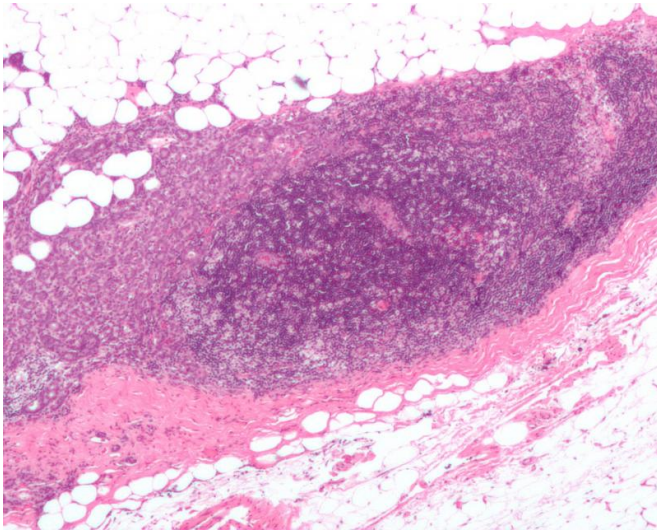


Discovery of genetic differences between relapsing/non-relapsing breast cancers

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Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Although most patients with breast cancer are cured after treatment, in about one in five the cancer will recur, returning either to the same place as the original tumour or spreading to other parts of the body (metastasis). Now, researchers have taken an important step towards understanding why some primary breast cancers return while others do not.

They have found that the genetic factors driving the cancers that recur are different from those found in the cancers that do not. This discovery could enable doctors to identify patients at high risk of their cancer returning and to target the genes responsible for recurrence when the cancer is first diagnosed in order to prevent its return.

Presenting the results to the 2015 European Cancer Congress tomorrow (Saturday), Dr Lucy Yates, MD, a clinical research oncologist from the

Wellcome Trust Sanger Institute, Cambridge, will say that her team analysed data from the genetic sequencing of 1,000 [breast cancer](#) patients' tumours. In 161 cases this included samples taken from recurring tumours or metastases. They compared the cancer genes found in cancers sampled at first diagnosis (primary tumours) with those found in relapsed cancers.

They found that there were genetic differences between primary and recurring tumours, with some differences being acquired during the later phases when the cancers recurred and started to spread.

The researchers say these findings have important implications for personalised medicine. If individual cancers can change genetically over time, this means that treatments that target a particular genetic mutation, either in the clinic or in trials, may have to change as the disease progresses, guided by taking regular samples of cancer tissue, rather than basing the treatment only on samples taken when the cancer is first diagnosed.

The study is the largest and most comprehensive carried out to date, say the researchers, in terms of the number of samples from relapsed breast cancers and the 365 genes involved in cancer-related pathways that have been investigated simultaneously.

"We have found that some of the genetic mutations that drive breast cancers that relapse are relatively uncommon amongst cancers that do not relapse at the point of primary diagnosis. We believe that the differences we have seen reflect [genetic differences](#) that can predispose a cancer to return, combined with mutations acquired throughout the period from first diagnosis to the subsequent relapse. Some of these genetic alterations are potentially targetable with drugs," Dr Yates will say.

Within an individual cancer, a wide range of genetic or epigenetic alterations accumulate and may

constrain later events that can promote the survival of the cancer through relapse. Alternatively, specific environmental factors such as the response of the immune system, different treatments, or the environment of the metastasis itself may have an influence on the occurrence of rare cancer genes.

Among these later stage mutations, the researchers found "compelling evidence" for the tumour suppression activity of two related genes called JAK2 and STAT3 that operate within the same signalling pathway. "Within some breast cancers, a disruption in this signalling pathway seems to be advantageous for survival of the cancer," Dr Yates will say. "Interestingly, this is in contrast to the role of JAK2 in some other cancers where over-activity of the gene drives malignancy rather than suppresses it."

Enhanced JAK-STAT signalling is known to play an important role in breast cancer stem cell development and cancerous cell line survival, and pre-clinical evidence seems to suggest that inhibiting the gene would be therapeutically advantageous. These findings have led to the development of clinical trials for breast cancer using JAK inhibitors in the hope that they will slow cancer progression.

"However, our findings suggest that, in a subset of cancers, inhibiting this pathway may have the opposite effect, and this requires further investigation. In general, the observation highlights the importance of understanding the diverse nature of breast cancers in the era of precision medicine," Dr Yates will conclude.

Professor Peter Naredi, the ECCO scientific co-chair of the Congress, who was not involved in the research, commented: "Information such as that which Dr Yates will present is very important in the era of precision medicine. Not only can we better choose the right treatment combination as our information about the primary tumour increases, and hence prevent over-treating patients who will not benefit, but this will also help us select the right therapy for each breast cancer patient. This study also underlines the fact that we should consider a recurrence of a cancer as a new event, and carefully select the right treatment for the recurrent

tumour as opposed to just relying on information from the first occurrence." ESMO spokesperson, Dr Jorge Reis-Filho, from the Memorial Sloan Kettering Cancer Center, New York, USA, who was not involved in the research, said: "This study highlights the differences between [genetic alterations](#) that drive relapsed and metastatic disease as opposed to primary breast cancers, and underlines the importance of analysing the genetic features of metastases when making treatment decisions. The extent of the differences in the repertoire of mutations among different metastatic sites within individual patients remains to be determined, however, as does the best way to obtain tumour-derived genetic material in patients with metastatic disease. We also need to know more about whether a single or multiple metastatic sites should be analysed in this context."

More information: Abstract no 1804. "The driver landscape of breast cancer metastasis and relapse". Breast cancer - advanced disease proffered papers session, 10.30-12.20 hrs (CEST), Saturday 26 September, Hall D1 (presenting at 11.40 hrs).

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