Hormone replacement therapy and breast cancer

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Abstract
The concern that postmenopausal hormone replacement therapy (HRT) may cause cancer of the breast has lead to an enormous volume of research in epidemiology, endocrinology and tumour cell biology. The epidemiology has become extremely sophisticated because the anticipated effect is small and there are several confounding factors. The consensus today is that long-term HRT (>10 years) is associated with an increase in the risk of breast cancer which, on average, is equivalent to delaying menopause for the same period of time that the patient is on treatment.

The risk is related to endogenous and exogenous oestrogen levels. Studies that have investigated individual susceptibility are reviewed, as are environmental factors such as the interaction of HRT with alcohol intake. The clinical implication of these data is that the dosage of HRT should be the smallest that is efficacious. Subcutaneous implants of oestrogen typically cause very high oestrogen levels and, in the opinion of this reviewer, should be restricted to women unable to take or absorb oestrogen by mouth or percutaneously.

Finally, the issue of HRT for women with a history of breast cancer is considered. The potential is discussed for treatment of women with severe symptoms of oestrogen deficiency with a low dose of oestrogen, together with a selective oestrogen receptor modulator to protect the breast.

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Introduction
Over the last few years there has been a steady increase in the evidence linking breast cancer to postmenopausal hormone replacement therapy (HRT). Increasingly powerful epidemiological studies have complemented a deepening understanding of the biology and endocrinology of cancer of the breast. The data presently available indicate an increase of the risk of breast cancer attributable to hormone treatment at least equivalent to deferring the menopause for the same period of time that the patient has received treatment. While this conclusion is intuitively quite plausible – after all, it has been known for many years that an early menopause protects against breast cancer and that the purpose of HRT is to reverse the endocrine deficit of the menopause – it is a conclusion that has taken a great deal of research over many years to establish.

In this review I emphasise aspects of the subject of practical importance to clinicians and their patients. Where data permit, I attempt to quantify the increase in the risk of breast cancer attributable to hormone treatment at least equivalent to deferring the menopause for the same period of time that the patient has received treatment. While this conclusion is intuitively quite plausible – after all, it has been known for many years that an early menopause protects against breast cancer and that the purpose of HRT is to reverse the endocrine deficit of the menopause – it is a conclusion that has taken a great deal of research over many years to establish.

Endogenous oestrogens and the risk of breast cancer
Late menopause has long been known to be associated with an increased risk and early menopause with a reduced risk of breast cancer (Hulka & Stark 1995). This observation is obviously consistent with the notion of prolonged exposure to endogenous oestrogen as an adverse risk factor (Colditz 1998). For every 1 year’s increase in age at the menopause, there is about a 3% increase in the risk of breast cancer (Colditz 1998). For every 1 year’s increase in age at the menopause, there is about a 3% increase in the risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 1997). The exact figure depends on the age at which the cancer is diagnosed and for women aged 50–59 it is as high as 4% per year. The incidence of breast cancer in relation to age and the time of the menopause is shown in Fig. 1, taken from the publication of Pike et al. (1993). As expected,
postmenopausal women have a lower risk of breast cancer than premenopausal women of the same age and childbearing pattern.

After the menopause, the major source of circulating oestrogens is extra-glandular conversion of androgens to oestrogens in fat tissue. The two most important determinants of the rate of extra-glandular oestrogen production are the availability of substrate and the subject's body weight (MacDonald et al. 1978). Serum oestrogen concentrations increase with body weight, the mean level in postmenopausal women of body mass index (BMI) equal to or greater than 29 kg/m² being double that of women with a BMI of less than 21 kg/m² (Hankinson et al. 1995). The relative risk of breast cancer in postmenopausal women increases with body weight (Ballard-Barbash & Swanson 1996), rising by 3.1% per kg/m² (Collaborative Group on Hormonal Factors in Breast Cancer 1997).

A number of studies have reported the risk of postmenopausal breast cancer in relation to hormone levels, as indexed by blood concentrations of oestrogens. A recent systematic review (Thomas et al. 1997) assessed 29 epidemiological papers: in the six prospective studies, the mean serum oestradiol concentration in women who subsequently developed cancer was 15% higher than the concentration in those who remained cancer free. These results have been confirmed in two further reports (Hankinson et al. 1998, Cauley et al. 1999), bringing the total number of cases studied in this way to 580 who subsequently developed cancer compared with 1655 who did not. It seems, therefore, that a single measurement of serum oestradiol concentration in a postmenopausal woman gives some prediction of the risk of breast cancer developing over the next few years. While there is some stability in serum oestrogen concentrations in postmenopausal women (Key 1999), the investigation of hormone concentrations has been complemented by studies in which the risk of breast cancer has been related to markers of hormone action. Such markers represent the impact of a long period of exposure to oestrogen. A reduced risk of breast cancer has been reported in postmenopausal women with a history of osteoporotic fracture (Olsson & Hagglund 1992, Persson et al. 1994), while it was found that, as bone mineral density increased, the risk of breast cancer increased (Kuller et al. 1997).

Figure 1 Log–log plot of age-specific incidence rates for (a) colorectal cancer (per 100 000) in white American women (1969–1971) and (b) breast cancer (per 100 000) in white American women (1969–1971). Note the shape of the curve for a non-hormone-dependant malignancy (a) compared with the inflection at the age of the menopause in women with breast cancer (b). Reproduced with permission from Pike et al. (1993).
Exogenous oestrogens and the risk of breast cancer

In a detailed review, Zumoff (1993) cited 69 epidemiological reports published between 1941 and 1996 that concerned the effect of hormone replacement on the risk of breast cancer. He reported that 27 studies showed a slight increase, 32 showed no difference and 10 a slight decrease in the risk of breast cancer in women taking HRT. There have been eight meta-analyses: three showed no difference (Armstrong 1988, Dupont & Page 1991, Steinberg et al. 1991, Sillerø-Arenas et al. 1992, Colditz et al. 1993, Barrett-Connor & Grady 1998). The most important advance in epidemiological assessment in the field has, however, been the re-analysis of published data undertaken by Beral and her colleagues in the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group on Hormonal Factors in Breast Cancer 1997). These authors collected individual data on 52 705 women with and 108 411 women without breast cancer from 51 epidemiological studies performed in 21 countries. The information was checked and analysed centrally. The analysis was based on 53 865 postmenopausal women whose age at the menopause was known, of whom 17 830 (33%) had used HRT at some time.

The main finding of the re-analysis was that, for current or recent (last 1–4 years) users of HRT, there was a statistically significant increase in the relative risk of breast cancer, which increased with duration of use. There was an important interaction with body weight, the relative risk of cancer developing during HRT declining with increasing body weight. Overall, the risk of having breast cancer diagnosed increased by 2.3% per year for each year of use (average duration of use 11 years). There was no increased risk of cancer in past users (>5 years previously) and 5 years after stopping HRT there was no significant excess of breast cancer. The cumulative numbers of cases of cancer attributable to HRT are shown in Table 1.

This very large data set, which represents about 90% of the published epidemiological evidence, permitted both stratification and analysis for confounding and bias. Failure to take time since the menopause into account would have resulted in a substantial underestimate of the risk of breast cancer associated with the use of HRT and the significantly increased risk with duration of use would not have been detected. Failure to stratify by body mass also underestimates risk. Thus it appears that HRT may have its largest impact in women who, by virtue of their low body weight, are least likely to develop breast cancer spontaneously. If a negative mammogram is required before oestrogens are prescribed, the risk of developing breast cancer will again be underestimated. Selection bias also results in an underestimate of risk if oestrogens are withheld from women at increased risk for breast cancer (i.e. those with a positive family history) or selectively prescribed to women at reduced risk (i.e. those with an early menopause). Surveillance bias is suggested by reports in which women with oestrogen-associated breast cancer had a better prognosis than women with breast cancer who were not being treated with oestrogen (Persson et al. 1996, Willis et al. 1996, Jernstrom et al. 1999), although one recent study has, in fact, reported an increase in fatal breast cancer as well (Grodstein et al. 1997). Differences in surveillance may also bias results in the other direction: if women who take oestrogen are more closely evaluated, as is likely, the risks may appear falsely high. It does seem, however, that most of the biases in these observational studies operate to underestimate the true risk of a woman receiving HRT developing breast cancer.

Information about which hormonal preparations were used was available to the Collaborative Group for 39% of the study population: 80% had used preparations mostly containing oestrogen alone. There was, however, insufficient information to determine whether addition of progestogen to treatment with oestrogen had a deleterious effect. The results from the Nurses’ Health Study indicated that, with respect to breast cancer, gestogens conferred no protection from the risk of treatment with oestrogen (Colditz et al. 1995). A recent report from the Breast Cancer Demonstration Project, a cohort study that included 2082 cases of breast cancer identified from 29 screening centres in the United States, suggested that the treatment with the combination increased breast cancer risk beyond that associated with oestrogen alone (Scharer et al. 2000). Nonetheless, with presently available data one cannot distinguish with certainty between the impact of oestrogen or progestogen on the risk of breast cancer. The simplest hypothesis is that the adverse effect is mediated through the proliferative effects of oestrogen on breast tissue, increasing the number of cell divisions and presumably the number of mutations too. Because of the enhanced rate of proliferation, the time available for DNA repair would be reduced. Such a hypothesis is certainly consistent with the beneficial effects of selective modulators of oestrogen receptor(s) in patients with breast cancer. Thus, treatment with tamoxifen improves survival in women with oestrogen-receptor positive cancer (Early Breast Cancer Trials’ Collaborative Group 1998), and, in the largest trial to

<table>
<thead>
<tr>
<th>Time on HRT</th>
<th>Breast cancers diagnosed over the 20 years from age 50 to 70</th>
<th>Extra breast cancers</th>
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<tr>
<td>Never</td>
<td>45/1000</td>
<td>—</td>
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<tr>
<td>5 years</td>
<td>47/1000</td>
<td>2/1000</td>
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<tr>
<td>10 years</td>
<td>51/1000</td>
<td>6/1000</td>
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<tr>
<td>15 years</td>
<td>57/1000</td>
<td>12/1000</td>
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date, prevented development of breast cancer in women at high risk of the disease (Fisher et al. 1998). Treatment of women with osteoporosis (who are at low risk of breast cancer) with raloxifene in a multicentre randomised placebo controlled trial was associated with a 90% reduction in the relative risk of developing oestrogen receptor-positive breast cancer (Cummings et al. 1999). These results with drugs that block certain of the peripheral actions of oestrogens have been complemented by those obtained with aromatase inhibitors (Santen & Harvey 1999) which reduce production of oestrogen. The beneficial effects of these various medications have been emphasized here because they are really only compatible with oestrogen being the malefactor in the impact of HRT on cancer of the breast. Moreover, the data are derived from randomised controlled clinical trials so they are very robust, in contrast to those from observational studies which are so prone to difficulties of interpretation. The notion that gestogens augment the proliferative actions of oestrogen on the breast continues to be strongly argued (Pike et al. 1993) and has received recent support from the report cited above (Schaerer et al. 2000).

The excess of cancer cases in the above compilation of results was largely due to localised disease (Collaborative Group on Hormonal Factors in Breast Cancer 1997). Two earlier studies had reported a higher risk of in situ than invasive cancer in association with HRT (Longnecker et al. 1996, O’Connor et al. 1998). More recent case series, however, described invasive cancers in women using HRT, although they were less aggressive than those seen in women not taking HRT (Holli et al. 1998). More persuasively, in a recent prospective cohort study, a positive relationship was found between the incidence of invasive breast cancer with a favourable history and duration of oestrogen use (Gapsur et al. 1999). The relationship was stronger for current than for past users. These results are consistent with reports that the prognosis in women with breast cancer developing during HRT is better than in women not taking oestrogen (Persson et al. 1996, Willis et al. 1996, Jernstrom et al. 1999), although at the present time one still cannot be sure to what extent this difference should be attributed to surveillance bias.

The relationship of HRT use and steroid receptor status has been the subject of several reports. While correlations have been described (Jones et al. 1994, Bonnier et al. 1998), in most of the studies (reviewed in Cobleigh et al. 1999) no significant differences in receptor profile between users and non-users of HRT have been detected. The position remains uncertain, however, because until recently the majority of studies used the dextran-coated charcoal assay (Habel & Stanford 1993). This method detects unoccupied receptors only and, in the presence of exogenous oestrogen, one might expect the sites to be occupied. The position will presumably be clarified when monoclonal antibody-based methods have been more widely used in this context.

Individual susceptibility and environmental factors

Since it is a small proportion of the population exposed to HRT that develops breast cancer, much interest is currently directed at discovering factors which may explain individual susceptibility. Some of these factors are related to observable changes in the breast, some to genetic factors which may, inter alia, determine hormone levels and some to environmental influences, such as an interaction of alcohol consumption with the effects of HRT.

An increase in breast density can be detected by mammography in 15–50% of women who take HRT (Grellande et al. 1999). Greater breast density is independently associated with a doubling of the risk of breast cancer (Warner et al. 1992). The risk persists for up to 9 years post-mammography, suggesting that masking of breast cancer in denser tissue is not the sole cause of the observed association (Barrett-Connor & Grady 1998). The results are consistent with stimulation by oestrogen of epithelial cell proliferation in the breast.

Mention has been made of the relation of endogenous hormone levels to the risk of breast cancer. Genetic mechanisms may help to explain some of the differences in hormone levels which have recently been investigated. A polymorphism of one of the genes that encodes enzymes responsible for adrenal and ovarian production of sex steroids (cytochrome P450c17α gene; CYP 17) has been described which, while not, as originally thought, involved in genesis of the polycystic ovary syndrome (Techatraisak et al. 1997), may be important in determining postmenopausal hormone concentrations. Thus, in one study, postmenopausal women with the CYP 17 A2/A2 genotype had significantly higher levels of oestrone (+14%) and dehydroepiandrosterone (+14.4%) than women with the A1/A1 genotype (Haiman et al. 1999). Similar elevations in mean serum oestradiol and androstenedione concentrations were found, although the differences did not reach statistical significance. In a separate study, it was reported that women who carry the CYP 17 A2/A2 genotype were about half as likely as women with the A1/A1 genotype to be current users of HRT (Feigelson et al. 1999). This result is consistent with the notion that it is women with the lowest endogenous hormone levels who are most likely to choose hormone treatment. Conversely, those with the highest endogenous hormone levels (who, as discussed above, are most at risk from breast cancer) are likely to be under-represented in users of HRT, so causing a statistical underestimate of the true risk of oestrogen treatment.

Thus far discussion has focused on production of hormones. For some years Bradlow (Bradlow et al. 1996) and Fishman (Fishman et al. 1995) and their colleagues have emphasized the importance for breast cancer risk of the metabolism of oestrogens. Oestradiol metabolism is predominantly oxidative, initially reversibly to oestrone,
subsequently and irreversibly, by one of two pathways. The first is by 2-hydroxylation to form the non-oestrogenic catechol, 2-hydroxyoestrone, the second is by 16α-hydroxylation to produce 16α-hydroxyoestrone and thence oestradiol. The latter compounds are oestrogenic. The impact of secreted or administered oestrogen depends on the balance between these metabolic pathways (Zumoff 1993). The original finding of increased 16α-hydroxylation in women with breast cancer (Fishman et al. 1984) has been confirmed recently in both a case control (Kabat et al. 1997) and a prospective cohort study (Meilahn et al. 1998). In the latter, postmenopausal women who went on to develop breast cancer showed, at baseline, about a 15% lower 2:16α-hydroxyoestrone ratio than matched control subjects.

Genetic factors are important in determining the direction of this metabolic pathway (Taioli et al. 1999) but body weight is also relevant, thin women (at lower risk of breast cancer) making more catechol metabolites, overweight women (at greater risk) more 16α metabolites (Fishman et al. 1975). Parenthetically, it may be possible to alter the direction of this metabolic pathway by administering relatively simple compounds (Hershcopf & Bradlow 1987), so designing chemoprevention strategies for those most at risk (Wong et al. 1997).

Alcohol ingestion was first reported to be associated with an increased risk of breast cancer in a large case control study in 1977 (Williams & Horm 1977). Since then the association has been examined in more than 50 epidemiological studies (Schatzkin & Longnecker 1994). A meta-analysis of 28 case control and 10 cohort studies indicated a dose–response association between the amount of alcohol consumed and the risk of breast cancer (Longnecker 1994). At a daily intake of 26 g ethanol, the risk of breast cancer relative to non-drinking was 1.24 (95% confidence interval 1.15–1.34). The risk associated with one alcoholic drink per day (approximately 13 g alcohol) was about 10% greater than in non-drinkers. There was, however, marked variation between studies, the association being strongest in countries with the highest per capita intake. A pooled analysis of six cohort studies from Canada, The Netherlands, Sweden and the United States (comprising 322 647 women of whom 4335 developed invasive breast cancer) has also revealed a linear increase in breast cancer incidence with increasing alcohol consumption (Smith-Warner et al. 1998).

The explanation for this association is not certain but an endocrine mechanism may provide the link. As recently reviewed (Purohit 1998), an increase of serum oestradiol concentrations in response to ingestion of alcohol was observed in two of six studies of untreated postmenopausal women. Two studies of women on HRT showed an increase of serum oestradiol concentrations after a single (but substantial) dose of alcohol. In women receiving HRT via a dermal patch the increase was modest (22%, n = 7 (Ginsburg et al. 1995)). In those taking oestrogen orally it was, however, really quite striking (300%, n = 12 (Ginsburg et al. 1996)). The results are consistent with an impact of ingestion of alcohol on splanchnic metabolism of oestrogens.

Several papers have described the receptor status of breast cancers in relation to alcohol consumption. A recent report (Enger et al. 1999), which describes the largest series to date, usefully summarises the literature. Based on their own data, the authors concluded that ingestion of alcohol preferentially increased the risk of oestrogen (and progesterone) receptor-positive breast cancer in postmenopausal women. Needless to say, contrary findings have also been reported (Gapstur et al. 1995). Two groups have reported that the major risk of breast cancer with postmenopausal HRT occurs in women who consume alcohol (Colditz 1990, Gapstur et al. 1992). While this point has been stressed in the endocrine literature (Zumoff 1997) the extent to which the association should be attributed to confounding is unresolved at present (Rosenberg et al. 1993). If genuine, the association would clearly be important because alcohol consumption is common and, in contrast to most of the currently recognized risk factors, it can be modified.

**Implications for treatment**

Until the results of randomised controlled clinical trials become available, the re-analysis by the Collaborative Group on Hormone Factors in Breast Cancer (1997) provides the best estimate of the average risk a woman takes when she embarks on oral oestrogen replacement therapy. The figures shown in Table 1 will, however, need to be modified according to the individual’s endogenous risk factors, as set out above. One practical implication of the extensive work reviewed here seems to the present author to be for women to use the lowest dose of oestrogen that is effective. As described by Barrett-Connor (1998), presently advised doses of oestrogen (Table 2) were designed to prevent bone loss, of progesterone to prevent endometrial cancer. The advice has not, however, been based on studies of a wide range of doses. Recent reports have indicated that for many women a daily dose as low as 0.3 mg conjugated oestrogen or its equivalent, together with 1 g dietary calcium, will suffice for the prevention of osteoporosis (Ettinger et al. 1987, 1992).

**Table 2 Bone-conserving doses of oestrogens (see text for discussion). These are average doses for a postmenopausal woman in her sixth decade. Younger women may require higher, older women may require lower doses**

<table>
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<tr>
<th>Oral</th>
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<tr>
<td>Conjugated equine oestrogens</td>
<td>0.625 mg daily</td>
</tr>
<tr>
<td>Oestrone sulphate</td>
<td>1.5 mg daily</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>1.2 mg daily</td>
</tr>
<tr>
<td>Transdermal</td>
<td>0.05 mg daily</td>
</tr>
<tr>
<td>Implant</td>
<td>50 mg 6-monthly</td>
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Data from Barrett-Connor (1998).
The issue of dosage raises the question of the wisdom of providing HRT with subcutaneous implants of oestrogen. With this form of therapy, one can achieve oestradiol levels within the physiological range, control symptoms and prevent bone rarefaction with implants of 25 mg given every 6–9 months (Owen et al. 1992, Holland et al. 1994). Nonetheless, most clinicians who advocate implants use larger doses (Studd & Smith 1993). Garnet and colleagues (1990), who administered implants containing 50 or 75 mg oestradiol every 6 months, reported that the mean serum oestradiol concentration in 1388 women seen in one clinic over 1 year was 767 pmol/l; the range was wide, with only 17.1% having a concentration below 500 pmol/l (Garnett et al. 1990). Three per cent of the women had serum levels exceeding 1750 pmol/l. Quite apart from the extraordinarily prolonged duration of action of these implants (gonadotrophin concentrations may be suppressed for up to 3 years after implants of 100 mg (Hunter et al. 1973), endometrial stimulation may continue for even longer (Gangar et al. 1990)), one cannot be sanguine about the proliferative effects on the breast of these very high oestradiol levels. Moreover, it appears that a proportion of women develop a need for reimplantation at shorter and shorter intervals (Gangar et al. 1989, Garnett et al. 1990). It seems likely that these patients and their doctors are not adhering to the axiom that oestrogens should be prescribed in the lowest effective dose for specific indications; rather, oestrogen implants are being inserted for psychological rather than endocrinological reasons (Buckler et al. 1995, O’Leary et al. 1999).

HRT for women with a history of breast cancer?

As a result of advances in diagnosis and treatment there is a large and growing cohort of women who can look forward to many years survival after treatment for breast cancer. Many are postmenopausal at the time of diagnosis; in a significant proportion of premenopausal cases cytotoxic treatment causes ovarian damage sufficient to precipitate menopause. The combination of these circumstances with the increasing concern of physicians and patients over the impairment by oestrogen deficiency of the patient’s quality of life has led to a reappraisal of the traditional advice that women with breast cancer should avoid oestrogen therapy. Based on review of the outcome of breast cancer diagnosed during pregnancy, of the effect of pregnancy subsequent to breast cancer (Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists 1997) and of breast cancer in relation to use of the oral contraceptive and HRT, it has been argued that it is now time to rethink the role of HRT in women with a past history of breast cancer (DiSaia 1993).

At present there are no randomised controlled trials upon which to base decisions and, given the understandable reluctance of patients to enter such trials, it is likely to be several years before robust data become available. At present, therefore, one has to start by reviewing case series. Vassilopoulou-Sellin, Theriault and Klein reported the results in 49 women who underwent a minimum of 2 years treatment with oestrogen replacement after diagnosis and treatment of localised breast cancer (Vassilopoulou-Sellin et al. 1997). They compiled results from four other groups (DiSaia et al. 1993, Powles et al. 1993, Wile et al. 1993, Eden et al. 1995), to which we may add another three (Stoll & Parbhoo 1988, Brewster et al. 1999, Ursic-Vrsacaj & Bebar 1999), to give a total of 501 patients who received short-term HRT after treatment for breast cancer. The cancers were of various stages. Thirty-seven (7.4%) of these patients suffered a recurrence while on treatment. A separate report described four patients who developed metastatic breast cancer while on HRT; in each, withdrawal of treatment resulted in regression of the metastatic disease (Dhodapkar et al. 1995).

Opinion is understandably divided on the safety of HRT after treatment of breast cancer and where possible non-hormonal treatment options are favoured (Santen et al. 1998). On the other hand, for some women quality of life is so impaired by oestrogen deficiency that withholding HRT is unreasonable. Obviously the indication for such treatment should be severe symptoms of oestrogen deficiency rather than the prevention of long-term complications. Treatment should be preceded by careful explanation and discussion; the dose should be the lowest that resolves symptoms. Combined treatment with oestrogen and tamoxifen has been described (Chang et al. 1996, Santen et al. 1998) on the basis that tamoxifen is effective in preventing breast cancer in premenopausal women, in whom oestrogen levels are higher than in postmenopausal women on low-dose HRT. An alternative approach would be the combination of oestrogen with raloxifene, the latter chosen because its oestrogen antagonism extends to the uterus (Khovidhunkit & Shoback 1999), so reducing the risk of endometrial stimulation and therefore the need for co-treatment with gestogens.

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