PREDICTING BREAST CANCER RISK

Professor Gareth Evans explains his test for genetic breast cancer, which could reduce unnecessary pre-emptive mastectomies.

When embarking on research into a genetic test for women with a family history of breast cancer in 2009, Gareth Evans, Professor and Consultant in Medical Genetics and Cancer Epidemiology at the University of Manchester and Saint Mary's Hospital, was sceptical.

His research team developed a saliva test – which will enter clinical practice at two Manchester hospitals early next year – that predicts the risk that women who have tested positively for 18 mutations of single nucleotide polymorphisms (SNPs) have of developing breast cancer. The research also found that these mutations have minimal risk in isolation, but when combined can increase or decrease the cancer risk considerably.

Predictions

Risk is a particular interest of Gareth's – he set up the first cancer genetics clinic in the north west of England and his work focuses on women with a family history of cancer. "I've always been interested in how you can assess and communicate risk," he says.

The test Gareth's research team developed used 18 SNPs identified by Clare Turnbull et al in a June 2010 paper published in *Nature Genetics* to refine the risks of developing breast cancer within the general population, those with a family history of breast cancer and carriers of genetic mutations.

"SNPs are extremely common by definition – many of the original ones identified are carried by 30% to 40% of the population – but the effects are relatively small," he explains. "So it might only increase the risk of breast cancer, compared to somebody who doesn't carry it, by about 10%, or maybe 15% to 20%. Some of the newer SNPs are even less than that – 5% or 6%."

"Individually, they are not very useful at all. However, if you combine the effects of these common variants, and you get a bad deal compared to a good deal of them, your risk can be 10 times higher."

Levels of risk

The test can also help refine the risk of carriers of extreme genetic variants, such as BRCA1 and BRCA2, and "moderately penetrant" genes, such as chek2 and the ATM gene, Gareth says.

The one in 800 to 900 people carrying the BRCA1 gene and one in 600 to 800 carrying the BRCA2 gene would usually have a lifetime risk of developing cancer of above 40%, which is four times the population's lifetime risks.

Carriers of faults like chek2 and ATM are more common – about one in 200 people – and face a 20% to 30% lifetime risk of developing cancer.

"In reality it is a range of risk," Gareth says. "And the range varies from as low as 30% up to 90%, but if a doctor gives a risk of 'between 30% and 87%', a woman tends to take home the more pessimistic estimate and assume her risk of getting breast cancer is 87%."

The research

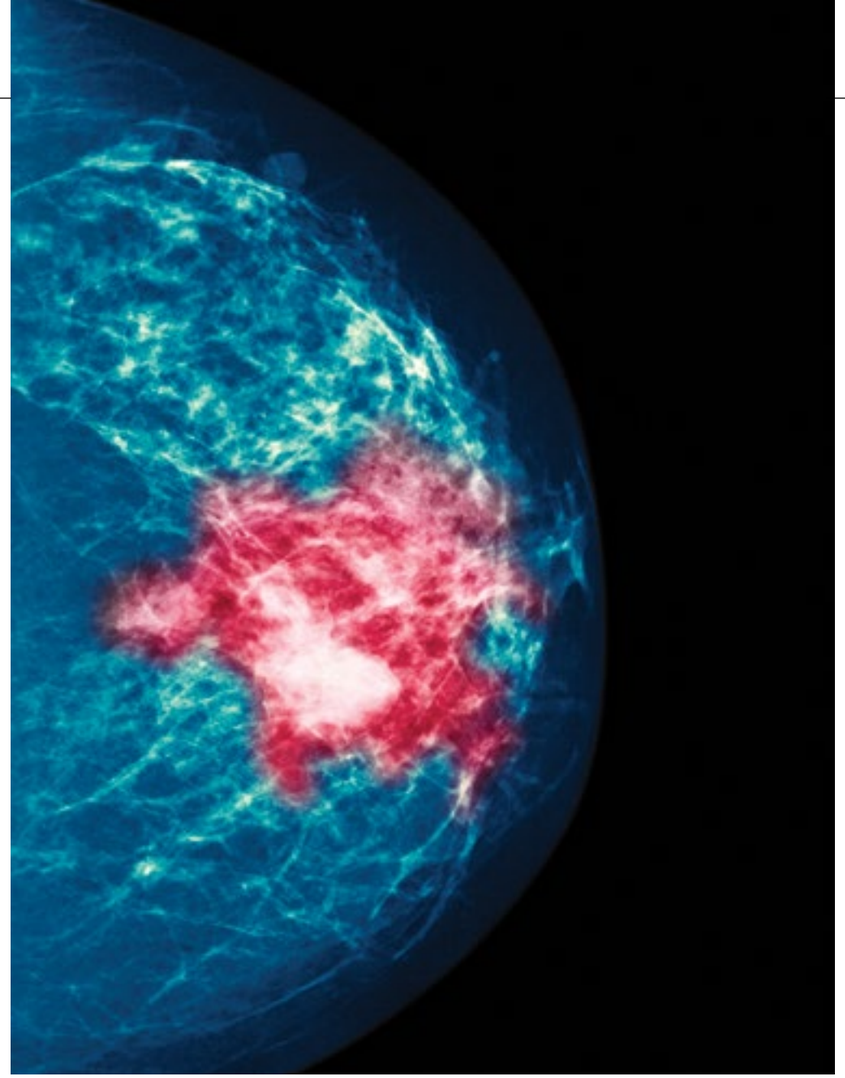
The risk of developing breast cancer depends on a number of factors addressed in the research and which work in the same way for BRCA1 and 2 carriers and the general population.

The researchers recruited a total of 451 women who had developed breast cancer and had a family history of breast cancer (112 of the cohort had the BRCA1 and 2 mutations), and compared the diagnosis of invasive breast cancer and genetic profile in this group with a control group of 1,605 women (691 of the cohort had BRCA1 and 2 mutations).

Blood samples were used to determine individual genetic makeup and predict an overall risk estimate.

These were used alongside other risk factors, which included age at first assessment, family history of first- and second-degree relatives, age at first child, first period and menopause, height and weight, and history of prior non-cancerous breast disease.

The predictions have been confirmed as accurate by a SNP study of 10,000 women, 455 of whom went on to develop breast cancer, by the charity Prevent Breast Cancer, which also helped fund Gareth's research.



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In addition, many women who were originally classified as having a high risk (above 30%) were reclassified to a lower risk of developing breast cancer.

Alternative treatment

This means that for those women who assume the worst-case scenario, a risk-reducing mastectomy will not be recommended. The study also goes on to suggest that the number of women with BRCA1 and 2 mutations who currently choose to have a preventative mastectomy could reduce from 50% to about 36%.

"The test indicates that SNPs work in the same way in mutations like BRCA as they do in the general population and, while you can't use exactly the same odds ratios as you would to [predict cancer] in the general population because they work slightly differently in BRCA, you can better guide women as to where they are on the risk range," Gareth says.

As a result, women can be offered alternative treatments, such as scans, chemo prevention and drugs, such as Tamoxifen, Raloxifene and Anastrozole. "Anastrazole costs 4p a day," Gareth says. "If you can more accurately identify women at high enough risk to take it, using our SNPs alongside density and standard risk factors in the general population, you could actually save the NHS money."

The future

If women are being tested at scale – running about 96 at a time – each test costs £60, and there is interest in expanding the test nationwide. "There is a plan to do a study offering BRCA carriers this test alongside their pre-symptomatic genetics test," says Gareth.

Genetic risks of other cancers could be predicted in the same way – a similar test for prostate cancer is under development and SNPs for bowel, ovarian, womb and lung cancer have been identified. "All of these are potentially amenable to the same tests that we have developed for breast cancer," Gareth adds.

"Predicting risk and enabling prevention and early detection can shape the future of cancer research and treatment."

ALL ABOUT GARETH

- ✔ Trained at St Mary's Hospital Medical School in London, specialising in paediatrics
- ✔ Interest shifted to genetics, so undertook an MD in cancer genetics between 1990 and 1992 while working as a senior research fellow at Manchester University
- ✔ Chairman of the NICE Familial Breast Cancer Guideline Development Group from 2002 to 2010, and has been clinical lead since 2011
- ✔ Developed a national training programme for clinicians, nurses and genetic counsellors in breast cancer genetics
- ✔ Published over 650 peer-reviewed research publications, over 100 reviews and chapters and has had a book published by Oxford University Press on familial cancer.