Hormone replacement therapy and breast cancer

H S Jacobs

Emeritus Professor of Reproductive Endocrinology, Royal Free and University College London Medical School, The Middlesex Hospital, Mortimer Street, London W1N 8AF, UK

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.

Endocrine-Related Cancer (2000) **7** 53–61

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. Problems of bias and confounding do remain, however, because most of the information has been acquired from observational rather than experimental studies. Given the probable relationship of the risk of cancer to the dose and duration of treatment, I make some broad recommendations concerning prescription of treatment. Finally, I suggest a tentative approach to the difficult problem of management of women with a history of breast cancer whose symptoms of hormone deficiency are severe enough to warrant treatment with oestrogen.

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 (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,

Online version via http://www.endocrinology.org

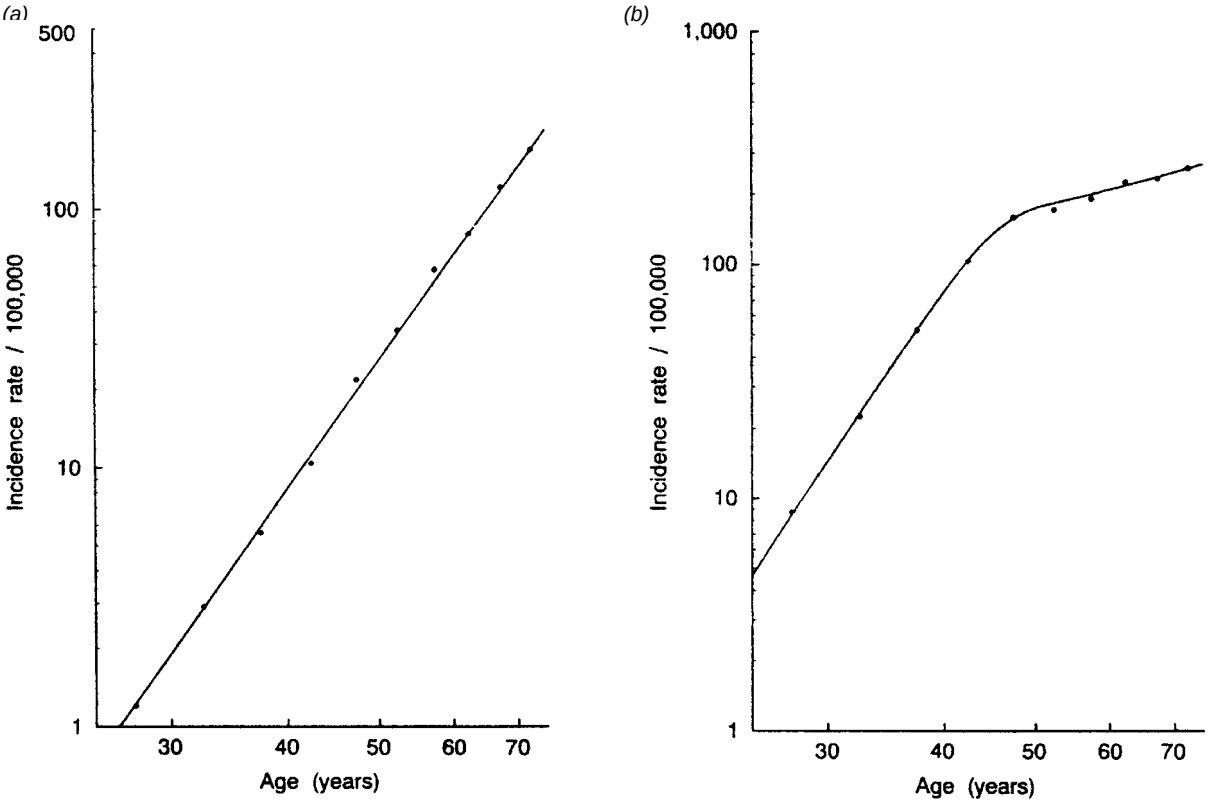

Figure 1 Log–log plot of age-specific incidence rates for (*a*) colorectal cancer (per 100 000) in white American women (1969-1971) and (*b*) breast cancer (per 100 000) in white American women (1969–1971). Note the shape of the curve for a non-hormone-dependant malignancy (*a*) compared with the inflection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

postmenopausal women have a lower risk of breast cancer than premenopausal women of the same age and child-bearing 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/m^2 being double that of women with a BMI of less than 21 kg/m^2 (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/m^2 (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).

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, Gambrell 1996) and five, including the most recent, showed an increase in risk from long-term use (Grady & Ernster 1991, Steinberg *et al.* 1991, Sillero-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.

Table 1 Breast cancer and HRT: results from the re-analysis of epidemiological studies by the Collaborative Group on Hormonal Factors in Breast Cancer (1997)

Time on HRT	Breast cancers diagnosed over the 20 years from age 50 to 70	Extra breast cancers
Never	45/1000	—
5 years	47/1000	2/1000
10 years	51/1000	6/1000
15 years	57/1000	12/1000

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 (Schairer *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 Trialists' Collaborative Group 1998), and, in the largest trial to

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 (Schairer *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 histology and duration of oestrogen use (Gapstur *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 (Greendale *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 that may help to explain some of the differences in hormone levels 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 oestriol. 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 progestogen 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 congugated 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

Oral	
Conjugated equine oestrogens	0.625 mg daily
Oestrogen sulphate	1.5 mg daily
Oestradiol	1.2 mg daily
Transdermal	0.05 mg daily
Implant	50 mg 6-monthly

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 oestrogen 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 lead 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-Vrscaj & 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.

References

Armstrong BK 1988 Oestrogen therapy after the menopause – boon or bane? *Medical Journal of Australia* **148** 213–214.

Ballard-Barbash R & Swanson CA 1996 Body weight: estimation of risk for breast and endometrial cancers. *American Journal of Clinical Nutrition* **63** 437S–441S.

Barrett-Connor E 1998 Hormone replacement therapy. *British Medical Journal* **317** 457–461.

Barrett-Connor E & Grady D 1998 Hormone replacement therapy, heart disease, and other considerations. *Annual Review of Public Health* **19** 55–72.

Bonnier P, Bessenay F, Sasco AJ, Beedassy B, Lejeune C, Romain S, Charpin C, Piana L & Martin PM 1998 Impact of menopausal hormone-replacement therapy on clinical and laboratory

characteristics of breast cancer. *International Journal of Cancer* **79** 278–282.

Bradlow HL, Telang NT, Sepkovic DW & Osborne MP 1996 2-Hydroxyestrone: the 'good' estrogen. *Journal of Endocrinology* **150** (Suppl) S259–S265.

Brewster WR, DiSaia PJ, Grosen EA, McGonigle KF, Kuykendall JL & Creasman WT 1999 An experience with estrogen replacement therapy in breast cancer survivors. *International Journal of Fertility and Women's Medicine* **44** 186–192.

Buckler HM, Kalsi PK, Cantrill JA & Anderson DC 1995 An audit of oestradiol levels and implant frequency in women undergoing subcutaneous implant therapy. *Clinical Endocrinology* **42** 445–450.

Cauley JA, Lucas FL, Kuller LH, Stone K, Browner W & Cummings SR 1999 Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Study of Osteoporotic Fractures Research Group. *Annals of Internal Medicine* **130** 270–277.

Chang J, Powles TJ, Ashley SE, Gregory RK, Tidy VA, Treleaven JG & Singh R 1996 The effect of tamoxifen and hormone replacement therapy on serum cholesterol, bone mineral density and coagulation factors in healthy postmenopausal women participating in a randomised, controlled tamoxifen prevention study. *Annals of Oncology* **7** 671–675.

Cobleigh MA, Norlock FE, Oleske DM & Starr A 1999 Hormone replacement therapy and high S phase in breast cancer. *Journal of the American Medical Association* **281** 1528–1530.

Colditz GA 1998 Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. *Journal of the National Cancer Institute* **90** 814–823.

Colditz GA 1990 A prospective assessment of moderate alcohol intake and major chronic diseases. *Annals of Epidemiology* **1** 167–177.

Colditz GA, Egan KM & Stampfer MJ 1993 Hormone replacement therapy and risk of breast cancer: results from epidemiologic studies. *American Journal of Obstetrics and Gynecology* **168** 1473–1480.

Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, Hennekens C, Rosner B & Speizer FE 1995 The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *New England Journal of Medicine* **332** 1589–1593.

Collaborative Group on Hormonal Factors in Breast Cancer 1997 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* **350** 1047–1059.

Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A & Jordan VC 1999 The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple outcomes of raloxifene evaluation. *Journal of the American Medical Association* **281** 2189–2197.

Dhodapkar MV, Ingle JN & Ahmann DL 1995 Estrogen replacement therapy withdrawal and regression of metastatic breast cancer. *Cancer* **75** 43–46.

DiSaia PJ 1993 Hormone-replacement therapy in patients with breast cancer. A reappraisal. *Cancer* **71** 1490–1500.

DiSaia PJ, Odicino F, Grosen EA, Cowan B, Pecorelli S & Wile AG 1993 Hormone replacement therapy in breast cancer. *Lancet* **342** 1232.

Dupont WD & Page DL 1991 Menopausal estrogen replacement therapy and breast cancer. *Archives of Internal Medicine* **151** 67–72.

Early Breast Cancer Trialists' Collaborative Group 1998 Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* **351** 1451–1467.

Eden JA, Bush T, Nand S & Wren BG 1995 A case control study of combined continuous estrogen–progestin replacement therapy among women with a personal history of breast cancer. *Menopause* **2** 67–72.

Enger SM, Ross RK, Paganini-Hill A, Longnecker MP & Bernstein L 1999 Alcohol consumption and breast cancer oestrogen and progesterone receptor status. *British Journal of Cancer* **79** 1308–1314.

Ettinger B, Genant HK & Cann CE 1987 Postmenopausal bone loss is prevented by treatment with low-dosage estrogen with calcium. *Annals of Internal Medicine* **106** 40–45.

Ettinger B, Genant HK, Steiger P & Madvig P 1992 Low-dosage micronized 17 beta-estradiol prevents bone loss in postmenopausal women. *American Journal of Obstetrics and Gynecology* **166** 479–488.

Feigelson HS, McKean-Cowdin R, Pike MC, Coetzee GA, Kolonel LN, Nomura AM, Le Marchand L & Henderson BE 1999 Cytochrome P450c17alpha gene (CYP17) polymorphism predicts use of hormone replacement therapy. *Cancer Research* **59** 3908–3910.

Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L & Wolmark N 1998 Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of the National Cancer Institute* **90** 1371–1388.

Fishman J, Boyar RM & Hellman L 1975 Influence of body weight on estradiol metabolism in young women. *Journal of Clinical Endocrinology and Metabolism* **41** 989–991.

Fishman J, Schneider J, Hershcope RJ & Bradlow HL 1984 Increased estrogen-16 alpha-hydroxylase activity in women with breast and endometrial cancer. *Journal of Steroid Biochemistry* **20** 1077–1081.

Fishman J, Osborne MP & Telang NT 1995 The role of estrogen in mammary carcinogenesis. *Annals of the New York Academy of Sciences* **768** 91–100.

Gambrell RDJ 1996 Hormone replacement therapy and breast cancer risk. *Archives of Family Medicine* **5** 341–348.

Gangar K, Cust M & Whitehead MI 1989 Symptoms of oestrogen deficiency associated with supraphysiological plasma oestradiol concentrations in women with oestradiol implants. *British Medical Journal* **299** 601–602.

Gangar KF, Fraser D, Whitehead MI & Cust MP 1990 Prolonged endometrial stimulation associated with oestradiol implants. *British Medical Journal* **300** 436–438.

Gapstur SM, Potter JD, Sellers TA & Folsom AR 1992 Increased risk of breast cancer with alcohol consumption in postmenopausal women. *American Journal of Epidemiology* **136** 1221–1231.

Gapstur SM, Potter JD, Drinkard C & Folsom AR 1995 Synergistic effect between alcohol and estrogen replacement therapy on risk of breast cancer differs by estrogen/progesterone receptor status in the Iowa Women's Health Study. *Cancer Epidemiology Biomarkers and Prevention* **4** 313–318.

Gapstur SM, Morrow M & Sellers TA 1999 Hormone replacement therapy and risk of breast cancer with a favorable histology:

results of the Iowa Women's Health Study. *Journal of the American Medical Association* **281** 2091–2097.

Garnett T, Studd JW, Henderson A, Watson N, Savvas M & Leather A 1990 Hormone implants and tachyphylaxis. *British Journal of Obstetrics and Gynaecology* **97** 917–921.

Ginsburg ES, Walsh BW, Gao X, Gleason RE, Feltmate C & Barbieri RL 1995 The effect of acute ethanol ingestion on estrogen levels in postmenopausal women using transdermal estradiol. *Journal of the Society for Gynecological Investigation* **2** 26–29.

Ginsburg ES, Mello NK, Mendelson JH, Barbieri RL, Teoh SK, Rothman M, Gao X & Sholar JW 1996 Effects of alcohol ingestion on estrogens in postmenopausal women. *Journal of the American Medical Association* **276** 1747–1751.

Grady D & Ernster V 1991 Invited commentary: Does post menopausal hormone therapy cause breast cancer? *American Journal of Epidemiology* **134** 1396–1400.

Greendale GA, Reboussin BA, Sie A, Singh HR, Olson LK, Gatewood O, Bassett LW, Wasilauskas C, Bush T & Barrett-Connor E 1999 Effects of estrogen and estrogen–progestin on mammographic parenchymal density. Postmenopausal estrogen/progestin interventions (PEPI) investigators. *Annals of Internal Medicine* **130** 262–269.

Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, Rosner B, Fuchs C, Hankinson SE, Hunter DJ, Hennekens CH & Speizer FE 1997 Postmenopausal hormone therapy and mortality. *New England Journal of Medicine* **336** 1769–1775.

Habel LA & Stanford JL 1993 Hormone receptors and breast cancer. *Epidemiologic Reviews* **15** 209–219.

Haiman CA, Hankinson SE, Spiegelman D, Colditz GA, Willett WC, Speizer FE, Kelsey KT & Hunter DJ 1999 The relationship between a polymorphism in CYP17 with plasma hormone levels and breast cancer. *Cancer Research* **59** 1015–1020.

Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer MJ, Longcope C & Speizer FE 1995 Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. *Journal of the National Cancer Institute* **87** 1297–1302.

Hankinson SE, Willett WC, Manson JE, Colditz GA, Hunter DJ, Spiegelman D, Barbieri RL & Speizer FE 1998 Plasma sex steroid hormone levels and risk of breast cancer in post-menopausal women. *Journal of the National Cancer Institute* **90** 1292–1299.

Hershcopf RJ & Bradlow HL 1987 Obesity, diet, endogenous estrogens, and the risk of hormone-sensitive cancer. *American Journal of Clinical Nutrition* **45** 283–289.

Holland EF, Leather AT & Studd JW 1994 The effect of 25-mg percutaneous estradiol implants on the bone mass of post-menopausal women. *Obstetrics and Gynecology* **83** 43–46.

Holli K, Isola J & Cuzick J 1998 Low biologic aggressiveness in breast cancer in women using hormone replacement therapy. *Journal of Clinical Oncology* **16** 3115–3120.

Hulka BS & Stark AT 1995 Breast cancer: cause and prevention. *Lancet* **346** 883–887.

Hunter DJ, Akande EO, Carr P & Stallworthy J 1973 The clinical and endocrinological effect of oestradiol implants at the time of hysterectomy and bilateral salpingo-oophorectomy. *Journal of Obstetrics and Gynaecology of the British Commonwealth* **80** 827–833.

Jernstrom H, Frenander J, Ferno M & Olsson H 1999 Hormone replacement therapy before breast cancer diagnosis significantly reduces the overall death rate compared with never-use among 984 breast cancer patients. *British Journal of Cancer* **80** 1453–1458.

Jones C, Ingram D, Mattes E & Hahnel R 1994 The effect of hormone replacement therapy on prognostic indices in women with breast cancer. *Medical Journal of Australia* **161** 106–110.

Kabat GC, Chang CJ, Sparano JA, Sepkovie DW, Hu XP, Khalil A, Rosenblatt R & Bradlow HL 1997 Urinary estrogen metabolites and breast cancer: a case-control study. *Cancer Epidemiology Biomarkers and Prevention* **6** 505–509.

Key TJ 1999 Serum oestradiol and breast cancer risk. *Endocrine-Related Cancer* **6** 175–180.

Khovidhunkit W & Shoback DM 1999 Clinical effects of raloxifene hydrochloride in women. *Annals of Internal Medicine* **130** 431–439.

Kuller LH, Cauley JA, Lucas L, Cummings S & Browner WS 1997 Sex steroid hormones, bone mineral density, and risk of breast cancer. *Environmental Health Perspectives* **105** (Suppl 3) 593–599.

Longnecker MP 1994 Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Causes and Control* **5** 73–82.

Longnecker MP, Bernstein L, Paganini-Hill A, Enger SM & Ross RK 1996 Risk factors for *in situ* breast cancer. *Cancer Epidemiology Biomarkers and Prevention* **5** 961–965.

MacDonald PC, Edman CD, Hemsell DL, Porter JC & Siiteri PK 1978 Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer. *American Journal of Obstetrics and Gynecology* **130** 448–455.

Meilahn EN, De Stavola B, Allen DS, Fentiman I, Bradlow HL, Sepkovic DW & Kuller LH 1998 Do urinary oestrogen metabolites predict breast cancer? Guernsey III cohort follow-up. *British Journal of Cancer* **78** 1250–1255.

O'Connor IF, Shembekar MV & Shousha S 1998 Breast carcinoma developing in patients on hormone replacement therapy: a histological and immunohistological study. *Journal of Clinical Pathology* **51** 935–938.

O'Leary A, Bowen-Simpkins P, Tejura H & Rajesh U 1999 Are high levels of oestradiol after implants associated with features of dependence? *British Journal of Obstetrics and Gynaecology* **106** 960–963.

Olsson H & Hagglund G 1992 Reduced cancer morbidity and mortality in a prospective cohort of women with distal forearm fractures. *American Journal of Epidemiology* **136** 422–427.

Owen EJ, Siddle NC, McGarrigle HT & Pugh MA 1992 25 mg oestradiol implants – the dosage of first choice for subcutaneous oestrogen replacement therapy? *British Journal of Obstetrics and Gynaecology* **99** 671–675.

Persson I, Adami HO, McLaughlin JK, Naessen T & Fraumeni JFJ 1994 Reduced risk of breast and endometrial cancer among women with hip fractures (Sweden). *Cancer Causes and Control* **5** 523–528.

Persson I, Yuen J, Bergkvist L & Schairer C 1996 Cancer incidence and mortality in women receiving estrogen and estrogen–progestin replacement therapy – long-term follow-up of a Swedish cohort. *International Journal of Cancer* **67** 327–332.

Pike MC, Spicer DV, Dahmoush L & Press MF 1993 Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiologic Reviews* **15** 17–35.

Powles TJ, Hickish T, Casey S & O'Brien M 1993 Hormone replacement after breast cancer. *Lancet* **342** 60–61.

Purohit V 1998 Moderate alcohol consumption and estrogen levels in postmenopausal women: a review. *Alcoholism: Clinical and Experimental Research* **22** 994–997.

Rosenberg L, Metzger LS & Palmer JR 1993 Alcohol consumption and risk of breast cancer: a review of the epidemiologic evidence. *Epidemiologic Reviews* **15** 133–144.

Santen RJ & Harvey HA 1999 Use of aromatase inhibitors in breast carcinoma. *Endocrine-Related Cancer* **6** 75–92.

Santen R, Pritchard K & Burger H 1998 The consensus conference on treatment of estrogen deficiency symptoms in women surviving breast cancer. *Obstetrical and Gynecological Survey* **53** S1–S83.

Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L & Hoover R 2000 Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* **283** 485–491.

Schatzkin A & Longnecker MP 1994 Alcohol and breast cancer. Where are we now and where do we go from here? *Cancer* **74** 1101–1110.

Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists 1997 Pregnancy after breast cancer. 12. London: Royal College of Obstetricians and Gynaecologists.

Sillero-Arenas M, Delgado-Rodriguez M, Rodigues-Canteras R, Bueno-Cavanillas A & Galvez-Vargas R 1992 Menopausal hormone replacement therapy and breast cancer: a meta-analysis. *Obstetrics and Gynecology* **79** 286–294.

Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, Graham S, Holmberg L, Howe GR, Marshall JR, Miller AB, Potter JD, Speizer FE, Willett WC, Wolk A & Hunter DJ 1998 Alcohol and breast cancer in women: a pooled analysis of cohort studies. *Journal of the American Medical Association* **279** 535–540.

Steinberg KK, Thacker SB, Smith SJ, Stroup DF, Zack MM, Flanders WD & Berkelman RL 1991 A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. *Journal of the American Medical Association* **265** 1985–1990.

Stoll BA & Parbhoo S 1988 Treatment of menopausal symptoms in breast cancer patients. *Lancet* **i** 278–1279.

Studd JW & Smith RN 1993 Oestradiol and testosterone implants. *Baillières Clinical Endocrinology and Metabolism* **7** 203–223.

Taioli E, Bradlow HL, Garbers SV, Sepkovic DW, Osborne MP, Trachman J, Ganguly S & Garte SJ 1999 Role of estradiol metabolism and CYP1A1 polymorphisms in breast cancer risk. *Cancer Detection and Prevention* **23** 232–237.

Techatraisak K, Conway GS & Rumsby G 1997 Frequency of a polymorphism in the regulatory region of the 17 alpha-hydroxylase-17,20-lyase (CYP17) gene in hyperandrogenic states. *Clinical Endocrinology* **46** 131–134.

Thomas HV, Reeves GK & Key TJ 1997 Endogenous estrogen and postmenopausal breast cancer: a quantitative review. *Cancer Causes and Control* **8** 922–928.

Ursic-Vrscaj M & Bebar S 1999 A case-control study of hormone replacement therapy after primary surgical breast cancer treatment. *European Journal of Surgical Oncology* **25** 146–151.

Vassilopoulou-Sellin R, Theriault R & Klein MJ 1997 Estrogen replacement therapy in women with prior diagnosis and treatment for breast cancer. *Gynecologic Oncology* **65** 89–93.

Warner E, Lockwood G, Tritchler D & Boyd NF 1992 The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. *Cancer Detection and Prevention* **16** 67–72.

Wile AG, Opfell RW & Margileth DA 1993 Hormone replacement therapy in previously treated breast cancer patients. *American Journal of Surgery* **165** 372–375.

Williams RR & Horm JW 1977 Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *Journal of the National Cancer Institute* **58** 525–547.

Willis DB, Calle EE, Miracle-McMahill HL & Heath CWJ 1996 Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. *Cancer Causes and Control* **7** 449–457.

Wong GY, Bradlow L, Sepkovic D, Mehl S, Mailman J & Osborne MP 1997 Dose-ranging study of indole-3-carbinol for breast cancer prevention. *Journal of Cellular Biochemistry* (Suppl) **28–29** 111–116.

Zumoff B 1993 Biological and endocrinological insights into the possible breast cancer risk from menopausal estrogen replacement therapy. *Steroids* **58** 196–204.

Zumoff B 1997 Alcohol, estrogens, and breast cancer. *Journal of Clinical Endocrinology and Metabolism* **82** 2378.