Breast density predicts endocrine treatment outcome in the adjuvant setting

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EDITORIAL

Breast density predicts endocrine treatment outcome in the adjuvant setting

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See related research article by Kim *et al.*, http://breast-cancer-research.com/content/14/4/R102.

Abstract

In their report, Kim and colleagues study the ability of changes in mammographic density over a period of 12 to 18 months to predict subsequent recurrence in 1,065 Korean women with oestrogen receptor-positive breast cancer. Based on 80 recurrences, a clear gradient for lower recurrence rates was seen among women with larger density reductions – with recurrence rates being more than twofold higher in women with no reduction compared with those presenting a reduction ≥10%. This extends previous work on predicting the effectiveness of tamoxifen in individual women from the preventive setting to the adjuvant setting, and also includes women treated with aromatase inhibitors, where a slightly larger effect was seen.

The report by Kim and colleagues makes an important contribution to tailoring endocrine therapy in oestrogen receptor-positive breast cancer to women most likely to benefit from it [1]. Oestrogen receptor-positive breast cancer is unique among common solid tumours in that it has a very long natural history, and it is not possible to accurately identify women who can safely be considered cured. As a result endocrine therapy is required for at least 5 years, and often longer for high-risk patients. Yet late recurrences are still common, being about 2.5% per year for 20 years with tamoxifen treatment [2] and about 2% per year with aromatase inhibitors for the 10 years for which follow-up data are currently available [3].

Aside from levels of oestrogen and progesterone receptors measured in the primary tumour, little information is available to predict response to treatment. Newer studies focusing on changes in Ki-67 and other cell cycle proteins measured before and after presurgical treatment

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may in the future help to determine which patients are responding to a given treatment [4], but current practise is to give at least 5 years of endocrine treatment to all patients and hope for the best. Early suggestions that 2D6 polymorphisms, which are involved in the metabolism of tamoxifen, might help to predict which patients would respond best to this treatment have not been confirmed in more recent large studies [5,6].

Breast density is a well-established risk factor for breast cancer in Caucasian women [7], and also in oriental women although their average density is higher [8]. Breast density responds to hormonal manipulations, being increased with hormone replacement therapy [9] and importantly reduced with the use of tamoxifen [10]. The possibility that changes in density might predict drug effectiveness was hypothesised some time ago [10]. This prediction was subsequently shown to be the case in the preventive setting, where tamoxifen reduced the incidence of breast cancer in high-risk women by about two-thirds when density was reduced by 10% or more after 12 to 18 months of treatment but had no effect when reductions were smaller or nonexistent [11]. The possibility that the same predictive value of density might also be true in the adjuvant setting and also for aromatase inhibitors was raised in [11], and the current study is the first to report such an effect.

In their report, Kim and colleagues studied 1,065 Korean women with oestrogen receptor-positive breast cancer, of which 127 (12%) had ductal carcinoma *in situ* [1]. All patients received endocrine therapy (tamoxifen or an aromatase inhibitor) for a mean duration of 5.1 years. Density was assessed in the cranio-caudal view of the contralateral breast at baseline and at a mean of 13.1 months after the start of therapy – blinded to treatment allocation and outcome – using the Cumulus software [12]. Sixty per cent of women had baseline density in the 25 to 50% range. Based on 80 recurrences overall, a clear gradient for lower recurrence rates in women with large reductions was seen – recurrence rates being more than twofold higher in women with no reduction compared with those presenting a reduction ≥10%. About one-quarter of women had changes in each of the four

categories of reduction: >10%, 5 to 10%, 0 to 5%, or an increase.

Greater density reductions were seen in women receiving tamoxifen (6.5% mean reduction) than in those receiving an aromatase inhibitor (3.1% mean reduction), but this appears to be due to their younger age and consequently their higher density at entry. Although tamoxifen was associated with greater changes in density, curiously the predictive value of density appeared to be greater with aromatase inhibitors and in postmenopausal women. The reasons for this increased density are unclear and need confirmation in further studies. Mechanisms underlying these findings are also needed, and if found could help to identify those women most likely to respond to a specific treatment before it is started, as opposed to the need to wait for the approximately 12 to 18 months after treatment has commenced to identify density changes in mammograms.

This study is the first to show that change in density predicts recurrences in the adjuvant setting, and raises the possibility of adjusting treatment in individual women according to their initial response to treatment in terms of density changes. This is an important step toward personalising treatment for this disease. Further work in Caucasian populations – more closely controlled for age and specific treatment, and integrating other factors such as levels of oestrogen and progesterone receptors, and baseline Ki-67 levels (and possibly, when presurgical endocrine treatment is used, evaluating changes in Ki-67 positivity in the tumour) – offers the prospect of more accurately choosing a specific treatment from which an individual woman is most likely to benefit.

Competing interests

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