International Agency for Research on Cancer

World Health Organization

Missense makes sense of breast cancer

Scientists have found that specific changes in DNA sequence have a greater impact on breast cancer risk than previously thought.

According to researcher Professor Georgia Chenevix-Trench from the Queensland Institute of Medical Research (QIMR), "Inherited mutations in ATM have long been known to increase the risk of breast cancer. However, there has been a lot of controversy about exactly which types of ATM mutations increase the risk."

Case-control study of inherited breast cancer

The international study that will be published in the American Journal of Human Genetics examined the ATM gene of 2,500 breast cancer cases with 2,200 healthy control women. Mutations that affect the function of the ATM protein, without destroying the protein, were found to confer the highest risk of breast cancer.

The study analysed the evolutionary history of ATM by comparing the gene in various vertebrate and invertebrate species to determine which components were crucial to ATM protein function.

It was found that a class of substitutions in the DNA sequence of the ATM protein that alter amino acids (known as missense mutations) have a greater association with breast cancer than expected. Previously, only one particular missense mutation was thought to impact greatly on breast cancer risk.

Public health perspective and methodological gains

"The methods developed during this study may provide an important tool for helping us to understand the significance of these missense variants in genes and their impact on a range of diseases," said Professor Chenevix-Trench.

"Results from this study could expand the scope of genetic counselling which currently focuses mainly on mutations that truncate and destroy the protein."

"More broadly, the methods developed during this study may provide an important tool for the analysis of whole genome sequencing data aimed at uncovering genes for other genetic diseases."

According to the lead researcher, Dr Tavtigian from the International Agency for Research on Cancer, "It is sometimes said that 'nothing in biology makes sense except in the light of evolution'. This is a clear instance where taking an evolutionary biology perspective has helped to solve a long-standing controversy in clinical cancer genetics. Moreover, the perspective embodied in this work will likely become more important as super high throughput sequencing leads to personalized genomic medicine".

This work arose from collaboration between the International Agency for Research on Cancer (IARC) in France, Regensburg University in Germany, and the Queensland Institute of Medical Research (QIMR) in Australia. Samples were obtained from the Breast Cancer Family Registry (BCFR), the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab), and IARC-Thai Breast Cancer Study.

Breast cancer: a global burden

Breast cancer is the leading cancer in women around the world, with approximately 1,150,000 new cases each year (Globocan 2002). It is estimated that among these, 57,500 cases of breast cancer are due to inherited mutations. Hormonal and other risk factors, many of which are directly linked to lifestyle, also contribute to a large fraction of breast cancer cases.

The study will be published in The American Journal of Human Genetics (AJHG) on September 24. The corresponding author, Professor Chenevix-Trench, also has a podcast available on the AJHG website.

About QIMR

QIMR is one of Australia's largest and most successful medical research institutes. Our researchers are investigating the genetic and environmental causes of more than 40 diseases as well as developing new diagnostics, better treatments and prevention strategies. The Institute's diverse research program extends from tropical diseases to cancers to indigenous health, mental health, obesity, HIV and asthma.

More information about QIMR can be found at http://www.qimr.edu.au.

About IARC

The International Agency for Research on Cancer (IARC) is part of the World Health Organization. IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

Website: http://www.iarc.fr.