Heart damage from cancer drugs linked to faulty genes

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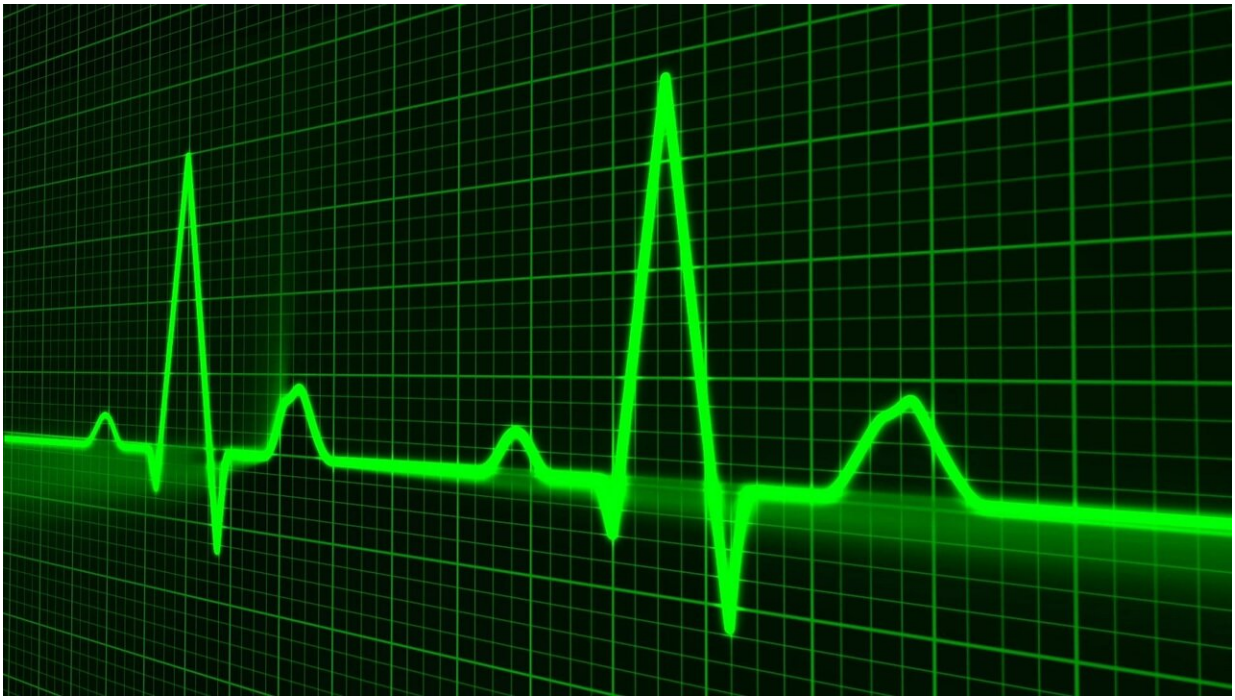

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Scientists have unveiled clues into why some cancer patients develop a serious heart condition after chemotherapy.

The new research, from a team of international scientists led by Imperial College London, Royal Brompton Hospital and the MRC London Institute of Medical Sciences, shows the heart condition may be linked

to a faulty gene called titin.

In the study, published in the journal *Circulation*, the scientists analysed the genes of more than 200 cancer patients—most of who had breast cancer—who had been diagnosed with a type of heart condition called cancer-therapy induced cardiomyopathy, or CCM.

The research team found patients who developed the heart condition were more likely to carry genetic faults linked to cardiomyopathy. In particular, patients were more likely to carry a faulty version of a gene called titin. The faulty titin gene was found in 7.5 percent of CCM patients, compared to 0.7 percent of healthy individuals.

A faulty titin gene is carried by more than half a million people in the UK. The gene is crucial for maintaining the elasticity of heart muscle, and faulty versions are linked to a type of heart failure called dilated cardiomyopathy.

The scientists behind the study say the new insights may help understand why some patients develop CCM, and even identify patients at risk of the condition.

More women affected

Dr. James Ware, senior author of the research from Imperial's National Heart and Lung Institute explains: "More patients than ever are surviving cancer, thanks to advances in treatment over the past decade or so. However we now have a key problem where some patients who have survived cancer are developing serious heart conditions, sometimes within the first year after finishing treatment."

He continues: "Until now, scientists didn't know why some patients developed heart damage, while others didn't. This new study suggests

faulty genes may play a role—and means we could potentially test patients for faulty genes before starting cancer treatment, so that we know which patients are at risk."

CCM affects up to one in ten cancer patients—with more women affected then men, and often strikes between six months and nine years after cancer treatment. The condition is caused by the chemotherapy drugs damaging heart muscle, leaving it unable to pump properly. Although many patients recover, it can lead to heart failure in around ten percent of patients.

Genetic clues

In the new study, funded by the Wellcome Trust, Medical Research Council, National Institute for Health Research and British Heart Foundation, the researchers tested 213 cancer patients with CCM for nine different types of faulty genes linked to the condition. Out of these patients, who were from Spain, the US, and the UK, 124 had breast cancer, 48 had other types of cancer, while 41 were children with acute myeloid leukaemia.

The vast majority of cases of CCM (90 percent) were linked with a type of drug treatment called anthracycline, and more than one in 20 patients (7.5%) were found to carry the faulty titin gene.

In further mouse studies, the team found that anthracyclines increased the risk of heart damage in mice with a faulty version of the titin gene.

Dr. Paul Barton, co-senior author from the Cardiovascular Research Centre at the Royal Brompton Hospital, said: "Although scientists know that anthracyclines are associated with CCM, this is the first time we've also seen a link with faulty genes directly involved in cardiomyopathy. and could enable doctors to potentially prevent the condition from

occurring."

Protecting the heart

Dr. Alexander Lyon, Senior Lecturer in Cardiology at Imperial and Consultant Cardiologist at the Royal Brompton Hospital and co-author of the new study added: "The new field of cardio-oncology is dedicated to helping treat, and ultimately prevent, cancer therapy-induced cardiovascular disease. This research provides a new opportunity to identify individuals at higher risk of developing CCM, and we believe this can lead to doctors being able to assess the individual risk of heart damage for each patient scheduled to receive potentially cardiotoxic chemotherapy. By analysing their genetic risk we could ensure that a patient's heart health is monitored by doctors during and after chemotherapy."

The research team would now like to perform further studies investigating genetic links to CCM in different types of cancer, as most of the patients in the current study had breast cancer. They will also look at patients with different ethnic backgrounds, as most patients in this study were white European.

"You can climb a mountain with a broken heart"

Kreena Dhiman, 39, from Crawley had chemotherapy for breast cancer in 2013, after she was diagnosed age 33. Three years after starting cancer therapy, she was diagnosed with heart failure. She explains:

"The first signs of heart failure were on a holiday to France in 2016, six months after I'd undergone reconstructive surgery following my cancer treatment. I had been pretty fit before my diagnosis, but on this holiday I was finding stairs increasingly tiring, and struggled to ride a bike. At

first, I blamed my breathlessness on the fact I was recovering from surgery.

A few months later I went to see friends in Vancouver, in what I hoped would be a trip of a lifetime, and a chance for my husband and I to celebrate my recovery.

But shortly after arriving, I found myself coughing constantly, and struggling to catch my breath.

By the third day we decided to go the walk in center, they referred me to a University hospital, where despite scores of tests they were unable to work out why I was so breathless, as my lungs were perfectly healthy.

Eventually I was transferred to Vancouver General hospital, after further tests, they called in a heart specialist, who took a scan of my heart. I'll never forget the specialist asking me if I was given a red drug during my chemotherapy. I nodded yes—at this point I was too breathless to speak. I remembered the drug vividly, we used to jest at its toxicity warning on the chemo ward!

He turned to his colleagues and said 'she has heart failure' and I was transferred to an intensive care ward.

I was told the drug I was given to treat my breast cancer—called epirubicin (a type of anthracyclin), can cause heart damage, and this damage may have been slowly getting worse since my cancer treatment.

I was distraught—and immediately assumed heart failure meant I was going to die. I didn't think I was going to make it home alive, and recorded voice notes to my family and friends telling them I loved them, and this was my final goodbye. The days that followed were difficult, both physically and emotionally. My sister flew out to Vancouver to be

with my husband and I and slowly but surely I responded to treatment.

At the time, I was advised that 50% of heart failure patients don't make it beyond 2 years. That statistic scared me more than anything I've heard before. If I'm honest, it still scares me today.

I was also put on a strict zero-salt diet while in hospital, as salt works to retain fluid in the body, not good news for a heart failure patient as it places extra strain on the heart.

After two months in in Canada, I was allowed to fly home with medical assistance.

I referred to Dr. Lyon in his London clinic, who confirmed the chemotherapy drug was the most likely culprit of my heart failure, however there was likely a genetic predisposition that triggered the reaction

My total recovery took around a year, but my heart function is now within a normal range with medication supporting it.

Around a year after my own diagnosis my mother was also diagnosed with heart failure. Genetic tests revealed both of us were found to have mutation in a specific gene which may have triggered the condition, though neither of us carried the faulty Titin gene.

Despite the roller coaster of the last six years, my life is better than ever. My husband and I just celebrated the first birthday of our beautiful daughter Amaala, who was born via a surrogate after we decided to freeze embryos prior to cancer treatment.

And I'm soon to climb the Himalayas to raise money for a charity who raises awareness of breast cancer in younger women, because that is

where my journey began, with a breast cancer diagnosis.

I also want show others that heart failure is certainly not a death sentence, and with support and expert care, you can climb a mountain with a broken heart!"

More information: Pablo Garcia-Pavia et al. Genetic Variants Associated With Cancer Therapy–Induced Cardiomyopathy, *Circulation* (2019). DOI: 10.1161/CIRCULATIONAHA.118.037934

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