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Use of risk determinants for different breast cancer prevention strategies

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Abstract

Almost all of the factors which are known to be associated with a high risk of breast cancer, other than high genetic risk, are associated with increased exposure to oestrogens. Thus, therapeutic manoeuvres targeted at oestrogen deprivation which have shown value in established breast cancers are attractive candidates for breast cancer prevention strategies. It is possible that such agents may reduce the incidence of ER-negative as well as ER-positive tumours. The potential use of these different drugs is restricted by menopausal status, e.g. aromatase inhibitors only after the menopause, and Gonadotropin-releasing hormone (GnRH) agonists prior to the menopause. There is a complex interplay between the anticipated benefit which may be derived from a respective agent and the side-effects associated with it. This article seeks to integrate the information from several sources and concludes that the prophylactic strategies should differ according to different risk profiles.

Keywords: Breast cancer; Oestrogens; Prevention; Risk profiles; Oestrogen deprivation; GnRH agonists

1. Introduction

In recent years the concept of the use of chemoprevention strategies to reduce the incidence of breast cancer has moved from a desirable and attractive concept through the conduct of randomised clinical trials to the licensing (in the USA) of tamoxifen for this purpose. Progress in ancillary areas has resulted in the availability of a series of other drugs, which are known to be effective in the treatment of established breast cancer and have generally good tolerability. In some cases evidence is available from their reduction of the incidence of contralateral breast cancer by their use in the adjuvant context which supports their likely prophylactic effectiveness. Some of these agents are only applicable in either pre- or postmenopausal women. Additionally they have side-effects, which may restrict their appropriate application to particular groups of women which are identified according to their risk profile. This article seeks to integrate three aspects which have impact on developments in this area: (1) the aetiology of breast cancer, which provides the evidence for the chemoprevention strategies under consideration; (2) consideration of the drugs which are available that can impede the development of breast cancer; and (3) consideration of the groups of women for whom these particular interventions might be most appropriate/acceptable.

2. Aetiology of breast cancer

The majority of the factors, which are known to be significantly associated with an increased risk of breast cancer, may be explained by a mechanism which depends on increased exposure to oestrogen. These may be considered according to three windows of exposure. Firstly, the premenopausal exposure of the breast to oestrogens prior to the differentiation of the breast during pregnancy. Thus early age of menarche and duration of nulliparity are all associated with a positive risk of breast cancer [1,2].

Secondly, prolonged or excessive exposure of the breast to oestrogens post-differentiation appears to be a less significant, but still measurable, risk factor as is evidenced by the association of increased breast cancer

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with late menopause [3]. There is inconsistent evidence on whether high plasma oestrogen levels in premenopausal women are associated with an increased risk [4]. This may be due to the absence of a significant relationship or to the difficulty of estimating exposure to oestrogens within the context of the highly variable levels through the menstrual cycle.

Thirdly, in postmenopausal women oestrogen-related risk factors include the use of hormone replacement therapy and a positive association with obesity [5,6]. The latter is associated with high plasma oestradiol and low sex hormone binding globulin (SHBG) levels which have the effect of increasing the proportion of biologically active oestradiol. In contrast to the situation for premenopausal women, a series of studies have indicated that postmenopausal women with the highest plasma oestradiol levels have the greatest risk of breast cancer, relative risks as great as 5 having been reported [7,8]. Complementary data indicate that a low SHBG level may also indicate an increased risk. Plasma testosterone levels have also been found to be a significant risk factor but in some cases [8] when this relationship was adjusted for oestradiol levels the risk associated with testosterone was completely lost. This may be explained by testosterone acting as a precursor for oestradiol through the aromatase enzyme.

Thus there is a persuasive amount of evidence that oestrogens play a causative role in breast cancer development and that interventions which restrict exposure of the breast to oestrogens may reduce breast cancer incidence.

3. Familial high risk

One group of women for whom prevention strategies are eagerly sought are those in which there is an established mutation in a breast cancer gene or in whom a similar very high risk has been established by pedigree analysis. The phenotype of those tumours which present in women who are *BRCA1*-positive is that of a hormone-resistant tumour, i.e. high grade/high proliferation rate and particularly oestrogen receptor and progesterone receptor negativity [9]. Thus, it has been speculated that the prevention of such tumours may not be achievable by hormonal means. However, encouraging data have been provided which indicate that the aetiology and prophylactic susceptibility of these tumours may be similar to sporadic tumours. For example, the relationship between risk of breast cancer and parity remains significant in *BRCA1* tumours [10] and Rebbeck and colleagues [11] have reported that breast tumour incidences were reduced in women with a *BRCA1* mutation that have received an earlier ovariectomy. Biological data on the oestrogen sensitivity of the breast epithelium from women with a high-risk pedigree have also been reported [12]; breast tissue explants from such women, when transplanted to nude mice showed a proliferative response to exogenous oestradiol.

There are potential explanations for a hormonally-related incidence of ER-negative tumours. For example, a reduction in normal breast cell proliferation may be achieved by oestrogen deprivation and thus reduced incorporation of mutations. Evidence has recently been gathered that oestrogens may have direct genotoxic effects that are independent of the oestrogen receptor status of the cell [13] and this again might lead to prevention strategies having an impact on both oestrogen-receptor positive and negative tumours. Overall, it seems appropriate to consider genetically determined high-risk groups for study in trials of oestrogen manipulation.

4. Risk profiling

Many of the above factors (plus others such as benign breast biopsy) have been brought together in a clinically utilisable form in the Gail model [14]. This was applied in the NSABP-P1 trial and will be applied (to postmenopausal women only) in the STAR trial. It should be noted that this tool may not be valid for all populations; e.g. in countries in which the frequency of breast biopsy is substantially lower than that in the USA.

5. Oestrogen-based prophylactic strategies

The evidence that the selective oestrogen receptor modulator (SERM), tamoxifen can reduce the early presentation of breast cancer as demonstrated by the NSABP-P1 study is irrefutable [15], although a question-mark remains over whether this prophylactic effect will be achieved in all patient populations since the Royal Marsden and Italian trials both showed negative results [16,17]. However, even in a population which showed prophylactic benefit from tamoxifen it is clear that it has significant unwanted side-effects which must be considered. These include detrimental effects on the cardiovascular system with increased incidence of thromboembolic events and also increased incidence of endometrial cancer [15]. To balance this there is a reduced incidence of osteoporotic fractures.

In premenopausal women tamoxifen is known to be associated with markedly increased plasma levels of oestradiol [18]. This appears to be due to an anti-oestrogenic effect of the compound at the hypothalamic-pituitary axis which leads to increased gonadal stimulation. It is likely that this leads to the increase in ovarian cyst formation in approximately 80% of premenopausal women on tamoxifen [19,20]. There is no evidence that this leads to an increase in ovarian cancer but it is of

concern that such effects may occur during the application of the drug to women at markedly increased risk of ovarian cancer (e.g. *BRCA1*/*BRCA2* patients).

A series of other SERMs is in various stages of development. Raloxifene is the most prominent of these in relation to prevention strategies. This has shown evidence of a reduced breast cancer risk in a trial of the compound in osteoporotic patients (who are at low risk of breast cancer) [21] and it is now being evaluated in a trial against tamoxifen in a high-risk population (STAR trial). There are no published data on the effect of this on premenopausal oestrogen levels but mechanistically an increase in ovarian stimulation similar to that seen in tamoxifen would be expected to be seen with this or any other agent in which anti-oestrogenic effects predominate on the hypothalamus/pituitary. Other agents that may have utility in the postmenopausal setting include aromatase inhibitors, such as anastrozole, letrozole and exemestane, each of which is in trials in the adjuvant setting. Each of these drugs causes a profound oestrogen deprivation and is an effective second-line agent in established advanced breast cancer [22]. Recent exciting data indicate that at least in some patient groups anastrozole may be more effective than tamoxifen [23]. Some complications may, however, occur as a result of the systemic deprivation of oestrogens by aromatase inhibitors, such as increased osteoporosis, and lipid changes which might enhance the incidence of cardiovascular accidents. However, no disadvantageous impact on endometrial cancer or thromboembolic events would be anticipated. Pure anti-oestrogens, such as ICI182780, may also eventually be useful in this prophylactic context but data on their use are very limited to date.

The application of aromatase inhibitors or pure anti-oestrogens to premenopausal women is likely to lead to the same type of ovarian complications as with SERMs. However, it is conceivable that aromatase inhibitors might be utilisable at a low-dose in premenopausal women: a substantial inhibition of aromatisation within the breast might be achieved, whilst at the same time increased gonadal stimulation might overcome the partial inhibitory effect of the aromatase inhibitor within the ovary. Thus, plasma oestrogen levels may be largely unchanged but tissue exposure in regions where significant local aromatase activity occurs (e.g. breast) may be markedly reduced (Fig. 1).

GnRH agonists such as goserelin (Zoladex) are an attractive option for oestrogen deprivation in premenopausal women and indeed there is now considerable experience of their use in both advanced breast cancer and in the adjuvant setting [24]. These agents operate by reducing gonadal stimulation and achieve an oestrogen environment similar to that in castrated patients. However, the sequelae from such oestrogen deprivation are substantial: menopausal side-effects such as hot flushes are reported almost universally, and loss of bone mineral density and possible cardiovascular effects are worrying aspects when considering long-term use in the prevention setting. There are, however, a number of other agents which may be combined with a GnRH agonist to restrict its metabolic and/or symptomatic effects; these agents might be utilisable in the chemopreventive setting according to the risk of contracting breast cancer (Fig. 2).

Each of the potential add-backs has predicted effects on prophylactic efficacy and/or side-effects which make their application in a prophylactic setting more or less appropriate according to the risk of breast cancer (Fig. 2). It has been argued for some years by the pioneering work of Pike and his colleagues [25] that a low-dose of HRT added to GnRH agonist treatment should relieve both the symptomatic and metabolic complications of the ovarian suppression but allow retention of some, but not all, of the preventive effects. The biological effectiveness of such approaches is supported by pilot studies on mammographic density [26] and by the results in benign gynaecology where this approach is widespread, e.g. [27].

The predicted partial loss of effectiveness by combining a GnRH agonist with HRT is likely to prove of particular concern to premenopausal women at very high risk who may be considering options such as ovariectomy or bilateral mastectomy. In these circumstances, some reduction in tolerability may be more acceptable in relation to the greater expected efficacy of

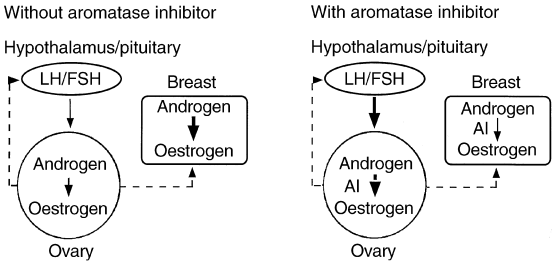

Fig. 1. Theoretical effects of low-dose aromatase inhibition in premenopausal women: increased luteinising hormone (LH) and follicle stimulating hormone (FSH) overcomes ovarian inhibition but local synthesis remains suppressed.

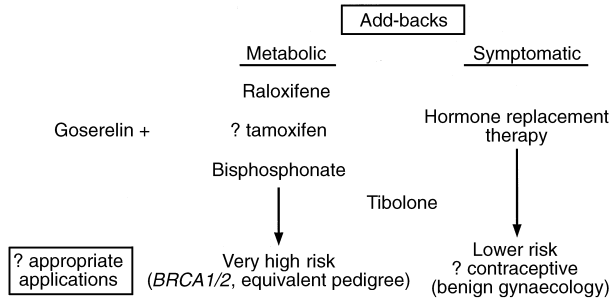

Fig. 2. Differential use of add-backs to goserelin according to risk of breast cancer in premenopausal women.

bone-sparing agents such as bisphosphonates or raloxifene. Use of the latter agent may have the possible bonus of enhanced prophylactic effectiveness [21]. Lastly an agent such as tibolone [28] which may have the potential for ameliorating both metabolic and symptomatic side-effects might be ideal, but less data on bone protection are available than with the other agents.

A series of pilot trials will shortly be initiated in premenopausal women at very high genetic risk to test the feasibility of conducting a large multicentre trial to evaluate goserelin + raloxifene or tibolone or ibandronate (the RAZOR, TIZOR and GISS studies).

6. Use of hormonal risk profiles to indicate appropriate prophylactic strategies

As mentioned above a series of prospective studies have found that high plasma oestradiol levels after the menopause are associated with a significantly higher breast cancer incidence [7]. Some of these studies also find associations with other hormones such as testosterone and/or binding proteins such as SHBG. Thus, it might be possible to derive a personal risk profile based on individual hormonal status. Whilst this is an attractive concept, problems include the relationship of risk with oestradiol levels being steep, i.e. for a small change in plasma oestradiol level there is a large change in the relative risk of breast cancer. This is exacerbated by the lack of widespread availability of assays of sufficient sensitivity to apply to postmenopausal women and the lack of agreement between laboratories. Overall this inevitably results in risk relationships which vary substantially between studies. The potential value of this approach for counselling women on their risk is, however, substantial and requires an investment in assay development for use in large prospective collections of plasma from healthy women prior to the development of breast cancer (e.g. EPIC and PACE studies). Development of such assays must ensure validity of measurement and high precision which is not necessarily commensurate with ease of analysis. These analytical issues may be overcome if genetic determinants of these hormone profiles can be identified which may allow more precise DNA-based identification of risk groups.

The potential application of these risk factors may be appreciated by consideration of the possible differential use of aromatase inhibitors and SERMs in postmenopausal women. A scenario may develop in which the bone and cardiac complications of postmenopausal women with particularly low oestrogen levels may be prevented by a SERM without the problems of the increased risk of breast cancer associated with HRT. In contrast, an aromatase inhibitor may be usable in postmenopausal women with particularly high levels of oestradiol to 'adjust' the levels back towards the median with an anticipated reduced risk of breast cancer but with problems of further oestrogen deprivation minimised. Alternatively an aromatase inhibitor could be used to achieve full oestrogen deprivation, in which case combination with a SERM might be a viable option.

Clinical trials of each of the above types of agent are proposed in different patient groups. Comprehensive collection of appropriate blood/urine/tissue samples from women in these studies should allow the validity of such hormonally targeted treatment to be evaluated.

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