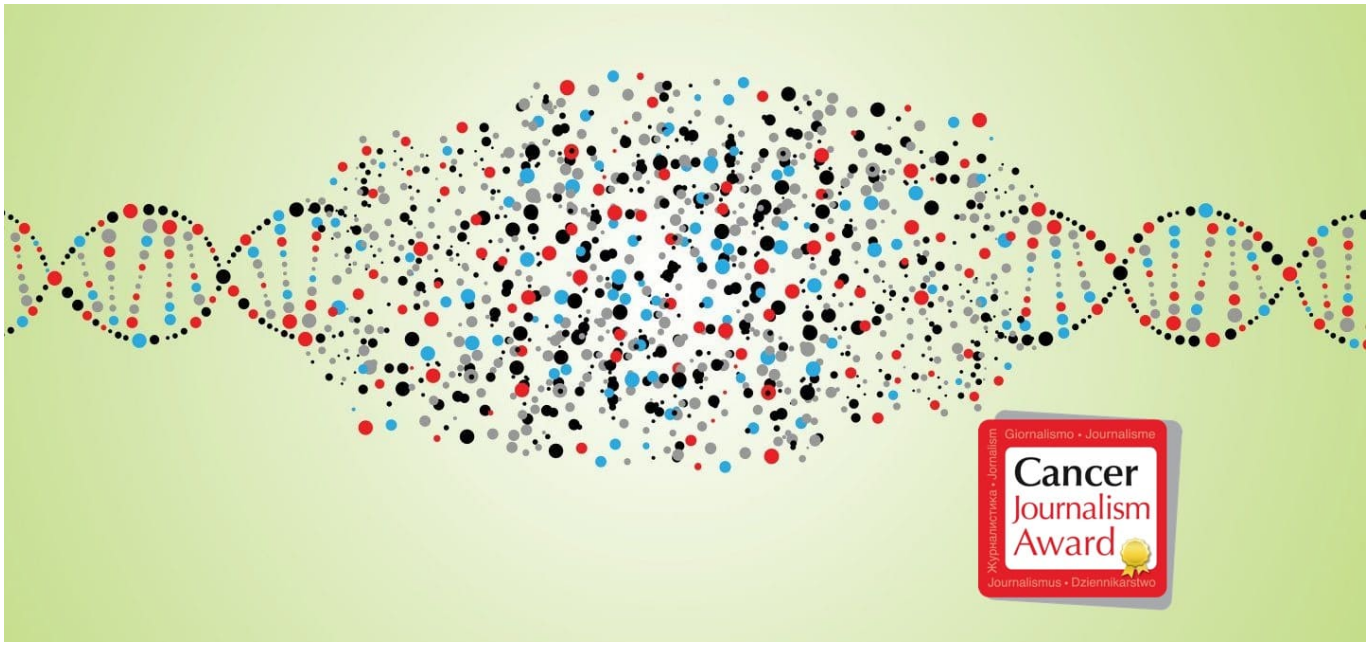
Cancerworld

How race to track mystery gene with links to three cancers saved millions

Robin McKie / 23 July 2021



Ten years ago, Tony Herbert developed a lump on the right side of his chest. The clump of tissue grew and became painful and he was tested for breast cancer. The result was positive.

“I had surgery and chemotherapy and that worked,” he says. But how had Herbert managed to develop a condition that is so rare in men? Only about 400 cases of male breast cancer are diagnosed every year in the UK compared with around 55,000 in women. A genetic test revealed the answer. Herbert had inherited a pathogenic version of a gene called *BRCA2* and this mutation had triggered his condition.

The genetic link was a crucial revelation that not only played a key role in Herbert’s recovery and survival over the next decade, but which has also helped many women and men fight breast cancer as well as cancers of the ovary and prostate. All three cancers are now known to be linked to mutated versions of *BRCA2* – a gene whose existence was first revealed 25 years ago this month in a paper in *Nature*.

Today it is calculated that in the UK alone there are tens of thousands of people who carry pathogenic versions of the gene, which is known as Breast Cancer 2 or *BRCA2*. It can be inherited from either parent and can spread through lineages with devastating effect. Revealing its existence – which was achieved by a research team led by Michael Stratton, who was then working at the

Institute of Cancer Research in London – has revolutionised the treatment of cancers for a great many individuals.

In the case of Herbert, his inheritance of the mutated gene meant he was susceptible not just to breast cancer but to prostate cancer as well, as doctors realised. “I was monitored for prostate cancer and it was found to be at quite an advanced stage. I was given radiotherapy and to be honest I now feel fine,” said Herbert who campaigns to raise awareness about breast cancer in men.

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The crucial point is that his fight against both the cancers that have touched his life would not have been possible without the discovery of *BRCA2*. Pinpointing the mutated, pathogenic gene, which is passed through families leaving carriers prone to breast, ovary and prostate cancers, was a medical milestone that involved UK scientists in a desperate race against US companies who wanted to find the gene and patent it for private gain. For good measure Stratton – who is now director of the Wellcome Sanger Institute in Cambridgeshire – was told by some researchers that he was wasting time when he launched his project. “One breast cancer gene, *BRCA1*, had already been found and it was unlikely there would be a second, I was told,” Stratton told the *Observer*.

Nevertheless he and his colleagues persisted and began investigating several large UK and Irish families who were suffering grim numbers of cases of breast and ovary cancers. Was there an unknown mutant gene being passed from one generation of women to the next, one that was leaving them vulnerable to tumours? “We looked at hundreds of genetic markers to see if we could find one that was carried only by women who got cancer. That would tell us where the new cancer gene was located.”

Genetic markers are small pieces of DNA that are found stretched across the 46 chromosomes that make up the human genome. A first attempt was made using 250 of such markers but failed to produce a result. “It was dispiriting,” admitted Stratton.

But the team persisted and developed a second set of 300 different markers. “I came into the laboratory one day and the results of our study were waiting. They clearly showed a piece of DNA on chromosome 13 that tracked women who went on to develop cancer. We had discovered a new breast cancer gene and, for good measure, we had found out where it lay on the human genome. It was a wonderful feeling, though we realised we still had to pinpoint the gene itself.”

> “We did not believe in patenting genes to make profits, however. So we decided to go our own way”

The breakthrough also came with a complication. Stratton’s team had been cooperating with several laboratories in their *BRCA2* hunt, including one in the US. “This group was backed by the company Myriad Genetics who had found the first breast cancer gene, *BRCA1*, and who had taken out a patent on it. We did not believe in patenting genes to make profits, however. So we decided to go our own way.”

So the race to find *BRCA2* began. Initially the prospects for Stratton's team looked poor. Myriad Genetics had already found one such gene. It had the experience and also plenty of funds to back its search for another cancer gene. However, an unexpected ally stepped in when the newly opened Sanger Centre (later renamed the Wellcome Sanger Institute) offered to turn its DNA sequencing prowess to explore the region of chromosome 13 where *BRCA2* was known to reside.

Sanger scientists provided precise details of the millions of units of DNA on that part of chromosome 13. "One morning we went through the most recent data and found a tiny piece of a gene on the chromosome that was missing, a deletion of several DNA units that would have destroyed its function as the gene in which it lay," said Stratton.

> Over the next two months, the team discovered different abnormalities in this gene in different breast cancer families

Crucially women who inherited that deletion in the family they were studying usually went on to develop breast cancer. "That was exactly the sort of thing that we had been looking for," said Stratton. "We had landed right on *BRCA2*. It was an extremely humbling moment."

Over the next two months, the team discovered different abnormalities in this gene in different breast cancer families. "It was incontrovertible evidence that this gene was *BRCA2*," added Stratton. In most families, *BRCA2* plays a role in DNA repair and so helps to prevent the triggering of cancers. In families where the gene is damaged, that protection is lost. The discovery was published in *Nature* and had a dramatically speedy clinical impact. "A woman in one of our families was very worried she would get breast cancer and was considering a double mastectomy. We tested her straightaway and found she had not inherited the mutated gene that ran in her family. That meant we were able to tell her she didn't need the operation," added Stratton.

Since then thousands of others have benefited from screening and treatments that have emerged in the wake of *BRCA2*'s discovery, a point stressed by Clare Turnbull, professor of cancer genomics at the Institute of Cancer Research. "If a woman gets breast cancer, and we find she is a gene carrier, we can treat her for that condition and also offer to operate to remove her ovaries if she's completed her family – because we now know of *BRCA2*'s link to ovarian cancer. Such an operation dramatically reduces the likelihood of women developing ovarian cancer.

In addition, siblings – who might have also inherited a pathogenic gene from a mother or father – can be tested. "For those who test negative, that knowledge relieves anxiety," added Turnbull. "For those who test positive, we can offer breast cancer screening while they are still in their 30s. They can also choose to have a mastectomy." In addition, drugs that can counter the effects of the pathogenic version of *BRCA2* gene have also been developed, added Turnbull.

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In the beginning, breast and ovary cancers formed the main targets of *BRCA2* research. However, more recently, it was found that cases of prostate cancer in men were also linked to the gene, as was

found in the case of Herbert.

“If a man inherits a pathogenic mutation in *BRCA2*, then, when he’s in his early 60s, we now know he will have a 20% chance of developing prostate cancer. That compares with the normal risk for that age of about 3%,” said Professor Rosalind Eeles, at the Institute of Cancer Research. “In addition, those cancers are a lot more aggressive than standard cases of prostate cancer.”

As a result, new European medical guidelines have recently recommended that men over the age of 40 who have a pathogenic *BRCA2* mutation should be offered annual screening for prostate cancer. “We also hope it will become a UK guideline in the near future,” added Eeles.

In addition, Eeles said research showed that prostate cancers in men with *BRCA2* mutations are more likely to spread to surrounding tissue but would respond better to surgery to remove tumours as opposed to using radiotherapy alone. “All this is a consequence of finding *BRCA2* 25 years ago,” she added.

But testing for *BRCA2* can also bring stress, a point made by Dee Gardner. In 2013, after being treated for ovarian cancer, she was urged to have a *BRCA2* test. “It was positive and I was completely sideswiped. I had three children – all young adults then – and I now knew each had a 50–50 risk of carrying a gene that could predispose them to cancer.”

Gardner’s children have since had a *BRCA2* test of their own. However, there was a further problem. “I come from a very large family with lots of cousins and I realised it was up to me to tell them they could also be carrying the gene. It really weighed heavily on me. They needed to be told of the risks,” said Gardner, a social worker who lives in Colchester, Essex, with her husband, Howard.

In the end, Gardner wrote to many of her cousins to pass on the troubling news, but it was a strain. “It was tough. I knew my letter would cause pain. The trouble is that there is no emotional support for people who are put in this situation, and that lack needs to be addressed.”

On the other hand, Gardner’s *BRCA2* status – picked up because she developed ovarian cancer – led her to undergo investigations for signs of breast cancer. “I was found to be in the early stages of a tumour and so elected to have double mastectomy,” she added. “So yes, finding I had the *BRCA2* gene may also have saved my life.”