Scientists discover gene linked to breast and ovarian cancer

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(Medical Xpress)—A team of researchers led by the Institute of Cancer Research, London, have found that rare mutations in a gene called PPM1D are linked to an increased risk of breast and ovarian cancer. The mutations are not inherited, and the discovery potentially reveals a new mechanism of cancer development.

The study suggests that around one in five women with PPM1D mutations will develop breast or ovarian cancer in the course of their lifetime, almost double the breast cancer risk and more than ten times the ovarian cancer risk of women in the general population. The discovery could have implications for genetic testing and targeted prevention, in particular for ovarian cancer, which is often diagnosed at an advanced stage.

The team analysed 507 genes involved in DNA repair in 1150 women with breast or ovarian cancer, identifying PPM1D gene mutations in five women. They then sequenced the PPM1D gene in 7781 women with breast or ovarian cancer and 5861 people from the general population.

There were 25 faults in the PPM1D gene in women with cancer and only one in the general population, a highly statistically significant difference.

The study found that the mutated genes were not passed down from parent to child and were not present in every cell. Even more surprisingly, there were no PPM1D mutations in the cancer cells or in the normal breast or ovarian cells; they were found only in blood cells.

The findings suggest that PPM1D works in a completely different way to other genes known to increase the risk of breast and ovarian cancer, such as BRCA1 and BRCA2, potentially highlighting a new cancer-causing mechanism.

The team found that the mutations made the molecule that is produced from the PPM1D gene shorter than usual. Such truncating mutations are usually thought to cause a loss of function; however, the team were surprised to find that in this case the PPM1D mutations seem to make it more active.

Study leader Professor Nazneen Rahman, head of genetics at the Institute of Cancer Research (ICR) and head of the cancer genetics clinical unit at the Royal Marsden NHS Foundation Trust, said: "This is one of our most interesting and exciting discoveries.

"At every stage the results were different from the accepted theories. We don't yet know exactly how PPM1D mutations are linked to breast and ovarian cancer, but this finding is stimulating radical new thoughts about the way genes and cancer can be related."

"The results could also be useful in the clinic, particularly for ovarian cancer, which is often diagnosed at an advanced stage. If a woman knew she carried a PPM1D mutation and had a one in five chance of developing ovarian cancer, she might consider keyhole surgery to remove her ovaries after completing her family."

Professor Alan Ashworth, chief executive of The Institute of Cancer Research and one of the study researchers, said: "This discovery really does turn conventional wisdom about the way genetic mutations can lead to cancer on its head. We are likely to gain many valuable insights into how cancers can occur as we continue to unravel this puzzle."

New genetic sequencing technologies that allow much deeper analysis of genes were crucial to enable the team to make the link between the PPM1D mutations and cancer. The discovery that the mutations were only present in some cells, a so-called mosaic pattern, would have been extremely difficult to detect with older sequencing methods.

It is possible that similar mosaic mutations in other genes, and in patients with other types of cancer, will emerge as more research groups are now using these deep sequencing techniques, the authors say.

Dr Michael Dunn, head of molecular and physiological sciences at the Wellcome Trust, said: "This study is an fantastic example of the power of next-generation sequencing to discover new cancer predisposing genes, offering opportunities for better diagnosis. The discovery also opens up a very exciting new avenue of research in the study of cancer development."

The study was funded by the Institute of Cancer Research, the Wellcome Trust, Cancer Research UK and Breakthrough Breast Cancer.

More information: Ruark E et al. Mosaic PPM1D mutations are associated with predisposition to breast and ovarian cancer. *Nature* 2012 (epub ahead of print).

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