Horizon
The EU Research & Innovation Magazine

European Commission

Genetic testing breakthrough helps women with high risk of breast cancer avoid surgery

EU-funded researchers are discovering new genes linked to breast cancer and refining evaluation of risk to help spare women from life-changing surgery.

20 August 2024 - By VITTORIA D'ALESSIO

They call it the Angelina Jolie effect: the popular belief that only a preventative double mastectomy can safeguard a woman from developing a tumour if she carries gene mutations linked to breast cancer.

Celebrity actress Jolie made headlines in 2013 when she underwent radical breast surgery after genetic testing revealed she carried a gene – BRCA1 – that significantly increased her odds of developing breast and/or ovarian cancer.

Fast forward a decade and eight more genes known to raise a woman's susceptibility to breast cancer have been discovered. Among these are BRCA2, which also greatly increases the chances of developing breast cancer, and four genes discovered by BRIDGES, an international research project funded by the EU.

Thanks in large part to ground-breaking work by EU-funded researchers, prophylactic surgery is no longer seen as inevitable for a woman to stay healthy if she carries a gene that increases her risk of breast cancer.

In parallel to these discoveries, medical understanding of risk – the likelihood of a woman developing breast cancer if she carries specific mutations – has also evolved significantly.

Avoiding surgery where possible

Greater clarity around the level of risk and the treatment options available is welcomed by women's cancer support groups.

'The ideal outcome of genetic screening is for women to get an accurate picture of their risk and be offered a personalised approach to tumour prevention,' said Marzia Zambon, executive director of Europa Donna, Europe's largest breast cancer advocacy group.

‘We’re pushing for genetic testing to always be done with the professional guidance of a genetic counsellor. If testing isn’t done right, it can cause a lot of stress and an unnecessary escalation of treatment.’

Researchers involved in BRIDGES and B-CAST – another EU-funded research initiative – have made huge advances in showing how both genes, lifestyle and environmental factors influence the risk of breast cancer. These non-genetic factors include a woman’s exposure to pollution, excess body weight, breast tissue density, low physical activity, alcohol consumption, exposure to birth control and other hormones, and the number of children borne.

‘Until recently, genetic testing could identify women carrying genes linked to breast cancer, but estimates of the risk these women were facing were quite imprecise,’ said Professor Peter Devilee, BRIDGES research coordinator and cancer geneticist at Leiden University in the Netherlands. This matters because imprecise risk evaluation can result in inaccurate treatment advice.

‘Women with a family history of breast cancer are being referred to labs for genetic testing, and mutations are being identified, but if you can’t translate a result into a fairly precise breast cancer risk, it can lead to improper risk management advice. We wanted to help clinics interpret results properly.’

Predicting with precision

In their quest to estimate the risk posed by any given gene mutation more precisely, the BRIDGES researchers sequenced all suspected breast cancer genes in the genomes of 113 000 women. Of these women, half were known to have had a breast cancer diagnosis, while the other half had not.

The genetic profiles of these patients were then crosslinked with data from 20 000 breast tumours analysed by the B-CAST team. In addition, the B-CAST researchers contributed information about the genetic profiles of patients’ close family members and those all-important lifestyle and environmental risks.

The BRIDGES team contributed an added tranche of data on genes that hadn’t yet been implicated in breast cancer, but which might impact the risk to develop breast cancer when appearing in a mutated form.

Finally, all this information was combined with the findings of earlier EU-funded research efforts which set out to find common DNA variations in the same cohort of women, including COGS, the world’s largest project on genome-wide association studies to predict cancer risk.

The result of all this data crunching? The BRIDGES and B-CAST teams were able to make vast improvements to a pre-existing tool that estimates the risk posed by any given gene mutation or combination of mutations.

Named CanRisk, this online tool, available in seven EU languages, is designed to give an expert – usually a clinical geneticist – an accurate estimate of a woman’s risk of developing a specific type of tumour. The higher the score, the greater the risk.

The hope is that more women with moderate-to-high risk of breast cancer will be identified early. CanRisk factors in the subtype of cancer linked to each cancer gene or gene combination. This is important as some tumour subtypes are far more dangerous than others and treatment options, as well as likely health outcomes, differ from subtype to subtype.

A handful of European clinics are currently piloting the user-friendly, CE-marked CanRisk tool. The researchers are hopeful that more will come on board in the years ahead.

More choices, better screening

Being informed of an elevated risk for developing breast cancer is important, but what actions should a woman take upon receiving this information?

‘Better precision in predicting breast cancer makes it easier for women to make informed choices about their bodies and their health,’ said Dr Marjanka Schmidt, B-CAST coordinator and an epidemiologist with an

expertise in breast cancer genetics based in the Netherlands.

‘Ultimately, it cuts overtreatment and reduces the incidence of unnecessary, life-changing surgery.’

Typically, women who are identified as at-risk using the CanRisk tool are offered mammograms from an earlier age than other women and/or more frequent mammograms. MRI scans might also be added to their screening protocol.

‘CanRisk has brought clear benefits to many, leading to reductions in the occurrence, severity and mortality of breast cancer. And as we continue to refine the tool, it’s likely to save more and more lives,’ said Schmidt, who leads a research group at the Netherlands Cancer Institute and is a professor of genetic epidemiology of (breast) cancer at Leiden University Medical Center.

Next steps

The research carried out by the BRIDGES and B-CAST teams between 2015 and 2021 has continued well beyond the initial funding provided by the EU.

The B-CAST team are now developing a tool that will help cancer doctors more accurately predict the health benefits of a specific course of treatment for a given woman with a given subtype of breast cancer.

‘Some treatments have quite serious side-effects, so it’s important for women and clinicians to know how much impact a particular treatment is likely to have on the tumour, and for decisions to be based on the survival benefits of this treatment,’ said Schmidt.

Meanwhile, the BRIDGES researchers continue in their quest to identify further genes associated with breast cancer.

‘We know about 55-60% of the genetic risk factors, but that leaves 40-45% that still need to be discovered,’ said Devilee.

The combined impact of their research is already being felt. It will continue to help guide both doctors and patients on the best way to decrease both the incidence of breast cancer and the human toll of this disease.

Research in this article was funded by the EU’s Horizon Programme. The views of the interviewees don’t necessarily reflect those of the European Commission. If you liked this article, please consider sharing it on social media.

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- B-CAST
- BRIDGES
- Europe’s Beating Cancer Plan
- EU Health research and innovation
- European Health and Digital Executive Agency