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New approaches to the endocrine prevention and treatment of breast cancer

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Abstract All major endocrine prevention approaches act via the estrogen receptor (ER). A simple hypothesis concerning ER expression and breast cancer risk is outlined. We review breast cancer prevention trials with tamoxifen, raloxifene, aromatase inhibitors, and ovarian suppression. Current and planned endocrine prevention trials in populations of pre- and postmenopausal women at risk of breast cancer are summarized and endocrine therapy after primary surgery and for advanced disease discussed.

Keywords Breast cancer · Prevention · Treatment · Endocrine

Introduction

Although incidence rates of breast cancer are beginning to stabilize and death rates are declining in many countries including the USA [23] and the UK [25], approximately one in eight and one in ten women develop the disease in these two countries, respectively. One of the reasons for a decline in death rates (30% in a 10–12-year period in the UK) is the increased use of postoperative or adjuvant endocrine therapies, particularly with the antiestrogen tamoxifen [25]. Five years of postoperative tamoxifen reduces the annual odds of death by approximately 25% [8]. Such treatment also reduces the incidence of new contralateral breast cancers by about 50%. Realization of this effect led to the introduction of breast cancer prevention trials, first with tamoxifen and more recently with raloxifene, ovarian ablation, and aromatase inhibitors.

All major endocrine prevention approaches act via the estrogen receptor (ER). Knowledge of the pattern of ER expression in normal and premalignant breast tissue may give an indication of the mechanisms of action and appropriate methods of treatment. Here we outline a simple hypothesis concerning ER expression and breast cancer risk. Thereafter we summarize current and planned endocrine prevention trials in populations of pre- and postmenopausal women at risk of breast cancer and discuss endocrine therapy after primary surgery and for advanced disease.

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The biology of the breast in relation to breast cancer prevention

In lobules of the normal breast, cells that express ER are found in the luminal layer, whereas myoepithelial cells, which abut the basement membrane, are ER-negative. In undifferentiated lobules, as seen in women before first pregnancy, approximately 20% of cells are ER-positive whereas more differentiated lobules found during and after pregnancy have fewer ER-positive cells. The luminal cells are also the main proliferative compartment of the lobule and divisions in myoepithelial cells are rare. We and others [5, 28] have shown that proliferating luminal cells do not express ER. It is likely that estrogen stimulates proliferation by initiating paracrine signals from a nondividing ER-positive sensor cell to an adjacent ER-negative proliferating cell. Separation between sensor and effector cell may be a mechanism to maintain the integrity of the epithelium and prevent

malignancy because one of the first alterations seen in some areas of ductal hyperplasia and most areas of atypical ductal hyperplasia is the appearance of ER-positive cells that have the capacity to divide. Normal ER-positive dividing cells increase in number in lobules with age, and it is hypothesized that such cells may be the precursors of postmenopausal breast cancer [29] because all ER-positive tumors contain ER-positive proliferating cells.

ER-positive proliferating cells also appear in the mammary glands of rodents following carcinogen treatment [12, 30]. Administration of hormones to such mice for 3 weeks, to mimic pregnancy, prevents the appearance of ER-positive dividing cells and also tumors in response to carcinogens. This may be the mechanism of the protective effect of early pregnancy in humans.

We know that ER-positive human breast cancers grow in postmenopausal women in response to low levels of estrogen that are insufficient to stimulate proliferation in adjacent normal breast tissue. Tumor cells must therefore adapt to low estrogen concentrations, as demonstrated using MCF-7 cells by Masamura et al. [22]. When these cells are placed in estrogen-deprived medium they stop growing for approximately 3 months and then begin to proliferate. Repeat of the estrogen dose-response curve shows maximal proliferation at 10^{-14} *M* estradiol, whereas maximal proliferation in wild-type MCF-7 cells occurs at 10^{-10}–10^{-9} *M* [22]. Thus tumor cells can become sensitized to low levels of estrogen, and this may be the reason tumors can grow in the postmenopausal low-estrogen environment and may regrow after response to aromatase inhibitors.

Chemoprevention can be defined as the use of natural or synthetic chemicals to reverse, suppress, or prevent the process of carcinogenesis [32]. Endocrine chemoprevention acting through the ER may prevent breast cancer initiation by inhibiting proliferation of ER-negative cells in a paracrine manner. After initiation and the appearance of ER-positive proliferating cells, treatment may act by suppressing premalignant or malignant lesions. However, these may regrow because of the adaptive mechanisms demonstrated by Masamura et al. [22]. Thus chemopreventive agents to prevent initiation may have to be given continuously, whereas intermittent or alternating therapy may be most appropriate for suppression.

Results of current breast cancer prevention trials

Tamoxifen prevention trials were initiated soon after the demonstration that this agent reduced contralateral breast cancer by 50% when given after surgery for primary disease [6]. Table 1 shows the entry criteria, treatment, and number of subjects entered for the four tamoxifen prevention trials, the overall result for the contralateral data from the adjuvant overview, and the result from the Multiple Outcomes of Raloxifene (MORE) trial. The Royal Marsden trial was started as a pilot study for the International Breast Cancer Intervention Study (IBIS-I) and together with the National Surgical Adjuvant Breast and Bowel Project P-1 study (NSABP-P1) entered patients predominantly with a family history of breast cancer. The Italian trial entered normal-risk women who had hysterectomy and the MORE trial entered patients with proven osteoporosis [7, 11].

Results of all the studies are shown as a Forrest plot in Fig. 1. The Royal Marsden and Italian studies show a nonsignificant advantage, whereas the NSABP-P1 and IBIS-I trials showed significant reductions in risk of breast cancer [7]. Overall there is a 38% (95% CI 28–46%; $P < 0.0001$) reduction in risk of breast cancer at an average follow-up of about 5 years. For the MORE trial there was a greater reduction in risk (64%, 95% CI 44–78%; $P < 0.0001$), which was significantly better than the combined tamoxifen trials ($P = 0.03$) [7].

It is important to realize that the MORE trial was set up with osteoporosis and not breast cancer as the major endpoint. The majority of the patients in the study have been rerandomized and are now continuing on either raloxifene 60 mg or placebo, with breast cancer endpoints to be reported at 5 and 7 years of follow-up. The original MORE trial was a randomization between raloxifene 120 mg or 60 mg and placebo, and reported at

Table 1 Entry criteria, treatment, and number of subjects entered for the four tamoxifen prevention trials. Adapted with kind permission of Elsevier from Table 1 of Cuzick et al. [7] (*NSABP-P1* National Surgical Adjuvant Breast and Bowel Project 1, *IBIS-I* International Breast Cancer Intervention Study 1, *MORE* Multiple Outcomes of Raloxifene study)

Trial	Entry dates	Population	Number randomized	Agent (vs placebo) and daily dose	Intended duration of treatment (years)
Royal Marsden	1986–1996	High risk, family history	2,471	Tamoxifen 20 mg	5–8
NSABP-P1	1992–1997	RR >1.6 over 5 years	13,388	Tamoxifen 20 mg	5
Italian	1992–1997	Normal risk, hysterectomy	5,408	Tamoxifen 20 mg	5
IBIS-I	1992–2001	RR >2-fold	7,140	Tamoxifen 20 mg	5
MORE	1994–1999	Normal risk, postmenopausal women with osteoporosis	7,705	Raloxifene 60 or 120 mg (three arm)	4
Adjuvant overview	1976–1995	Women with ER-positive operable breast cancer in 14 trials	~15,000	Tamoxifen 20–40 mg with/without chemotherapy in both arms	≥3 (average ~5)

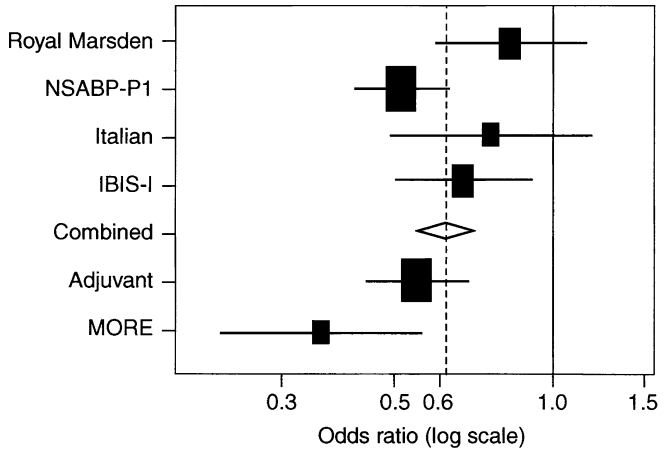

Fig. 1 Results of the four tamoxifen prevention trials (Royal Marsden, NSABP-P1, Italian, and IBIS-I) and when combined in comparison with reduction of contralateral breast cancer in the Oxford overview (adjuvant) and the results of the raloxifene trial (MORE). Adapted with kind permission of Elsevier from Fig. 1 of Cuzick et al. [7]

4 years [7] and the 60-mg dose is now accepted by the US Food and Drug Administration for the treatment of osteoporosis. Two other trials will give an indication of the effectiveness of raloxifene in breast cancer prevention. The Raloxifene Use for The Heart (RUTH) study has completed recruitment of 10,011 women with a history or at-risk of heart disease. Reduction in breast cancer and cardiovascular disease are both primary endpoints. The effect of raloxifene on breast cancer risk will be reported after the second mammogram at 4 years in 2005 [34]. The Study of Tamoxifen and Raloxifene (STAR) trial will compare raloxifene 60 mg with tamoxifen 20 mg given for 5 years. Over 13,000 of the target 19,000 subjects required have been randomized to date and the trial is due to report in 2008 or 2009 [4].

The modern aromatase inhibitors anastrozole, letrozole, and exemestane have been successful for the treatment of advanced breast cancer and are now in clinical trial as adjuvant treatment after primary surgery for the disease [14]. Preliminary results of an adjuvant trial that compared anastrozole with tamoxifen and both treatments combined (Arimidex, Tamoxifen, Alone or in Combination; ATAC) have been reported and show a significant improvement in disease-free survival for anastrozole compared with the other two treatments [1]. Importantly, the incidence of contralateral breast cancer was reduced by 46% compared with tamoxifen alone. If it were assumed that tamoxifen reduces the incidence of contralateral breast cancer by 50% compared with untreated control patients, then anastrozole would reduce the risk of a contralateral breast cancer by 77% compared with 'control' [1].

The ATAC results have led to an interest in aromatase inhibitors for breast cancer prevention. A trial comparing anastrozole with placebo in postmenopausal women at moderate to high risk of breast cancer (IBIS-II) has just started recruiting (February 2003). Over 7000 women will be entered and there are subprotocols to assess the effects of anastrozole on body composition, bone density, and cognition. A trial of exemestane versus a combination of exemestane with a cyclooxygenase-2 inhibitor with placebo is planned to begin in North America in 2003 and there is an ongoing trial of exemestane versus placebo in women at risk because they are *BRCA1* and *BRCA2* mutation carriers. Tamoxifen is not the control arm in any of the aromatase inhibitor trials despite it being clear that tamoxifen significantly reduces the risk of breast cancer. However, the trials have reported after a median follow-up of only 5 years and it is not clear, given the known toxicity of tamoxifen, whether the risk–benefit ratio of this agent is favorable in the preventive setting.

Tamoxifen reduces risk of breast cancer equally in pre- and postmenopausal women [11]. However, both raloxifene and aromatase inhibitors are used in postmenopausal women only. Theoretically raloxifene should be as effective as tamoxifen in premenopausal women but it has never been tested appropriately in this clinical situation. In a study of 90 healthy premenopausal women with uterine leiomyomas, raloxifene treatment for 6 months did not alter tumor stage or change menstrual frequency at doses of 60 and 180 mg/day. In view of the hypothalamic pituitary drive to the ovaries, it is unlikely that aromatase inhibitors will be effective in premenopausal women as single agents [24].

An alternative preventive approach in premenopausal women is to suppress ovarian function to reduce estrogen levels. Epidemiological studies indicate that bilateral oophorectomy at an early age reduces breast cancer risk. Hirayama and Wynder [16] reported a 59% reduction in breast cancer risk in women treated before age 37 years, and in other similar studies the risks of breast cancer were reduced by 64–75% [10]. Ovarian suppression as a method for reducing breast cancer risk was pioneered by Pike and colleagues in California [26]. They demonstrated that a gonadotrophin-releasing hormone agonist (leuprolide acetate), with add-back low-dose estrogen (conjugated equine estrogen 0.625 mg/day orally for 6 days out of 7) given to maintain bone density and a progestogen (medroxyprogesterone acetate 10 mg/day for 13 days every fourth 28-day cycle) given to prevent endometrial cancer, caused a reduction in mammographic density, which was used as an intermediate endpoint of cancer risk [31]. The reduction in mammographic density was reversed and returned toward pretreatment levels 6–12 months after the cessation of treatment [15]. Despite add-back estrogen, bone density had declined by 2–3% at 1 year. Subsequent studies have focused on adding back androgen in addition to the other hormones and giving the entire group of drugs by nasal spray [33].

European ovarian suppression trials have all used monthly subcutaneous injections of goserelin in women with a greater than 25% lifetime risk of developing breast cancer. Each trial combines goserelin with a drug to maintain bone density; in the UK study this is

raloxifene, in the German study the bisphosphonate ibandronate, and in the Dutch study tibolone. In the UK study, 53 of 80 projected subjects have been entered. Women are randomized to treatment for 2 years versus no treatment and endpoints of the study are acceptability of randomization and tolerability. Acceptability of randomization is approximately 10% in subjects asked and tolerability is high [9]. These studies will give information on whether it is appropriate or possible to perform large-scale randomized studies to determine whether temporary ovarian ablation affects the incidence of breast cancer.

Adjuvant endocrine therapy

Tamoxifen given for 5 years is standard endocrine therapy in ER- and/or progesterone receptor-positive pre- and postmenopausal women. It reduces the annual odds of recurrence by approximately 50%, and the annual odds of death by 25% [8]. Five years of tamoxifen is more effective than shorter durations, whereas longer duration of treatment is the subject of current clinical trials.

Modern aromatase inhibitors are being tested in adjuvant trials compared with tamoxifen or sequenced with tamoxifen (Fig. 2). In the first of these trials to report, anastrozole was found to be significantly superior to tamoxifen (HR 0.83, CI 0.71–0.96, $P = 0.0129$) or the combination of tamoxifen and anastrozole with respect to disease-free survival [1]. These results were presented at a median follow up of 33.3 months and the benefit of anastrozole remained at a recent update of the study after 4 years of follow-up. Time to distant recurrence and survival analysis of this large trial (9366 patients were randomized) will be available in 2007.

A number of other trials with aromatase inhibitors are in progress (Fig. 2), but no results are available to date. The data produced by the trials will not only provide information concerning the optimal ways of treating patients, but help elucidate whether some of the hypothetical suggestions outlined above concerning the development of hormonal resistance are likely to be true. If occult tumor cells adapt to tamoxifen (by seeing it as an estrogen) or to the low concentrations of estradiol produced by aromatase inhibition, sequential change to an alternative treatment should be superior to continuous treatment.

Surgical ovarian ablation is the oldest treatment for advanced breast cancer [2] and ovarian irradiation was the first form of adjuvant therapy after surgery for breast cancer. Several recent studies have demonstrated that 2–3 years of ovarian suppression with monthly subcutaneous injections of goserelin are equivalent to standard adjuvant chemotherapy regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF) or fluorouracil, epirubicin, and cyclophosphamide [20] and the combination of goserelin and tamoxifen may be significantly superior to CMF [19]. Currently, we do not know whether the combination is superior to goserelin alone in the adjuvant setting, but in advanced premenopausal breast cancer, this is the case [21]. Trials are in progress to determine whether goserelin and anastrozole are superior to goserelin and tamoxifen as adjuvant endocrine therapy in premenopausal women [13].

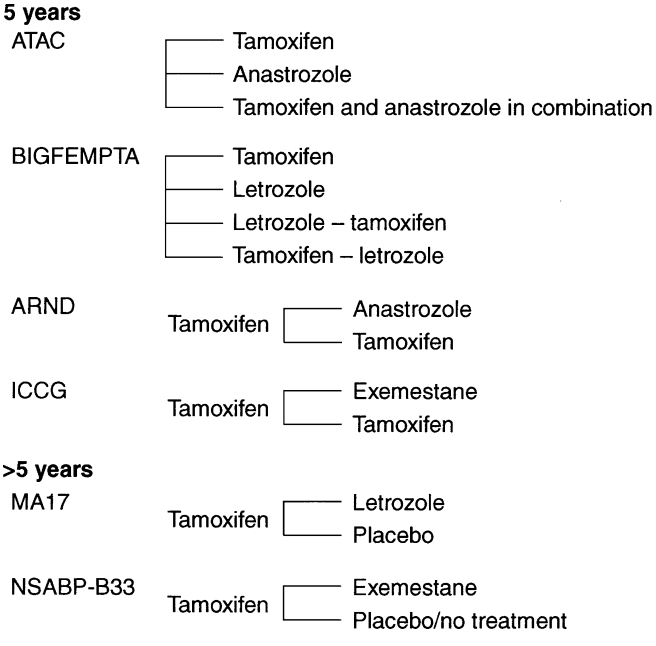

Fig. 2 Adjuvant endocrine trials in progress (*BIGFEMPTA* Breast International Group FEMTA, *ARND* German study, *ICCG* International Collaborative Cancer Group, *MA17* Canadian study)

Endocrine therapy for advanced breast cancer

Advanced ER-positive breast cancer has been the traditional test bed for new endocrine therapies. Attempts to find the selective ER modulators (SERMs) superior to tamoxifen have not been successful. New SERMs such as draloxifene, idoxifene, toremifene, raloxifene, arzoxifene, EM-800 and ERA 923, have activity and toxicity similar or inferior to that of tamoxifen and have not replaced it [17]. The pure antiestrogen fulvestrant is structurally and functionally different from SERMs, in that it is an estrogen analog with a bulky side-chain in the 7α position that causes downregulation of ER. Fulvestrant is active in tamoxifen-resistant breast cancer and equivalent to anastrozole as second-line therapy for advanced disease [17, 18]. Surprisingly, fulvestrant was not superior to tamoxifen when compared as first-line therapy for advanced disease. Fulvestrant is now licensed in the USA as an additional treatment for advanced breast cancer and new estrogen analogs are being developed that are orally bioactive (e.g. ZK 191703).

Modern aromatase inhibitors have been shown to be superior to megestrol acetate for second-line treatment and to tamoxifen for first-line treatment of advanced breast cancer [3]. Only one direct comparative trial of

two aromatase inhibitors has been reported. There were no differences in response rate (in ER-positive tumors), duration of response, and survival between letrozole and anastrozole [27], suggesting that these agents are interchangeable.

Conclusions

The physiological basis of standard endocrine therapies for breast cancer remains unchanged. Therapies either reduce estrogen concentrations affecting target cells (aromatase inhibitors and ovarian ablation) or block the effect of estrogen at the ER (antiestrogens and high-dose estrogens). Advances have been made in methods to reduce estrogen in that aromatase inhibitors have become more potent and ovarian suppression may be produced pharmacologically. There have been few advances in the development of classic SERMs despite intensive activity in this field. Paradoxically, raloxifene may be more effective than tamoxifen as a preventive agent despite its lack of efficacy in advanced breast cancer. However, results of current trials are required to confirm this. The steroidal antiestrogen fulvestrant provides an additional endocrine therapy for advanced breast cancer because it is effective in tamoxifen-resistant disease. It is unlikely to be used for prevention because of the need for intramuscular administration, but the newer oral steroidal antiestrogens may ultimately be used in this clinical situation.

All endocrine therapies in use today act via the ER. There is little good evidence that currently available agents work by any other mechanism. In the prevention trials all have shown reduction in ER-positive tumors only, with no difference in the incidence of ER-negative tumors on active treatment or placebo. We predict that if endocrine preventive methods are started relatively early in reproductive life, they will prevent breast cancer initiation and thus reduce ER-positive and ER-negative tumors because evidence suggests that ER-negative cells are stimulated to proliferate by ER-positive cells in the normal breast. After initiation, ER-positive cells are capable of proliferation and possibly adaptation to ambient estrogen concentrations. Data from adjuvant trials of sequential approaches will give an indication of the validity of this hypothesis because changing therapy would be predicted to be more beneficial than continuous therapy in cancer suppression. It is probable that most current preventive therapies are started too late to prevent ER-negative tumors because there is little evidence of their reduction in current trials.

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