Eur J Cancer Clin Oncol, Vol. 25, No. 12, pp. 1909–1913, 1989.
Printed in Great Britain

0277-5379/89$3.00 + 0.00

Special Article

Hormone Replacement Therapy in Women Treated for Breast Cancer

BASIL A. STOLL
Department of Oncology, St. Thomas' Hospital, London, U.K.

Abstract—*We must still maintain the conventional advice that unopposed low dosages of oestrogen should not be used for the treatment of menopausal symptoms in women treated previously for breast cancer. There is, however, epidemiological, laboratory and clinical evidence that certain combinations of oestrogen and progestagen are more likely to be beneficial than harmful, in respect to the risk of reactivating subclinical residual breast cancer or causing progression in premalignant lesions. It is no longer justifiable to deprive a woman with a history of breast cancer treatment of a hormonal therapy capable of safely relieving symptoms which are making her life intolerable. A clinical trial of such treatment is reported.*

PRACTICALLY all gynaecologists and oncologists currently advise against the use of any hormone replacement therapy (HRT) containing oestrogen in women previously treated for breast cancer and free of clinical recurrence. While such caution was justified in the past, there is a need to revise this attitude because of new knowledge and recent changes in the formulation of HRT. This review examines evidence for the safety of HRT containing both oestrogen and progestagen in the management of women treated previously for breast cancer, or those considered to be at high risk to the disease. It reports a clinical trial of such treatment and its rationale.

EXOGENOUS OESTROGEN AND BREAST CANCER

At present, women with a history of treatment for breast cancer who complain of severe menopausal sweats or hot flushing are generally given a trial of clonidine, a non-hormonal agent which reduces the responsiveness of peripheral vessels to vasodilation stimuli. If they complain of symptoms of vaginal or urethral atrophy, they may be given low dosage of a progestagen such as norethisterone. Unfortunately, neither agent is effective in the woman with severe symptoms. The reasons given by clinicians for avoiding oestrogen-containing HRT in such cases are (a) the risk of reactivating the growth of residual breast cancer cells; (b) the risk of stimulating proliferative activity in mammary epithelial cells which have already undergone malignant transformation [1].

The evidence that oestrogen is implicated in the promotion of human breast cancer is convincing although still indirect [2]. In the case of established breast cancer, however, there is abundant clinical and laboratory evidence of the effect of oestrogen administration, and wide agreement that it is dose-dependent — low dosage of oestrogen may stimulate tumour growth activity while high dosage inhibits it [3]. Similar dose-dependancy has been observed for the effect of oestrogen on human breast cancer cell cultures in the laboratory [4]. This clinical and laboratory evidence supports the conventional advice that for women who have been previously treated for breast cancer, the administration of unopposed low dosage oestrogen is not advisable, whether given by mouth, vaginal cream, skin patch or implant [1].

With regard to epidemiological evidence, a large number of studies have looked for a change in the incidence of breast cancer in postmenopausal women receiving HRT (mainly oestrogen replacement therapy). Some studies have found a lowered risk of breast cancer [5, 6], some have found an elevated risk in at least some subgroups [7–10], while others have reported no change in the risk [11–13].

Accepted 2 August 1989.

New light has been thrown on the reason for this conflicting epidemiological evidence by a recent report on the incidence of breast cancer in a series of 3303 women in the U.S.A. who had had breast biopsy for a benign lesion whose histology was carefully assessed [14]. Dupont *et al.* have shown that the administration of exogenous oestrogen (almost entirely HRT for menopausal symptoms) was associated with a *lowered* risk of subsequently developing breast cancer in those women showing histopathological evidence of proliferative disease (even to the extent of atypical hyperplasia). The risk was reduced whether or not there was a history of breast cancer in a first degree relative.

The report explains the conflicting epidemiological observations in the literature by showing that in their series, the lowered risk occurred only in women receiving HRT after the mid 1950s. They point out that, at that time, agreement was reached in the U.S.A. to reduce the dosage of natural conjugated oestrogen (widely used in the treatment of HRT) to 0.625 mg daily. Several reports have confirmed that the risk of breast cancer following HRT is increased by higher doses of oestrogen [7–10].

In addition to this evidence that very low doses of oestrogen given to postmenopausal women may inhibit progression of histological atypia in the breast, three epidemiological studies have reported that the addition of cyclical progestagen to the oestrogen in HRT can lower the incidence of breast cancer in postmenopausal women [15–17]. One series reported that women who did not receive HRT had a five times greater incidence of breast cancer than did those who received an oestrogen/progestagen formulation, while those who received oestrogen alone had an intermediate incidence [16].

OESTROGEN AND PROGESTAGEN IN THE DEVELOPMENT AND GROWTH OF BREAST CANCER

There are very few reports on the effect of oestrogen/progestagen combinations on the proliferation of normal human mammary cells in tissue culture. While Longman and Buehring [18] found no significant effect by a combination of oestrogen and progestagen on such cells, Gompel *et al.* [19] found that some types of progestagen could inhibit the mitogenic effct of oestradiol. It should be noted that in the latter experiments, the concentration of the agents was in the physiological range, whereas in the former experiments they were at much higher levels. Gompel *et al.* suggest that, under physiological conditions, some types of progestagen when given after oestrogen priming are likely to induce terminal differentiation in the mammary cells, and in this way the progestagen acts as an *antimitogen*. Further laboratory studies are clearly needed.

In the case of mammary carcinoma cells, there are considerably more laboratory and clinical observations to support the hypothesis that the addition of some types of progestagen may counteract the mitogenic effect of oestrogen. It is now widely accepted that oestrogen-mediated stimulation of growth in hormone-dependent human mammary cancer is unlikely to be due to a direct effect of the oestrogen on the cancer cell [20]. Oestrogen appears to regulate secretion of autocrine and paracrine growth factors such as IGF1, TGF alpha and TGF beta which control the proliferative and invasive activity of the cancer cell. But some hormone-independent breast cancer cells also secrete these growth factors in increased amounts, and it is therefore no longer meaningful to distinguish hormone-dependent from hormone-independent breast cancers, except on the basis of sex steroid receptor levels.

Local growth factors may either be stimulated or inhibited according to the relative levels of oestrogen and progestagen. Evidence of this includes the following observations (a) addition of progestagen inhibits the stimulatory effect of oestrogen on human mammary cancer cells in culture [21, 22]; (b) treatment by progestagen inhibits the stimulatory effect of oestrogen on the growth of DMBA-induced rat mammary carcinoma [23, 24]; (c) the progestagen gestodene (a component of a widely used oral contraceptive) has been shown to arrest the growth of human mammary cancer cells in culture [25]. The agent stimulates secretion of TGF beta, a growth factor known to arrest the growth of breast cancer cells, and research has shown the presence of a high affinity receptor site for gestodene in breast cancer cells but not in normal mammary epithelial cells [25].

There is also an abundant literature reporting clinical regression of advanced breast cancer under treatment by progestagens, both in postmenopausal and premenopausal women [26]. In the former group of women, tumour regression is much more likely in patients showing evidence of persistent oestrogen secretion [27], suggesting that oestrogen priming of the tumour will favour its regression by progestagen therapy. This hypothesis is supported by a report of 65 postmenopausal women with advanced breast cancer treated by a combination of oestradiol and the progestagen, lynoestrenol, at contraceptive dosage [28]. After up to 6 months of therapy, regression of breast cancer was observed in 22% of cases. In addition, menopausal symptoms were controlled or abolished by the low dosage oestrogen/progestagen combination in those patients in whom they were recorded before treatment was started.

CLINICAL TRIAL OF COMBINATION HRT IN BREAST CANCER PATIENTS

Based on the epidemiological, laboratory and clinical evidence set out in the preceding section, a clinical trial of combination HRT has been reported in a group of women previously treated for breast cancer but remaining clinically free of recurrence [29]. Postmenopausal women were selected for treatment if they complained of very severe sweats or hot flushes which had failed to respond to a trial of clonidine therapy 0.05 mg bd, or else symptoms of severe vaginal or urethral atrophy. They were given a combination of natural conjugated equine oestrogen (0.625 mg) and norgestrel (0.15 mg) given daily continuously without break for 3 months. Treatment was continued for a further 3 months if symptoms were not completely relieved.

All treated patients in the trial showed marked control or abolition of menopausal symptoms, whether flushes or genital atrophy. The patients were followed for at least 2 years afterwards and no cases of tumour reactivation were observed during the period of observation. However, it is intended to confirm the effect of this oestrogen/progestagen combination on the proliferative activity of breast cancer, by monitoring serial fine needle biopsies of skin nodules in a group of treated patients, using flow cytometry and [^{3}H]thymidine labelling. There is one report of increased labelling index in a few cases within 9 days of initiating low dosage oestrogen/progestagen therapy [30] but much more prolonged monitoring in a much larger series is required.

The combination of conjugated equine oestrogen and norgestrel was chosen in the clinical trial because it is widely used in HRT both in Europe and the U.S.A. Although in the general population the progestagen component is given for only 7–12 days each month in a cyclic manner, it was considered advisable in this trial to give it continuously throughout the month in order to counteract any possible mitogenic effect of oestrogen on mammary tissue. It should be noted that the absorption of synthetic progestagens varies widely among patients [31] and a dose that is adequate for one patient may be insufficient for another. Thus, considerably more investigation is required before the optimal type and dosage of progestagen can be decided. The report noted above of a selective effect by the agent gestadine in inhibiting breast cancer growth, is an important first step.

It should be noted that added progestagen has been widely introduced into HRT in order to protect against the oestrogen-induced development of endometrial hyperplasia [32], and a Consensus Conference has concluded that such a regimen carries no risk of increasing the incidence of breast cancer among postmenopausal women [33]. A recent report on a cohort of 23,244 women confirms that the cyclical addition of progestagen to oestrogen does indeed considerably reduce the risk of endometrial cancer in women who retain their uterus [34].

Nevertheless, the addition of progestagen to HRT may have some disadvantages. In some women, it causes short-term side-effects such as depression, loss of energy or a bloated feeling. The long-term risks of the combined therapy are still uncertain, and a postulated drawback is that progestagens suppress high density lipoprotein cholesterol levels. This might negate the long term beneficial affect of oestrogen in reducing the incidence of myocardial infarction.

CONCLUSION

There is obvious need for more biological investigations on the effect of different oestrogen/progestagen combinations on normal and malignant human mammary cells in the laboratory. This may lead to the development of new combinations capable of protecting postmenopausal women (and possibly also premenopausal women) against the risk of developing breast cancer. In order to select the optimal combinations, we need experimental models in which transplanted mammary tissue or breast cancer can be induced to grow and differentiate under the influence of oestrogen/progestagen combinations. The use of explants into thymectomised mice has been suggested for this purpose [35].

While considerably more investigation is required, the foregoing evidence suggests that it is no longer justifiable to deprive those women who have received treatment for breast cancer of hormonal treatment which can relieve symptoms which are making their lives intolerable. Certain levels of oestrogen dosage and combinations with progestagens have already shown themselves to be capable of inhibiting the growth of breast cancer or progression in premalignant lesions.

Some clinicians may argue against the use of combined oestrogen/progestagen replacement therapy on the basis that they may have seen a new case of breast cancer manifest in a woman while on such therapy. It can in no way be assumed in such a case that the treatment has stimulated tumour activity. It is possible either that hormonal autonomy has developed after temporary growth inhibition or that autonomy was present from the start. Moreover, in the general population, added progestagen is recommended on a cyclic basis (progestagen for 1 week in 4) whereas for the breast cancer patient, continuous oestrogen/progestagen therapy is being advocated. The question of counteracting any mitogenic activity of oestrogen by progestagen may depend on this point [3].

REFERENCES

1. Stoll BA. Can oral contraceptives reduce cancer risk? In: Stoll BA, ed. *Women at High Risk to Breast Cancer.* Kluwer, Dordrecht, 1989, 85–94.
2. Key TJA, Pike MC. The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. *Br J Cancer* 1988, **24**, 29–43.
3. Powles TJ. Treatment of menopausal symptoms in breast cancer patients (corresp). *Lancet* 1988, **2**, 345.
4. Welsch CW. Personal communication, 1988.
5. Gambrell PD Jr. Hormonal medication and mitogenic dangers. In: Stoll BA, ed. *Endocrine Management of Cancer: Contemporary Therapy.* Karger, Basel, 1988, 126–143.
6. McDonald JA, Weiss NS, Daling JR. Francis AM, Polissar L. Menopausal estrogen use and the risk of breast cancer. *Breast Cancer Res Treat* 1986, **7**, 193–199.
7. Brinton LA, Hoover RN, Szklo M, Fraumeni JF Jr. Menopausal estrogen use and risk of breast cancer. *Cancer* 1981, **47**, 2517–2522.
8. Hoover R, Gray LA Sr, Cole P, MacMahon B. Menopausal estrogens and breast cancer. *N Engl J Med* 1976, **295**, 401–405.
9. Ross RK, Paganini-Hill A, Gerkins VR *et al.* A case control study of menopausal estrogen therapy and breast cancer. *JAMA* 1980, **243**, 1635–1639.
10. Hoover R, Glass A, Finkle WD, Azevedo D, Milne K. Conjugated estrogens and breast cancer risk in women. *J Natl Cancer Inst* 1981, **67**, 815–820.
11. Casagrande J, Gerkins V, Henderson BE, Mack T, Pike MC. Brief communication. Exogenous estrogens and breast cancer in women with natural menopause. *J Natl Cancer Inst* 1976, **56**, 839–841.
12. Hiatt RA, Bawol R, Friedman GD, Hoover R. Exogenous estrogen and breast cancer after bilateral oophorectomy. *Cancer* 1984, **54**, 139–144.
13. Buring JE, Hennekens CH, Lipnick RJ *et al.* A prospective cohort study of postmenopausal hormone use and risk of breast cancer in U.S. women. *Am J Epidemiol* 1987, **125**, 939–947.
14. Dupont WD, Page DL, Rogers LW, Parl FF. Influence of exogenous estrogens proliferative breast disease and other variables on breast cancer risk. *Cancer* 1989, **63**, 948–957.
15. Nachtigall LE, Nachtigall RH, Nachtigall RD *et al.* Estrogen replacement; a prospective study on the relationship to carcinoma and cardiovascular and metabolic problems. *Obstet Gynecol* 1979, **54**, 74–76.
16. Gambrell RD Jr, Maier RC, Sanders BJ. Decreased incidence of breast cancer in postmenopausal estrogen–progestogen users. *Obstet Gynecol* 1983, **62**, 435–438.
17. Lauritzen C, Meier F. Risks of endometrial and mammary cancer morbidity and mortality in long term estrogen treatment. In: Herendael H *et al.* eds. *The Climacteric — an Update.* MTP Press, Lancaster, 1984, 207–216.
18. Longman SM, Buehring GC. Oral contraceptives and breast cancer; *in vitro* effect of contraceptive steroids on human mammary cell growth. *Cancer* 1987, **59**, 281–287.
19. Gompel A, Malet C, Spritzen P *et al.* Progestin effect on cell proliferation and 17B dehydrogenase activity in normal breast cells in culture. *J Clin Endocrinol Metab* 1986, **63**, 1174–1180.
20. Lippman ME, Dickson RB, Bates S *et al.* Autocrine and paracrine growth regulation of human breast cancer. *Breast Cancer Res Treat* 1986, **7**, 59–70.
21. Allegro JC, Kiefer SM. Mechanisms of action of progestational agents. *Semin Oncol* 1985, **12** (suppl 1), 3–5.
22. Calaf G, Garrido F, Moyano C, Rodriguez R. Influence of hormones on DNA synthesis by breast tumors in culture. *Breast Cancer Res Treat* 1986, **8**, 223–232.
23. Huggins C, Yang NC. Induction and extinction of mammary cancer. *Science* 1962, **137**, 257–262.
24. Grubbs CJ, Juliana MM, Whitaker LM. Short-term hormone treatment as a chemopreventative method against mammary cancer initiation in rats. *Anticancer Res* 1988, **8**, 113–117.
25. Baum M. Studies point to pill hope in breast cancer. *Hosp Doctor* 1989, **22**, 36 (Abst).
26. Buzdar AU. Progestins in cancer treatment. In: Stoll BA, ed. *Contemporary Endocrine Therapy in Cancer.* Karger, Basel, 1988, 1–15.
27. Stoll BA. Progestin therapy of breast cancer; comparison of agents. *Br Med J* 1967, **3**, 338–341.
28. Stoll BA. Effect of Lyndiol, an oral contraceptive, on breast cancer. *Br Med J* 1967, **1**, 150–153.
29. Stoll BA, Parbhoo S. Treatment of menopausal symptoms in breast cancer patients. *Lancet* 1988, **1**, 1278–1279.
30. Dao TL, Sirha DK, Nemoto T, Patel J. Effect of estrogen and progesterone on tumour labelling index of breast cancer. *Cancer Res* 1982, **42**, 259–362.
31. Padwick ML, Pryse-Davies J, Whitehead MJ. A simple method for determining optimal dosage of progestin in postmenopausal women receiving estrogens. *New Engl J Med* 1986, **315**, 930–934.
32. Whitehead MJ, Townsend PT, Pryse-Davies J *et al.* Effects of oestrogen and progestins on

the biochemistry and morphology of the post-menopausal endometrium. *N Engl J Med* 1981, **305**, 1599–1605.
33. Consensus Development Conference. Prophylaxis and treatment of osteoporosis. *Br Med J* 1987, **295**, 914–915.
34. Persson J, Adami HO, Bergkvist L *et al.* Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens; result of a prospective study. *Br Med J* 1989, **298**, 147–151.
35. McManus MJ, Welsch CW. The effect of estrogen, progesterone, thyroxine and HPL on DNA synthesis of human breast ductal epithelium maintained in athymic nude mice. *Cancer* 1984, **54**, 1920–1927.