

Tracking breast cancer cell genetics reveals longer potential treatment window

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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

Breast cancer cells break away and spread to other parts of the body relatively late on in breast tumour development, an international team of scientists has shown. The research, jointly led by Dr Peter Van Loo at the Francis Crick Institute, could help refine cancer therapy and is published in the journal *Genome Biology*.

The team of scientists in the UK, Belgium, Norway and the USA tracked the genetics of particular cancer cells that can go on to form secondary tumours in other parts of the body, such as the [bone marrow](#). Such cells are known as disseminated [tumour cells](#) or DTCs.

The group's findings suggest there is a longer window than previously thought for cancer to be diagnosed and treated before it spreads. The majority of people who die from cancer lose their lives when it spreads throughout the body, a process called metastasis.

Dr Van Loo worked with colleagues from Oslo University Hospital in Norway, the University of Leuven in Belgium and the University of Chicago in the USA.

The team used the latest single-cell sequencing techniques to read out the full DNA genomes of 63 [individual cells](#) isolated from bone marrow samples donated by six [breast cancer patients](#). The scientists have not only shown that cancer cells spread late, but also that when DTCs are present elsewhere in the body they are genetically very similar to the patient's original tumour.

This knowledge could help clinicians to choose the therapy most likely to destroy the cancer. Although the project focused on breast cancer, the team believes the results could be applied to other cancers too.

Dr Jonas Demeulemeester of the Francis Crick Institute, one of the joint first authors, said: "Although how tumours spread throughout the body is

not well understood, we do know that some mutations increase a cell's ability to move about. Cells like this may leave the crowded environment of the primary tumour and enter blood vessels. Swept away by the bloodstream, they may exit the vessels again at distant sites and nest themselves in other tissues, such as the bone marrow. Cells surviving this whole process are known as disseminated tumour cells and can lay undetected and dormant for many years, often resisting therapy, before re-activating and giving rise to a new tumour, a metastasis."

The study focused on patients diagnosed with localised breast cancer - people with a tumour in their breast but no evidence of it having spread anywhere else in the body. The team took tumour and bone marrow samples when the patients were diagnosed and in one case, took samples again three years later.

Next they looked at the genetic information held in cells from both the tumour and bone marrow. The team developed sensitive methods to interrogate the genome of each sample that allowed them to spot both large and small-scale genetic changes.

Cancer happens when a series of genetic changes corrupts cell behaviour. The changes, or mutations, create a DNA signature specific to the cancer cell and the copies it makes of itself. By tracking mutations in cells from the original tumour and cells found in the bone marrow, they could compare the evolution of their DNA signatures and figure out when DTCs sprang from the tumour.

They found that when DTCs are present they are genetically very similar to the patient's original tumour.

"This knowledge is crucial to help determine the right therapy for patients. If a treatment is chosen specifically to target a mutation present in all cells of a patient's primary tumour then it is most likely the

disseminated tumour cells will also carry this mutation and will also respond," explains Dr Demeulemeester.

The number of tumour cells detected in bone marrow also has a value in figuring out a patient's prognosis: the more tumour cells are found, the worse the outlook for the patient.

The new study suggests the number used as an indicator of outcome could be considerably refined.

The team discovered that some cells found in the patients' bone marrow didn't share any genetic history with the original breast tumour cells. These cells nonetheless had large-scale genetic changes and appeared to accumulate over time, suggesting that genetic mistakes can occur in normal, healthy tissues as well. The next stage of research is to look at what the relevance of these intermediate cells is to the development of [cancer](#).

Dr Demeulemeester said: "Only a subset of those cells previously believed to be [cancer cells](#) have really spread from the patient's primary tumour. A refined indicator means a more accurate prognosis and a more tailored therapy for patients, avoiding over- or under-treatment."

Dr Justine Alford, Cancer Research UK's senior science information officer said: "Understanding more about how and when tumour cells spread is important, and this early research sheds light on the origins of these [cells](#) in [breast cancer](#) patients. When cancers spread they are often harder to treat, but this new study could help researchers develop new ways to tackle the disease more effectively."

More information: Jonas Demeulemeester et al, Tracing the origin of disseminated tumor cells in breast cancer using single-cell sequencing, *Genome Biology* (2016). [DOI: 10.1186/s13059-016-1109-7](https://doi.org/10.1186/s13059-016-1109-7)

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