MANAGEMENT OF SYMPTOMATIC MENOPAUSAL WOMEN WITH BREAST CANCER, BENIGN BREAST DISEASE OR A FAMILY HISTORY OF BREAST CANCER

Managing a symptomatic postmenopausal woman who has breast disease can be problematic.

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The management of women with menopausal symptoms and breast cancer or benign breast disease or a family history of breast cancer is a common clinical problem. Hormone replacement therapy (HRT) is often regarded as contraindicated in such women because of the increased risk of promoting breast cancer or its recurrence. Non-hormonal and 'alternative' therapies for menopausal symptoms however are frequently ineffective. Some recent publications have shed fresh light on this difficult problem.

BREAST CANCER

Breast cancer is one of the commonest female malignancies and the overall lifetime risk in the UK is 1:9. Breast cancer mortality is falling in most countries due to the increased use of screening, earlier treatment and the greater use of postoperative adjuvant therapy. The 5- and 10-year survival rates in women with breast cancer detected by mammography are 95% and 90% respectively, and the number of breast cancer survivors is increasing.

In women with hormone-sensitive tumours adjuvant therapy involves the use of agents that decrease oestrogen synthesis (ovarian suppression in premenopausal women and aromatase inhibitors in postmenopausal women) and the use of anti-oestrogen drugs such as tamoxifen. These agents frequently induce menopause symptoms. Adjuvant chemotherapy often results in premature menopause. With CMF (Cytoxan, methotrexate and 5-FU) for example, permanent amenorrhoea occured in 40% of women under the age of 40 and 70% of women over 40 years.

The prevalence of menopausal symptoms including hot flushes, vaginal dryness and dyspareunia in women with adjuvant therapy is high. In survivors of breast cancer diagnosed before the age of 50 hot flushes occurred in 17%, 51% and 71% respectively in pre-, peri- and postmenopausal women. Breast cancer survivors are 5.3 times more likely to experience menopausal symptoms and 7.4 times more likely to try non-hormonal preparations than similar aged controls. These preparations are often ineffective, and a survey of breast cancer survivors found that 1 in [3]women were prepared to use HRT to alleviate their symptoms and to accept the potential risks.

HRT in breast cancer survivors

A review of 15 previous studies, including 3 controlled studies, of 1 416 breast cancer survivors concluded that HRT was not associated with an increase in cancer recurrence, cancer-related mortality or total mortality. In a meta-analysis of 10 trials (8 observational and 2 randomised) of HRT in 1 316 breast cancer survivors the overall recurrence rate was 11.7% in HRT users and 18.2% in non-users. In the 8 observational studies the risk of recurrence was decreased

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For women with refractory symptoms the relief of hot flushes and the improvement in wellbeing with HRT may outweigh any possible increased risk of recurrence.

(relative risk (RR) 0.64, 95% confidence interval (CI) 0.50 - 0.82) but the HRT users were younger and more likely to be lymph node negative. In the two randomised studies the risk of recurrence was increased (RR 3.41, 95% CI 1.59 - 7.33) but the overall risk in the HRT users was not significantly different (RR 0.84, 95% CI 0.5 - 1.3). In an observational study of 1 472 breast cancer survivors treated with HRT, with or without tamoxifen, there was no increased risk of recurrence in the women treated with HRT and tamoxifen therapy (hazard ratio (HR) 0.67, 95% CI 0.14 - 3.24). It has been hypothesised that HRT may be safe in breast cancer survivors with receptor-negative disease, those on tamoxifen, which blocks the oestrogen receptor (ER), and those cured of the disease.

A large randomised controlled trial of HRT in women after breast cancer (HABITS) in Scandinavia, which was started in 1997, was terminated after 434 women had been recruited and a median of 2.1 years' follow-up because of an unacceptably high risk of breast cancer recurrence (RR 3.3, 95% CI 1.5 - 7.4), and all participants were advised to stop HRT. Most of the women were ER positive but only 21% were taking tamoxifen. In contrast, in a subset of this trial in Stockholm in which 378 women were recruited and followed up for a median of 4.1 years there was no increased risk of recurrence (RR 0.82, 95% CI 0.35 - 1.90). The reasons suggested for this difference include (*a*) the higher usage of tamoxifen (52%) in the Stockholm study and (*b*) the use of long-cycle combined therapy by most women in the Stockholm study whereas most women received continuous combined HRT in the HABITS study.

Overall data on the risk of HRT in breast cancer survivors are inconclusive. In menopausal women without breast cancer there is increasing evidence that the addition of progestin to oestrogens is associated with a significant increase in risk of breast cancer whereas in women given oestrogen alone there is either a much smaller, or no increase in risk. In the combined oestrogen plus progestin arm of the Women's Health Initiative (WHI) trial the risk of breast cancer was increased (HR 1.49, 95% CI 1.13 - 1.96 in adherent women) whereas in the oestrogen-only arm in hysterectomised women the risk was decreased (HR 0.67, 95% CI 0.47 - 0.97 in adherent women). If it is decided to use HRT for the treatment of vasomotor symptoms in breast cancer survivors a good case can be made for using oestrogen-only therapy in all women and monitoring the endometrium with pelvic ultrasound in those with an intact uterus. An alternative is the use of oestrogen with a progestogen-containing intrauterine system. Another alternative is the steroidal hormone tibolone, which is effective in relieving vasomotor symptoms in menopausal women, and is claimed not to stimulate the endometrium or the breasts. A large randomised trial of tibolone and breast cancer risk (the LIBERATE study) is in progress and the results should be available in the next few years.

Non-hormonal or 'alternative' treatments for menopausal symptoms

A wide variety of non-hormonal or 'alternative' agents have been used to treat menopausal symptoms including selective serotonin reuptake inhibitors (SSRIs) (venlaflaxine, paroxetine, fluoxetine), central adrenergic agonists (clonidine), gabapentin, vitamin E and herbal agents (black cohosh) and isoflavones from genistein, red clover and soy. In randomised placebo-controlled trials all these different agents have been claimed to reduce the incidence of hot flushes by between 25% and 60% but some agents have side-effects and long-term safety is unproven. Most of the trials have been of short duration (up to 12 weeks).

A Cochrane review of all double-blind, controlled trials found that oral HRT reduced the incidence of vasomotor symptoms in perimenopausal and postmenopausal women by an average of 65% and 90% respectively and was by far the most efficacious regimen. A recent comprehensive review of the treatment of menopausal symptoms concluded that 'there is not enough evidence that any of the complementary therapies available are any better than placebo for menopausal symptoms, and few safety data exist'. A meta-analysis of 43 randomised double-blind placebo-controlled trials of non-hormonal therapies gave a combined estimate of a reduction of one hot flush per day for SSRIs and clonidine and two flushes per day for gabapentin. It was concluded that such therapies 'may be most useful for highly symptomatic women who cannot take oestrogen' but that 'they are not optimal choices for most women'.

Recommendations

Most women fear breast cancer and women who have had breast cancer fear that HRT may cause a recurrence. This is a major consideration in the management of women with menopausal symptoms with or after

breast cancer. In general therefore the first line of treatment should be with non-hormonal agents even if the response is largely a placebo one. The choice of agent will depend upon availability and cost, bearing in mind that menopausal symptoms usually persist for many months or years. In women with vasomotor symptoms and depression SSRIs would be a first choice. Efficacy can usually be assessed within 3 - 4 weeks and if one agent is not effective, or is associated with side-effects, another can be tried. In women who have menopausal symptoms that have a major effect on their quality of life and are refractory to all non-hormonal agents HRT may be considered in discussion with each patient. In women with ER-negative disease, or with ER-positive disease receiving tamoxifen, HRT may carry little or no increased risk. For women with refractory symptoms the relief of hot flushes and the improvement in wellbeing with HRT may outweigh any possible increased risk of recurrence. In these circumstances it is unreasonable to withhold HRT and either unopposed oestrogens or tibolone may be the treatment of choice.

BENIGN BREAST DISEASE

Benign breast disease (BBD) encompasses a spectrum of histological entities usually subdivided into non-proliferative lesions, proliferative lesions without atypia and atypical hyperplasia. BBD is an important risk factor for breast cancer that can develop in either breast. The risk of breast cancer associated with the different histological types of BBD has been clarified in a recent report from the Mayo Clinic of 9 087 patients with BBD diagnosed on biopsy and followed up for a median of 15 years. There were 707 cases of breast cancer and the incidence was compared with a similar demographic population in the Iowa Registry.

The overall relative risk of breast cancer in the women with BBD was 1.56 (95% CI 1.45 - 1.68). Age and family history were found to be important risk factors for the development of breast cancer independent of the histological findings (Figs 1 and 2). The only group of women with no increased risk was that with non-proliferative histology and no family history of breast

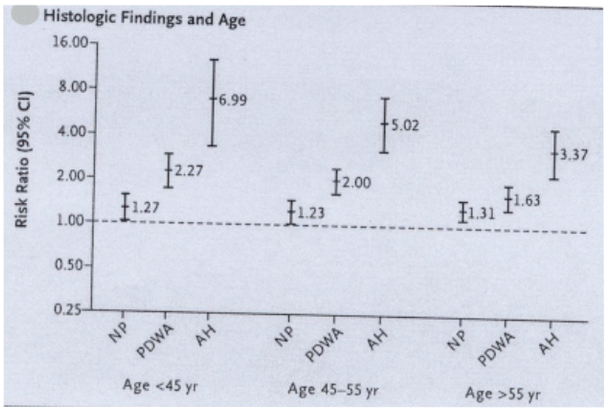

Fig.1. Relative risk of breast cancer in women with benign breast disease by age and histology (NP = non-proliferative disease; PDWA = proliferative disease without atypia; AH = atypical hyperplasia).

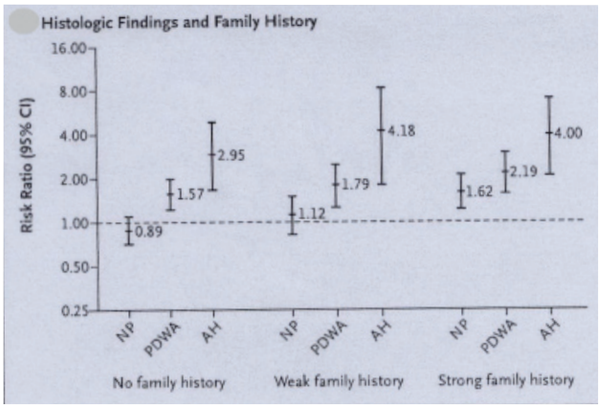

Fig. 2. Relative risk of breast cancer in women with benign breast disease by family history (strong = at least one first-degree relative with breast cancer < 50 years, weak = any lesser degree of family history) and histology (NP = non-proliferative disease, PDWA = proliferative disease without atypia, AH = atypical hyperplasia).

cancer. The effect of HRT on the incidence of breast cancer in women with BBD however was not investigated in the Mayo Clinic study.

Recommendations

It has been postulated that HRT may stimulate the growth of existing, small, undetected, occult malignant lesions but does not initiate neoplastic change whereas a family history of breast cancer is associated with a greater propensity to breast neoplasia.

On this hypothesis women with BBD and non-proliferative histology and no family history of breast cancer may be managed in the same way as women without breast disease.

Women with atypical hyperplasia, particularly those with a family history of breast cancer, should be regarded as having pre-malignant lesions and should be managed in the same way as women who have had breast cancer.

Table I. **Family history and risk of breast cancer pooled estimate of 74 studies**

Family history	Relative risk*	95% CI
None	1.0	Referent
Any	1.9	1.7 - 2.0
1st degree	2.1	2.0 - 2.2
Mother	2.0	1.8 - 2.1
Sister	2.3	2.1 - 2.4
Daughter	1.8	1.6 - 2.0
Mother + sister	3.6	2.5 - 5.0
2nd degree	1.5	1.4 - 1.6

*Risks further increased in women < 50 years and women with relatives diagnosed at < 50 years.

A family history of breast cancer, moreover, eliminates the benefit of factors that tend to reduce the risk, such as late menarche, early menopause and multiple pregnancies.

It is generally held that although a family history is an important risk factor for breast cancer, the use of HRT does not increase the risk further and that a family history of breast cancer is not a contraindication to HRT.

Women with proliferative lesions without atypia or with a family history of breast cancer should be regarded as being at increased risk of later development of breast cancer and placed under close breast surveillance but HRT is not contraindicated in women with menopausal symptoms.

Table II. **Referral criteria for counselling and testing for BRCA1 and 2 gene mutations**

- Three cases of breast or ovarian cancer in first-degree relatives, one of whom is under age 50
- Two cases of breast or ovarian cancer in first-degree relatives, one of whom is under age 40
- One case of ovarian or breast cancer in a relative under age 30
- More than one cancer in the same person is counted as two different cases and bilateral cancers in a single relative count as two relatives

FAMILY HISTORY OF BREAST CANCER

A family history of breast cancer, particularly in a first-degree relative, is an important risk factor for breast cancer (Table I). Women with more than one affected relative, particularly if they are first-degree relations such as a mother and sister, are at much higher risk. The earlier the age at which breast cancer first develops in a relative, the greater the increase in risk.

A family history of breast cancer, moreover, eliminates the benefit of factors that tend to reduce the risk, such as late menarche, early menopause and multiple pregnancies. Women with a very strong family history of breast and/or ovarian cancer are at increased risk of inheriting a BRCA1/2 gene mutation with a high risk of developing breast or ovarian cancer. Such women require investigation, counselling and management in a specialised centre, and recommended referral criteria are shown in Table II.

The effect of HRT on the incidence of breast cancer and on total mortality in women with a family history of breast cancer was investigated in an observational study of 41 837 women aged 55 - 69 in Iowa, USA. There was no statistically significant increase in the risk of breast cancer in the HRT users with one or more first-degree affected relatives compared with those with no family history, but the number of current HRT users with first-degree affected relatives was small (Table III). In the Collaborative Analysis, the Million Women Study26 and the WHI trial of Conjugated Equine Estrogen (CEE) plus medroxyprogesterone acetate (MPA) the RRs for breast cancer with HRT were not significantly higher in the women with a family history. HRT in

Table III. **Incidence of breast cancer in postmenopausal women according to HRT use and family history of breast cancer**

Use of HRT	No 1st-degree relative			One or more 1st-degree relative		
	N	Incidence /1 000 person-years (95% CI)	Adjusted RR* (95% CI)	*N*	Incidence /1 000 person-years (95% CI)	Adjusted RR* (95% CI)
Never	528	36 (32 - 39)	1.00 (Referent)	97	46 (36 - 55)	1.0 (Referent)
Past < 5 yrs	202	37 (31 - 42)	1.01 (0.85 - 1.20)	45	54 (38 - 70)	1.19 (0.81 - 1.73)
Past > 5 yrs	27	29 (17 - 40)	0.80 (0.53 - 1.09)	8	51 (14 - 87)	1.17 (0.55 - 2.47)
Current < 5 yrs	41	46 (31 - 61)	1.31 (0.94 - 1.83)	7	70 (17 - 22)	1.37 (0.59 - 3.18)
Current > 5 yrs	67	41 (31 - 51)	1.13 (0.86 - 1.50)	13	61 (28 - 94)	1.35 (0.72 - 2.53)

* Adjusted for age, age at menarche, type of menopause, age at first birth, waist-hip-hip ratio, body mass index at age 18, education level and alcohol use.

women with a family history of breast cancer nevertheless needs further investigation as in the (CEE)-only arm of the WHI trial women without a family history had a decreased risk of breast cancer (HR 0.68, 95% CI 0.50 - 0.92) whereas those with a family history had an increased risk (HR 1.75, 95% CI 0.95 - 3.22).

Recommendations

It is generally held that although a family history is an important risk factor for breast cancer, the use of HRT does not increase the risk further and that a family history of breast cancer is not a contraindication to HRT. A family history of breast cancer is, however, an indication for close surveillance of the breasts starting at age 40, clinically and by mammography, and for the investigation by biopsy or aspiration cytology of any suspicious lesions.

Further reading

Batur P, Blixen CE, Moore HC, Thacker HL, Xu M. Menopausal hormone therapy (HT) in patients with breast cancer. *Maturitas* 2006; **53**:123-132.

Berry DA, Cronin KA, Plevritis SK, *et al.* for the Cancer Intervention and Surveillance Modeling Network Collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 2005; **353**:1784-1792.

Chlebowski RT, Hendrix SL, Langer RD, *et al.* for the WHI Investigators. Influence of oestrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. *JAMA* 2003; **289**:3243-3253.

Collaborative Group on Hormonal Factors. 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.

Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. *Breast Cancer Res* 2005; **7**:R535-540 (Epub).

Couzi RJ, Helzlouser KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes towards oestrogen replacement therapy. *J Clin Oncol* 1995; **13**: 27-37.

Crandall C, Petersen L, Ganz PA, Greendale GA. Association of breast cancer and its therapy with menopause related symptoms. *Menopause* 2004; **11**: 519-530.

Dew JE, Wren BG, Eden JA. Tamoxifen, hormone receptors and hormone replacement therapy in women previously treated for breast cancer: a cohort study. *Climacteric* 2002; **5**: 151-155.

Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year of breast cancer diagnosis. *J Clin Oncol* 1999; **17**: 2365-2370.

Harris PF, Remington PI, Trentham-Dietz A, Allen CI, Newcomb PA. Prevalence and treatment on menopausal symptoms amongst breast cancer survivors. *J Pain Symptom Manage* 2002; **23**: 501-509.

Hartmann LC, Sellers TA, Frost MH, *et al.* Benign breast disease and the risk of breast cancer. *N Engl J Med* 2005; **353**: 229-237.

Hickey M, Davis SR, Sturdee DW. Treatment of menopausal symptoms: what shall we do now? *Lancet* 2005; **366**: 409-421.

Holmberg L, Anderson H for the HABITS steering and data monitoring committees: HABITS (hormone replacement therapy after breast cancer – is it safe), a randomized comparison: trial stopped. *Lancet* 2004; **363**: 453-455.

Kerlikowske K, Miglioretti DL, Ballard-Barbash R, *et al.* Prognostic characteristics of breast cancer among postmenopausal hormone users in a screened population. *J Clin Oncol* 2003; **21**: 4314-4321.

Kroiss R, Fentiman IS, Helmond FA, *et al.* The effect of tibolone in post menopausal women receiving tamoxifen after surgery for breast cancer: a randomised trial. *Br J Obstet Gynaecol* 2005; **112**: 228-233.

Kwan K, Ward C, Marsden J. Is there a role for hormone replacement after breast cancer? *J Br Menopause Soc* 2005; **11**: 140-144.

MacLennan AH, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2002; **1**: CD002978.

Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; **362**: 419-427.

Nelson HD, Vesco KK, Haney E, *et al.* Nonhormonal therapies for menopausal hot flashes. *JAMA* 2006; **295**: 2057-2071.

Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: A systematic review and meta-analysis. *Int J Cancer* 1997; **71**: 800-809.

Raudaskosi T, Tapainen J, Tomas E, *et al.* Intrauterine 10 mcg and 20 mcg levonorgestrel systems in postmenopausal women receiving oral oestrogen replacement therapy: clinical, endometrial and metabolic response. *Br J Obstet Gynaecol* 2002; **109**:136-144.

Sellers TA, Mink PJ, Cerhan JR, *et al.* The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Ann Intern Med* 1997; **127**: 973-980.

Stefanick ML, Anderson GL, Margolis KL, *et al.* for the WHO Investigators. Effect of conjugated equine oestrogens on breast cancer and mammographic screening in postmenopausal women with hysterectomy. *JAMA* 2005; **295**:1647-1657.

Von Schoultz E, Rutqvist LE on behalf of the Stockholm Breast Cancer Study Group. Menopause hormone therapy after breast cancer: The Stockholm randomised trial. *J Natl Cancer Inst* 2005; **97**: 533-555.

Von Smitten K. Prophylactic mastectomy why and when? *J Br Menopause Soc* 2003; **9**: 151-155.

Wal ES, Dýachkova Y, Olivotto IA, *et al.* Comparison of 1- and 2- year screening intervals for women undergoing screening mammography. *Br J Cancer* 2005; **92**: 961- 966.

IN A NUTSHELL

The number of breast cancer survivors is increasing due to the increased use of mammographic screening and adjuvant therapy.

Adjuvant therapy for breast cancer increases the severity of menopausal symptoms and the incidence of amenorrhoea.

Overall data on risk of HRT on breast cancer survivors are inconclusive.

SSRIs, gabapentin or clonidine may be the best of the non-hormonal agents for treatment of vasomotor symptoms.

Non-hormonal agents are often ineffective and one-third of women are prepared to use HRT.

HRT is the most efficacious treatment and is an option in women with severe vasomotor symptoms refractory to non-hormonal agents.

Benign breast disease is a risk factor for breast cancer depending on histology and family history.

Women with a family history of breast cancer are at increased risk depending on the degree and number of relatives and require close surveillance.

HRT is not thought to increase the risk further in women with a family history of breast cancer, and HRT is not contraindicated.