Study reveals drug interactions that may reduce mortality in breast cancer patients

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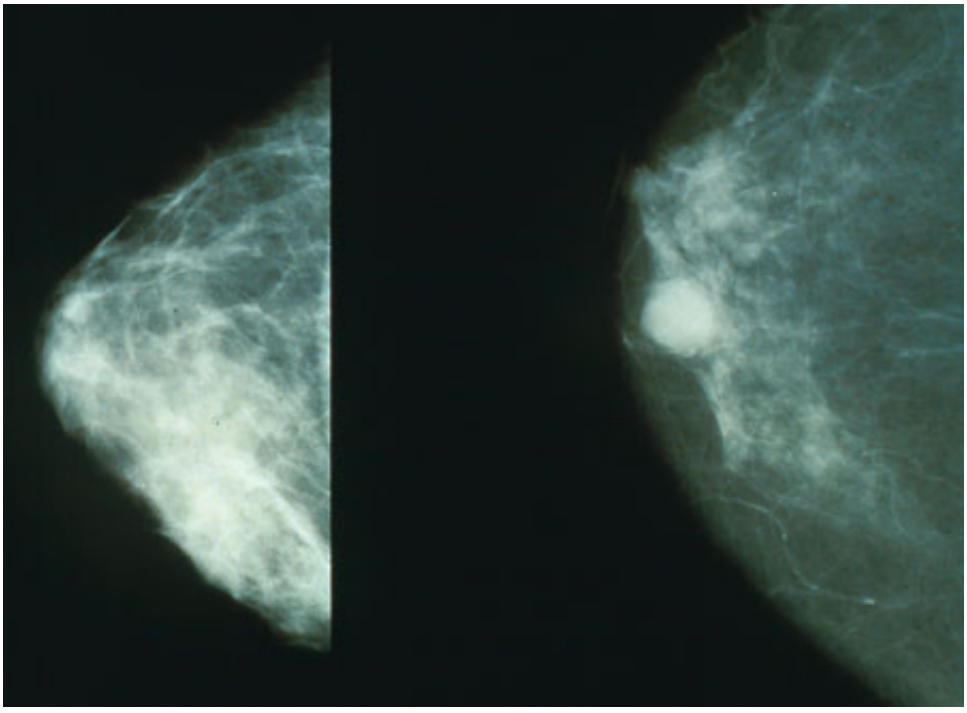

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

Patient health records revealed two drug combinations that may reduce mortality rates in breast cancer patients, according to a study led by researchers at the Stanford University School of Medicine.

The drugs involved were commonly used drugs that turned out to be associated with a longer average survival rate in breast cancer patients.

The study will be published online Dec. 9 in the *Journal of the American Medical Informatics Association*. The lead author is Stanford postdoctoral scholar Yen Low, PhD. The senior author is Nigam Shah, MBBS, PhD, associate professor of medicine and of biomedical data science.

Often, when different drugs are taken together, they can have unexpected side effects. For example, some antibiotics and antifungal drugs can interfere with the effectiveness of birth control pills. It occurred to Shah and his team that the opposite could also be true—that some drug interactions might help patients.

"What if we looked for combinations of drugs that have an accidental beneficial effect?" Shah said.

Combing through records

The researchers decided to comb through a breast cancer database built at Stanford called Oncoshare, which takes de-identified patient information—including tumor and treatment information for each patient—from Stanford Health Care and from the Palo Alto Medical Foundation and links it to patient outcomes in the California Cancer Registry.

The team searched for drugs that patients just happened to be taking and that were statistically associated with better outcomes. "By integrating different kinds of data, we can ask questions we couldn't ask before. Usually, you don't find both survivorship data and all the different kinds of drugs and other treatments patients get all in the same place," said Allison Kurian, MD, associate professor of medicine and of health research and policy.

"We looked at all the noncancer drugs that breast cancer patients were on," said Shah. "People have other things going on in life. They might

have hypertension, they might have high cholesterol or diabetes. They would be taking drugs for those as well. So the question we were asking was, do any of the drugs they are taking associate with better outcomes for breast cancer?"

The team looked at data from nearly 10,000 adult women diagnosed with breast cancer between 2000 and 2013, of whom about 12 percent died within five years of the diagnosis. The team examined 294 drugs in more than 43,000 pairwise combinations. Specifically, they looked for combinations of drugs in which the beneficial effect on survival was greater than the effect of either drug by itself.

"So we ran the analysis, and we found a few drug combinations that seemed to associate with better survival," said Shah.

'How do we know it's true?'

Specifically, there were three pairs of drug types: anti-inflammatory drugs, such as aspirin or naproxen, and blood-lipid modifiers, such as statins; lipid modifiers and drugs such as fluticasone used to treat asthmalike conditions; and anti-inflammatories and hormone antagonists—typically, drugs that suppress the synthesis of estrogen.

"But how do we know it's true, and not just an association?" said Shah.

The researchers needed to look for confirmation in a data set they had not yet examined. To do so, they turned to Shah's former student Andrew Radin, a co-author of the paper and co-founder of a company called twoXAR that searches for drug interactions using gene-expression data. Radin's company looks for common molecular pathways that might account for drug pairs with apparent synergistic effects, searching for drug-protein interactions in the company's database.

Said Shah, "So I asked Andrew, 'If I give you two drugs and a disease, can you tell me if there is any molecular-level evidence that would lead you to believe that, yes, these drugs might have a beneficial effect in treating this disease?' So we gave them our list of three drug pairs, and they looked at the protein targets for all the drugs."

Two of the three drug pairs showed a likely molecular mechanism that a reasonable person might think had to do with survival in breast cancer, the study said. These were anti-inflammatories and lipid modifiers, and anti-inflammatories and anti-cancer hormone antagonists.

A joint effort

"This study is a nice example of an analysis spanning multiple data modalities. It's the kind of thing that can only happen at Stanford," said Shah, pointing out how his lab worked with Oncoshare, twoXAR, oncologists and statisticians to bring the study off.

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

"It's a proof of principle that this kind of data mining has strong practical clinical applications," said Kurian. With electronic health records, she said, the challenge has been getting the data organized in a way that allows fruitful explorations like this one.

The key, said Shah, is to ask why these drugs and their protein targets have something to do with breast cancer and to leverage that information for better treatment. "This is a holistic look at the data—EHR, gene expression, protein targets of drugs—all in one analysis," he said.