestin.

When the analysis was performed according to type of HRT used, women who used continuous combined HRT had significantly lower risks of death from all causes (adjusted RR, 0.27; 95% CI, 0.10–0.73) and from the primary tumour (adjusted RR, 0.32; 95% CI, 0.12–0.88) compared with the no-HRT group. Women who used progestin alone also had significantly lower risks of death from all causes (adjusted RR, 0.34; 95% CI, 0.12–0.93) and from the primary tumour (adjusted RR, 0.33; 95% CI, 0.12–0.91), while those who used vaginal oestrogen alone had a significantly lower risk of recurrence or new breast cancer (adjusted RR, 0.18; 95% CI, 0.04–0.75).

When stage of disease was included in the regression models as a covariate rather than a stratification variable, adjusted RRs were little changed. As expected, the earlier the stage of disease, the less the chance of cancer recurrence or new breast cancer (P < 0.001), and the longer the disease-free interval (P < 0.001) and survival time (P < 0.001). In all regression analyses, the stage–HRT interaction term was non-significant, implying that the observed prognostic effect associated with HRT use is seen over all stages of disease.

DISCUSSION

We found that women who used HRT after diagnosis of breast cancer had a significantly lower risk of cancer recurrence or new breast cancer than women who did not use HRT (RR, 0.62). Women who used HRT also had significantly lower risks of death from all causes (RR, 0.34) and from the primary tumour (RR, 0.40). These risks were determined after adjustment for other variables found to be significantly associated with outcome — tumour size (all outcomes), age at diagnosis (death from all causes only), year of operation (death from primary tumour and death from all causes) — and after stratification for stage of disease (all outcomes).

All HRT regimens were associated with smaller risks of recurrence and death than no HRT use, with the exception of unopposed oestrogen for risk of death from primary tumour. However, not all the differences reached statistical significance. Similar results were obtained from previous analyses of early data from our study,[7-9] as well as other observational studies of women with a history of breast cancer who took any HRT[5,10-12,14,16] or continuous oestrogen–progestin regimens.[13] A recent systematic review and quantitative assessment of breast cancer recurrence also concluded that HRT taken after diagnosis has no significant effect on recurrence.[15]

There are potential sources of bias in our study. We observed that women with Stage I and II breast cancer were more likely to use HRT than women with Stage III or IV disease, and that, as expected, the earlier the stage of disease, the lower the risk of recurrence or new breast cancer and death. This is a potential source of bias leading to more favourable outcomes for HRT users. However, the regression analyses were stratified by stage of disease to adjust for this effect. Similarly, although women who used HRT were younger at breast cancer diagnosis than non-users, also potentially leading to bias, the regression analysis for death from all causes was adjusted for age at diagnosis.

Length bias may also have favoured outcome for HRT users, as women with longer times to recurrence or longer survival have more opportunity to use HRT. However, as HRT is usually administered around the time of menopause, longer survival does not imply longer exposure to HRT. Therefore, we consider the length bias unlikely to be clinically significant. In addition, the exclusion of some women from the analyses because of missing data also led to potential bias. However, as analyses included 84%–89% of women, we consider any potential bias to be of no clinical importance.

It is surprising that women diagnosed between 1964 and 1979 seemed to have longer survival times than those diagnosed later, as surveillance and treatment have supposedly improved with time. We are unable to explain this result.

As our study was not a randomised controlled trial, the observed association between HRT use and risks of breast cancer recurrence and death cannot be inferred to be causal. HRT was used to treat menopausal symptoms, thereby confounding the two factors. A

possible explanation of the results is that women with oestrogen deficiency tend to have better outcomes after breast cancer. Nevertheless, we conclude that women who use HRT after diagnosis of breast cancer do not have an increased risk of recurrence or death. In particular, we found that use of continuous combined HRT had no adverse effect.

HRT is usually not recommended for breast cancer patients because of reports of an increased risk of breast cancer in normal postmenopausal women. A 1997 meta-analysis of 51 studies from 21 countries reported a per annum increased risk of breast cancer of 1.7% with use of oestrogen alone, 1.8% with oestrogen plus continuous progestins, and 7.6% with oestrogen plus cyclic progestins.[17] Other recent observational studies also suggest that the use of sequential or cyclic progestins in HRT may increase the risk of breast cancer.[18-20]

In contrast, our results suggest that HRT is a safe treatment for women with a history of breast cancer. These results need to be confirmed in a randomised trial before HRT can be advocated for all women who have had breast cancer. However, we believe that the current practice of withholding HRT from women with breast cancer who suffer menopausal symptoms may need review.

COMPETING INTERESTS

None identified.

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REFERENCES

1. Australian Institute of Health and Welfare. Cancer in Australia, 1998. Incidence and mortality data. Canberra: AIHW, 2002.
2. Love RR, Cameron L, Connell BL, Leventhal H. Symptoms associated with tamoxifen treatment in postmenopausal women. *Arch Intern Med* 1991; 151: 1842-1847.
3. Speroff L. Postmenopausal hormonal therapy and breast cancer. *Obstet Gynecol* 1996; 87: 44-54.
4. 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.
5. Beckmann 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. Vassilopolou-Sellin R, Zolonski C. Estrogen replacement therapy in women with breast cancer: a survey of patient attitudes. *Am J Med Sci* 1992; 304: 145-149.
7. Eden JA, Bush T, Nand S, Wren BG. A case–control study of combined continuous estrogen–progestin replacement therapy among women with personal history of breast cancer. *J North Am Menopause Soc* 1995; 2: 67-72.
8. Eden JA, Wren BG. Hormone replacement therapy after breast cancer: a review. *Cancer Treat Rev* 1996; 22: 335-343.
9. Dew J, Eden J, Beller E, et al. A cohort study of hormone replacement therapy given to women previously treated for breast cancer. *Climact* 1998; 1: 137-142.
10. Marsden J, Baum M, Sacks NPM. Hormone replacement therapy in women with previous breast cancer. *Trends Endocrinol Metab* 1998; 9: 32-38.
11. 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: 1482-1487.
12. Natrajan PK, Soumakis K, Gambrell RD. Estrogen replacement therapy in women with previous breast cancer. *Am J Obstet Gynecol* 1999; 181: 288-295.
13. Uršis-Vršèaj M, Bebar S. A case–control study of hormone replacement therapy after primary surgical breast cancer treatment. *Eur J Surg Oncol* 1999; 25: 146-151.
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: 754-762.
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: 2357-2363.
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: 828-832.
17. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal 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.
18. Schairer C, Lubin J, Troisi S, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000; 283: 485-491.
19. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormonal replacement therapy on breast cancer risk: Estrogen versus estrogen plus progestogen. *J Natl Cancer Inst* 2000; 92: 328-332.
20. Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and risk of breast cancer with a favourable histology. Results of the Iowa women's health study. *JAMA* 1999, 281: 2091-2097.

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