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Immunotherapy treatment option for selected breast cancer patients, genetic study suggests

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Immunotherapy drugs could help some breast cancer patients based on the genetic changes in their tumours, researchers at the Wellcome Trust Sanger Institute and their collaborators find. Published today (13 September) in *Cancer Research*, scientists identify particular genetic changes in a DNA repair mechanism in breast cancer.

The results open up the possibility to another therapy option for around 1,000 breast cancer patients in the UK, who could benefit from existing drugs.

Breast cancer is the most common cancer in the UK, affecting nearly 55,000 women a year. Globally it accounts for nearly 1.7 million cancer cases.

In the study, scientists found that a particular group of breast cancer patients have genetic changes, or mutations, that occur because of an abnormality of a DNA repair mechanism known as mismatch repair. These mutations are found in other cancers, such as colorectal cancer, but are rarely looked for in breast cancer.

Colorectal cancers with deficient mismatch repair have recently been treated with immunotherapies called checkpoint inhibitors in the US, including the drug pembrolizumab. Immunotherapies exploit the fact that, under the influence of check point inhibitors, highly mutated tumour cells can be recognised as 'foreign' by the patient's immune system.

The results of this new study suggest that these immunotherapies could also be effective for some breast cancer patients based on the same mutation patterns seen in their tumours. Therefore clinical trials are required to determine if immunotherapies could help selected breast cancer patients.

In the study, the team analysed the whole genome sequences of 640 breast cancer tumours. They looked for patterns in the mutations, known as mutational signatures, which indicated abnormalities in the mismatch repair mechanism. From the mutational signatures, the team identified 11 tumours that had the mismatch repair defects causing the breast cancer.

Dr Serena Nik-Zainal, lead author from the Wellcome Trust Sanger Institute, said: "We've unequivocally found mismatch repair deficient breast cancers. As these tumours have the same mutational signatures as those of other cancers, like colorectal cancer, they should in theory respond to the same immunotherapy drugs. Our results suggest expanding the cohort of cancer patients that could possibly be treated with checkpoint inhibitors to include these mismatch repair deficient breast cancer patients."

Dr Helen Davies, first author from the Wellcome Trust Sanger Institute, said: "Using whole genome sequencing we can start to stratify breast cancer patients into different categories based on their mutational signatures. Current clinical criteria means these tumours would not have been detected as being deficient in the mismatch repair pathway. We have shown that there is in fact another category of breast cancers - those with defective mismatch repair."

Professor Karen Vousden, Cancer Research UK's chief scientist, said: "Immunotherapies have shown promise for some cancer patients, but the challenge for doctors has been predicting which patients they are likely

to help. This study, using a technique called whole genome sequencing, reveals more about the genetic patterns that could show which women with breast cancer are more likely to respond to immunotherapy treatments. The next step will be to test this approach in clinical trials to find out if identifying these patterns and using them to tailor breast cancer treatments helps to improve survival."

More information: Helen Davies et al. (2017) Whole-genome sequencing reveals breast cancers with mismatch repair deficiency. *Cancer Research*. DOI: 10.1158/0008-5472.CAN-17-1083

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