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Tamoxifen, hormone receptors and hormone replacement therapy in women previously treated for breast cancer: a cohort study

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Key words: TAMOXIFEN, ESTROGEN RECEPTORS, HORMONE REPLACEMENT THERAPY, BREAST CANCER

ABSTRACT

Objective To determine the risk of recurrence of breast cancer associated with the use of hormone replacement therapy (HRT) in the management of menopausal symptoms in women previously treated for breast cancer who were taking concurrent tamoxifen or who were estrogen receptor-positive.

Methods The study group comprised 1472 women with histologically confirmed breast cancer, of whom 342 subjects (23.2%) elected to use hormonal therapy in the management of their menopausal symptoms. Women were not excluded from treatment with hormonal therapy if they were taking adjuvant tamoxifen or if they had receptor-positive breast cancer. The response of these patients was compared with that of the rest of the database. A Cox regression analysis was performed with sex hormone usage as time-dependent covariate. Disease-free interval was the outcome measured.

Results Subjects who took concurrent tamoxifen with combined continuous estrogen–progestogen therapy had a hazard ratio of 0.67 (95% confidence interval (CI) 0.14–3.24, $p = 0.62$), while concurrent tamoxifen and topical vaginal estrogen users had a hazard ratio of 0.31 (95% CI 0.10–2.57, $p = 0.28$). The hazard ratio for the estrogen–progestogen users who were estrogen receptor-positive was 0.24 (95% CI 0.10–1.49, $p = 0.14$).

Conclusions The use of HRT was not associated with an increased risk of recurrence of breast cancer in women taking concurrent tamoxifen or who were estrogen receptor-positive.

INTRODUCTION

Tamoxifen

Adjuvant tamoxifen therapy for women with breast cancer results in improved survival[1]. However, tamoxifen may aggravate climacteric symptoms, or may result in the premature onset of flushes before a natural menopause. With the results of large multicenter trials becoming available, and indications for its use in the management of breast cancer being expanded, tamoxifen is used in more patients and for longer periods of time. As a consequence, there will almost certainly be a greater number of breast

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cancer survivors who will present with vasomotor instability, a recognized side-effect of tamoxifen occurring in approximately 70% of users[2] and being severe in 20%[3]. Also, among those women with breast cancer who seek hormonal treatment for the relief of their menopausal symptoms there will be an increasing number taking adjuvant tamoxifen. However, there are both theoretical concerns and potential benefits of prescribing tamoxifen in combination with hormone replacement therapy (HRT).

A concern with the administration of the combination of estrogen and tamoxifen is that exogenous estrogen might antagonize the inhibitory effect of tamoxifen on the breast[4]. However, there is clear evidence that endogenous estrogen, in premenopausal women with early and/or metastatic breast cancer, does not detract from the clinical benefit of adjuvant tamoxifen therapy[1,4,5]. Therefore, as premenopausal women who have high estradiol levels respond to tamoxifen, one can argue that postmenopausal women receiving estrogen replacement therapy (ERT) may also respond to a combination of estrogen and tamoxifen. Indeed, tamoxifen has been shown to stimulate increased estradiol secretion in premenopausal women, resulting in levels 2–3 times those seen in a normal menstrual cycle. Despite such high levels of estradiol, these premenopausal women respond to tamoxifen[4].

Tamoxifen may even block the proliferative effects of estrogen on the breast. Tamoxifen acts by blocking the estrogen receptor (ER), by decreasing the secretion of stimulatory growth factors such as epidermal growth factor (EGF), transforming growth factor-α (TGF-α), insulin-like growth factors (IGFs) and platelet-derived growth factor (PDGF) (all of which are stimulated by estrogen) and by increasing the secretion of inhibitory growth factors such as TGF-β. It blocks protein kinase C and calmodium action, alters cell membrane permeability and modulates immunoregulatory function by stimulating natural killer activity (reviewed in references 4 and 6). Its therapeutic effects, therefore, are not solely due to its action via the ER.

Thus, the addition of tamoxifen may even protect women from the proliferative effects of exogenous estrogens on the breast. Powles and colleagues[7] did not deny HRT to women with intolerable menopausal symptoms, but added tamoxifen 20 mg to all those taking HRT, to avoid disease activation on the basis that tamoxifen has been proven effective in the treatment of postmenopausal women with breast cancer. In their small series of 35 patients, there was no evidence of rapid disease progression in women receiving HRT and tamoxifen, nor did tamoxifen compromise the effectiveness of the HRT. Chang and colleagues[8] further investigated the safety of HRT administered with tamoxifen within a preventive trial, and found no detrimental interaction of this hormonal combination on serum cholesterol, bone mineral density and clotting factors. Because of tamoxifen's estrogenic properties, it may act synergistically with HRT in maintaining bone mass and decreasing heart disease through a beneficial effect on lipid profiles[8]. However, these beneficial effects probably only last as long as the HRT or tamoxifen is taken.

Receptors

The estrogen receptor and progesterone receptor (PR) have been found in normal ductal and lobular epithelial cells of the breast[9], although usually at low or unmeasurable levels[10]. In contrast, 50–80% of new breast cancers are ER-positive[10,11]. Breast cancer in postmenopausal women is more likely to be ER-positive, while two-thirds of breast cancers in premenopausal women are ER-negative.

Theoretically, HRT poses a greater risk in ER-positive disease than in those with ER-negative tumors. There is concern that estrogen may have a proliferative effect on ER-positive breast cancers, while it is generally believed that women with ER-negative cancers are less likely to be adversely affected by ERT/HRT.

It has been established in the treatment of breast cancer that estrogens, progestogens and ablation all result in a partial remission response rate of 30–35%[5], and nearly 50% response in ER-positive patients. While tamoxifen gives an overall partial remission response rate of 30–35%, it produces a 75% response rate in ER-positive women. However, some ER-negative tumors respond to hormonal manipulation and to tamoxifen, suggesting that the mode of action is not just via the ER[11].

METHOD AND STATISTICS

In the present studies, patients who were experiencing severe menopausal symptoms were not excluded from treatment with hormonal therapy if they had an ER-positive tumor or if they were taking adjuvant tamoxifen therapy. Information on receptor status was available for 23% of the total database. Fifty-one per cent (751) of all

1472 subjects were using tamoxifen as adjuvant therapy. Tamoxifen was continued as well as their hormonal therapy.

A cohort study of the use of hormonal therapy in the management of menopausal symptoms after breast cancer was performed. The subgroups of hormone users were compared with all other subjects in the database for each of combined continuous oral estrogen plus progestogen therapy, progestogen-only therapy and topical vaginal estrogen therapy. An investigation was carried out to determine the effect of tamoxifen therapy in combination with hormonal therapy on the risk of breast cancer recurrence. A further study was performed to determine whether having either an ER- or PR-positive breast cancer, and taking hormonal therapy, had an effect on the risk of breast cancer recurrence. The results of these analyses of the groups of women who elected to use hormonal therapy are discussed below.

The response of these patients was compared with that of the rest of the database. A Cox regression analysis was performed with sex hormone usage as time-dependent covariate. Disease-free interval was the outcome measured. Results are expressed as hazard ratio with 95% confidence intervals (CI). The hazard ratio is defined as the probability of a subject dying over the study period.

RESULTS

Among the 167 women taking oral combined continuous estrogen–progestogen, the estrogens used were conjugated equine estrogens in 47%, estrone sulfate in 41%, estradiol patches in 7.8% and estradiol valerate in 4.8%. Amongst the estrogen users, the median time interval from diagnosis to starting estrogen therapy was 3 (range 0–26) years. The median time on therapy was 1.6 (0.25–22) years. The median follow-up was 7.3 years, the range being 0.25–22 years. In this group, the main progestogens used were medroxyprogesterone acetate in 49% and norethisterone acetate in 38% of patients. In those on progestogen-only therapy, the main progestogens used were medroxyprogesterone acetate in 64% and norethisterone acetate in 34%. Amongst the progestogen-only users, the median time from diagnosis of breast cancer to starting therapy was 2 (range 0–16) years, with a median time on therapy of 1.0 (range 0.05–5.8) year. The median follow-up was 2.9 years, the range being 0.1–19.2 years. In those on topical vaginal estrogen therapy the low-dose vaginal estrogens used were estriol creams and pessaries (Ovestin®; Organon) in 52% and estradiol 25 μg tablets (Vagifem®; Novo Nordisk) in 48%. Amongst the vaginal estrogen users, the median time interval from diagnosis to starting estrogen therapy was 5.25 (range 0–20) years. The median time on therapy was 1.0 (range 0.1–5) year. The median follow-up was 5.5 years, the range being 0.5–29 years.

Cox regression analysis comparing patients using tamoxifen with those not using tamoxifen

Of the 167 women using oral combined continuous estrogen–progestogen, 52 took concurrent tamoxifen. The hazard ratio for the estrogen–progestogen users taking tamoxifen was 0.67 (95% CI 0.14–3.24, $p = 0.62$). This analysis showed a non-significant decrease in risk of breast cancer recurrence for those taking tamoxifen.

It was not possible to carry out an analysis comparing patients using tamoxifen with those not using tamoxifen in women taking progestogen-only therapy, as there were insufficient patients in the no-tamoxifen category. Of the 106 patients, only three had not taken concurrent tamoxifen.

Of the 69 women who used topical vaginal estrogen in the management of their vaginal dryness, 33 took concurrent tamoxifen. The hazard ratio for the topical vaginal estrogen users taking tamoxifen was 0.31 (95% CI 0.10–2.57, $p = 0.28$). This analysis showed a non-significant decrease in risk of breast cancer recurrence for those taking tamoxifen.

Cox regression analysis comparing patients with estrogen receptor-positive and -negative tumors

Among those using combined continuous estrogen–progestogen hormonal therapy, 34 patients were known to be ER-positive and 22 ER-negative. The hazard ratio for the estrogen–progestogen users with ER-positive tumors was 0.24 (95% CI 0.10–1.49, $p = 0.14$). This analysis showed a non-significant decrease in risk of breast cancer recurrence for those women who were ER-positive.

An analysis was not performed comparing patients with a history of ER-positive versus ER-negative breast cancer in those using progestogen-only therapy, as there were insufficient patients in either category. Nineteen were ER-positive and eight ER-negative.

An analysis was also not performed comparing patients with a history of ER-positive versus ER-negative breast cancer in those using topical vaginal estrogen therapy, as there were insufficient patients in either category. Twelve were ER-positive and 11 ER-negative.

An analysis was not performed comparing patients with a history of PR-positive versus PR-negative breast cancer in any study group, as information regarding PR status was available for even fewer subjects than in the case of ER status, and there were insufficient patients in each category.

DISCUSSION

In the present study, HRT was used in combination with tamoxifen, and was not associated with an increased risk of recurrence of breast cancer. The findings suggest that concurrent HRT and tamoxifen appears to be safe for use in women successfully treated for breast cancer who are experiencing significant menopausal symptoms. These results of this study are encouraging, but the numbers of patients involved are small, and the confidence intervals wide.

In view of the increasingly widespread use of tamoxifen and its associated induction of hot flushes, there will almost certainly be a greater need for the combined use of HRT and tamoxifen in those with uncontrollable menopausal flushing. Thus, the interaction between HRT and tamoxifen with respect to the relief of menopausal symptoms, changes in the breast and endometrium, in mammographic patterns, in bone density and in heart disease, and, most important, the risk of breast cancer recurrence needs to be studied further. It is also important that this is performed as part of a randomized controlled trial.

It can be argued that, in those women with breast cancer who use an estrogen, the estrogen should be used in combination with a moderate dose of a progestogen because of the theoretical reduction in breast cell mitotic rates[12,13]. Also, since both estrogen and tamoxifen increase the risk of endometrial cancer, it seems prudent to use a progestogen either alone or in combination with an estrogen in those women also taking tamoxifen.

In one small pilot study, our group[14] was able successfully to treat women experiencing hot flushes with tamoxifen with a moderate dose of oral progestogen; all of the patients responded without requiring additional estrogen.

It is also possible that the combination of HRT and tamoxifen is the ideal means of prescribing HRT to control menopausal symptoms in women with breast cancer, or to protect against breast cancer in those at high risk of the disease[7,8]. This will only be established in a randomized controlled trial of HRT with and without tamoxifen.

In the present study, HRT was safely used in women with a history of ER-positive breast cancer, and was not associated with an increased risk of recurrence of breast cancer. The finding of a non-significant decrease in risk of breast cancer recurrence for those women who were ER-positive does not support the concern that estrogen may have a proliferative effect on ER-positive breast cancers, or poses a greater risk with ER-positive disease than in those with ER-negative tumors, nor the notion that women with ER-negative cancers are less likely to be adversely effected by ERT/HRT.

Confounding is always an important issue when considering cohort studies. However, an obvious difference between the HRT users and the rest of the database is that the treatment group presented because of significant menopausal symptoms. There are data to suggest that women who have severe, persistent hot flushes are significantly more estrogen-deficient than women not having symptoms or only having mild symptoms[15]. The present study did not correct for factors known to affect breast cancer prognosis such as tumor size, number of axillary nodes involved, age at diagnosis, age at menarche and parity.

The findings need to be confirmed in a larger study and in a randomized, prospective, clinical trial.

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