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Genetic testing may help select women with ER+ breast cancer for extended hormone therapy

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Genetic analyses of results from 1125 postmenopausal women being treated for oestrogen responsive breast cancer have shown that some of them are more likely than others to have a late recurrence of their cancer and might benefit from ten years of hormone therapy rather than five.

Prof Mitch Dowsett told the opening press conference at the European Breast Cancer Conference (EBCC-9) that his research had shown that women who had tumours that were negative for the human epidermal growth factor protein (HER2-) but which were very sensitive to the oestrogen hormone, had more than double the risk of their cancer recurring between five and ten years after surgery and five years of adjuvant hormone therapy.

"Our data suggest that these patients, who are those that appear to benefit most from the current standard five years of endocrine treatment, may also benefit from adjuvant hormone treatment that extends beyond that five years," said Prof Dowsett, who is Professor of Biochemical Endocrinology at The Institute of Cancer Research, London, UK, and Head of Biochemistry at The Royal Marsden NHS Foundation Trust, London. The work is a collaboration between his team and that of Professor Jack Cuzick at the Wolfson Institute of Preventive Medicine, Queen Mary University of London, UK.

The findings are the latest to come from the ATAC trial (Arimidex,

Tamoxifen Alone or in Combination), a double-blinded phase III clinical trial that randomly assigned postmenopausal women with early, oestrogen receptor positive (ER+) breast cancer to receive the hormone therapies anastrozole or tamoxifen, or a combination of the two.

Prof Dowsett and his colleagues at The Royal Marsden, The Institute of Cancer Research and Queen Mary University of London used data from the OncotypeDx® 21-gene Recurrence Score that are not usually available from this test in order to analyse the genetic make-up and to predict the likelihood of cancer recurring within ten years in these women.

"The OncotypeDx result is reported as a single score but it is made up of 16 informative genes and five control or "housekeeper" genes that we have studied in detail. Some of the 16 are considered as groups rather than individual genes, and one of these is the E-module, which consists of four genes that are related to oestrogen signalling, including the oestrogen receptor itself," he explained.

OncotypeDX has been used for over 350,000 tests and the ATAC team had previously shown that its prediction of recurrence was poorer in the second five years after a patient's diagnosis than in the first five years. The researchers wanted to find out the reason for this, and to do so they determined the relationship between the expression of the individual genes and gene modules and early (up to five years) and late (between five and ten years) recurrence rates in women with ER+ HER2- breast cancer.

They assessed the gene expression and recurrence rates in 1125 women in the ATAC trial, who had an average of ten years of follow-up. Nearly 90% of the women were HER2- and there were 215 recurrences during the ten years.

They found that recurrence rates were highest in the first five years for women with HER2+ breast cancer, compared with the subsequent five years, but for women with HER2- cancer, the recurrence rates were higher between five and ten years.

"When we looked at the women with HER2- breast cancer and defined them according to their E-module score, which indicated how sensitive to oestrogen their tumours were, we found that there was a striking difference," said Prof Dowsett. "Among women with tumours most sensitive to oestrogen, with a high E-module score, the recurrence rate more than doubled from 5.7% in the first five years to 13.6% in the subsequent five years. However, if they had a low E-module score, there was little difference in recurrence rates between the first five years and the next five years: 10.3% versus 12.3%."

The researchers say that their results show that, despite similar overall recurrence rates for patients with ER+ tumours between the first five years and the next five to ten years, there were important differences between groups of tumours with different genetic expression profiles.

"Importantly, HER2- tumours that are very sensitive to oestrogen are usually considered to be relatively low risk, yet these were the tumours that showed an increase in recurrence after five years, which coincided with the cessation of adjuvant hormonal therapy," said Prof Dowsett. "It is commonly thought that the reduction in recurrence achieved by five years of endocrine therapy 'carries-over' into the next five years. Our results suggest this effect may differ markedly between different groups of ER+ tumours. We need to do more detailed analyses on large numbers of tumours to find out if this is the case."

He said the results also suggested a way in which methods of predicting recurrence using genetic signatures may be improved. "Better predictors of recurrence than the OncotypeDX and others currently being used

should be possible based on the different recurrence rates of different groups of tumours and their different sensitivity to endocrine therapy." He and his colleagues are already working to see if they achieve this.

"We are already testing over 900 tumours from the ATAC trial to see if we can identify the oestrogen-sensitive tumours better than by the genes in the Oncotype test. This will allow us to see whether, using the knowledge from this work, we can indeed create better predictors of recurrence both for the first five years and subsequent years after diagnosis," he said.

The findings could change clinical practice: women with HER2-, high oestrogen signalling breast cancer might be considered for adjuvant hormone therapy that is extended to ten years. However, the results need to be confirmed in other sets of tumours first. "This should be done by testing the tumours of patients that are participating in ongoing trials of extended versus no extended adjuvant therapy," said Prof Dowsett.

Prof Cuzick added: "It has long been known that women with ER+ cancers have a higher late recurrence rate than those with ER-negative tumours. This work makes clear that even within ER+ cancers the level of expression is important. Further work is needed to see if genetic expression profiles are better at doing this than more conventional quantitative immunohistochemistry. We are about to start a trial called IBIS-3 of extended therapy with aromatase inhibitors in long-term survivors with ER+ breast cancer with other unfavourable characteristics, and also adding new drugs used in other conditions that show promise in preventing breast cancer recurrence – a bisphosphonate (bone sparing drug) and metformin (diabetes drug). Hopefully, this biomarker work will help to pinpoint more accurately which patients need additional treatment."

Professor Giuseppe Viale, chair of EBCC-9 and Head of the Department

of Pathology at the University of Milan, commented: ""Late recurrence for patients with hormone receptor-positive breast cancer after five years of endocrine treatment unfortunately is a sizeable risk, with devastating effects on the quality of life of affected patients. Clinical trials have already documented the possible benefit of extending endocrine therapy beyond five years in unselected populations of post-menopausal patients, but we do not have the means to identify the subgroup of patients actually benefitting from this extended treatment. These latest findings from the ATAC trial may pave the way for a better tailoring of hormone therapy beyond the first five years. Certainly, confirmatory studies are needed, and it remains to be assessed whether the same prognostic parameters may also hold for pre-menopausal patients."

More information: O-216, "Oestrogen module of 21-gene recurrence score predict increased late recurrence for ER+HERT2- breast cancer". Thursday 20 March at 15.30-17.00 hrs. "Relapse After Systemic Treatment – Can We Predict it?" session, Clyde Auditorium.

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