Medical Xpress

Ultrasound and microbubbles flag malignant cancer in humans

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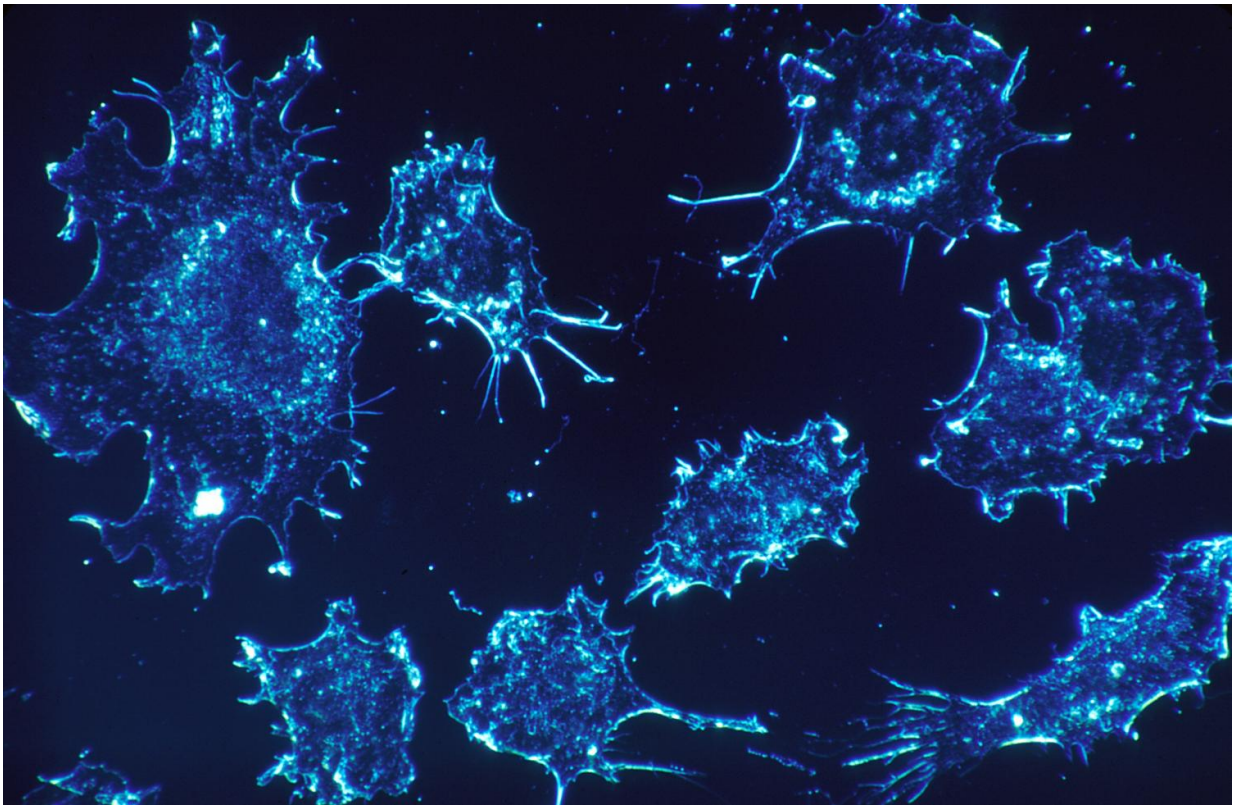

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A team led by researchers from the Stanford University School of Medicine has demonstrated a way to diagnose cancer without resorting to surgery, raising the possibility of far fewer biopsies.

For this first-in-humans clinical trial, women with either breast or ovarian tumors were injected intravenously with microbubbles capable of binding to and identifying cancer.

Jürgen Willmann, MD, a professor of radiology at Stanford, is lead author, and Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology, is the senior author of the study, which was published online March 14 in the *Journal of Clinical Oncology*.

For the study, 24 women with ovarian tumors and 21 women with breast tumors were intravenously injected with the microbubbles. Clinicians used ordinary ultrasound to image the tumors for about a half-hour after injection. The high-tech bubbles clustered in the blood vessels of tumors that were malignant, but not in those that were benign.

The ultrasound imaging of patients' bubble-labeled tumors was followed up with biopsies and pathology studies that confirmed the accuracy of the diagnostic microbubbles.

What are microbubbles?

Medical microbubbles are spheres of phospholipids, the same material that makes up the membranes of living cells. The bubbles are 1 to 4 microns in diameter, a little smaller than a red blood cell, and filled with a harmless mixture of perfluorobutane and nitrogen gas.

Ordinary microbubbles have been approved by the Food and Drug Administration and in clinical use for several years now. But such microbubbles, a kind of ultrasound "contrast agent," have only been used to image organs like the liver by displaying the bubbles as they pass through blood vessels. Up to now, the bubbles couldn't latch onto blood vessels of cancer in patients.

Safe but better microbubbles

The microbubbles used in this study were designed to bind to a receptor called KDR found on the tumor blood vessels of cancer but not in healthy tissue. Noncancerous cells don't have such a receptor. Under ultrasound imaging, the labeled microbubbles, called MBKDR, show up clearly when they cluster in a tumor. And since benign breast and ovarian tumors usually lack KDR, the labeled microbubbles mostly passed them by.

In this small, preliminary safety trial, the technique appeared to be both safe and very sensitive, said Willmann, who is chief of the Division of Body Imaging at Stanford. And it also works with ordinary ultrasound equipment. "So, there's no new ultrasound equipment that needs to be built for that," he said. "You can just use your regular ultrasound and turn on the contrast mode—which all modern ultrasound equipment has."

Willmann said now that the phase-1 trial has shown that the MBKDR contrast agent is safe for patients, his team is moving forward in a larger phase-2 trial. In that trial, the team will measure how well the combination of MBKDR and ultrasound differentiate cancer from noncancer in breast and in ovarian tumors. The team will also try to find out how small a tumor can be imaged using KDR microbubbles. Because the diagnostic approach can, in principle, be used with any kind of cancer that expresses KDR, they plan to image pancreatic cancer tumors as well.

One of the advantages of MBKDR, Willmann said, is that the bubbles remain attached to the tumors for several minutes and as long as half an hour—the longest time tested in the trial. That should give clinicians time to image both breasts or ovaries without having to start over with a new injection of contrast agent.

If all goes as hoped, the KDR microbubbles could improve diagnoses and reduce unnecessary surgeries in women suspected of having breast or ovarian cancer.

"The difficulty with ultrasound right now," Willmann said, "is that it detects a lot of lesions in the breast, but most of them are benign. And that leads to many unnecessary biopsies and surgeries."

Distinguishing benign from malignant tumors with harmless ultrasound imaging could save millions of patients from biopsies they don't need, Willman said. "To decrease those unnecessary biopsies and surgeries would be a huge leap forward," he said. "We could make ultrasound a highly accurate screening technology that is relatively low cost, highly available and with no radiation." And since ultrasound technology is accessible almost everywhere, he said, the technology could potentially help patients all over the world.

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.

More information: Jürgen K. Willmann et al. Ultrasound Molecular Imaging With BR55 in Patients With Breast and Ovarian Lesions: First-in-Human Results, *Journal of Clinical Oncology* (2017). DOI: 10.1200/JCO.2016.70.8594

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