In lung cancer, not all HER2 alterations are created equal

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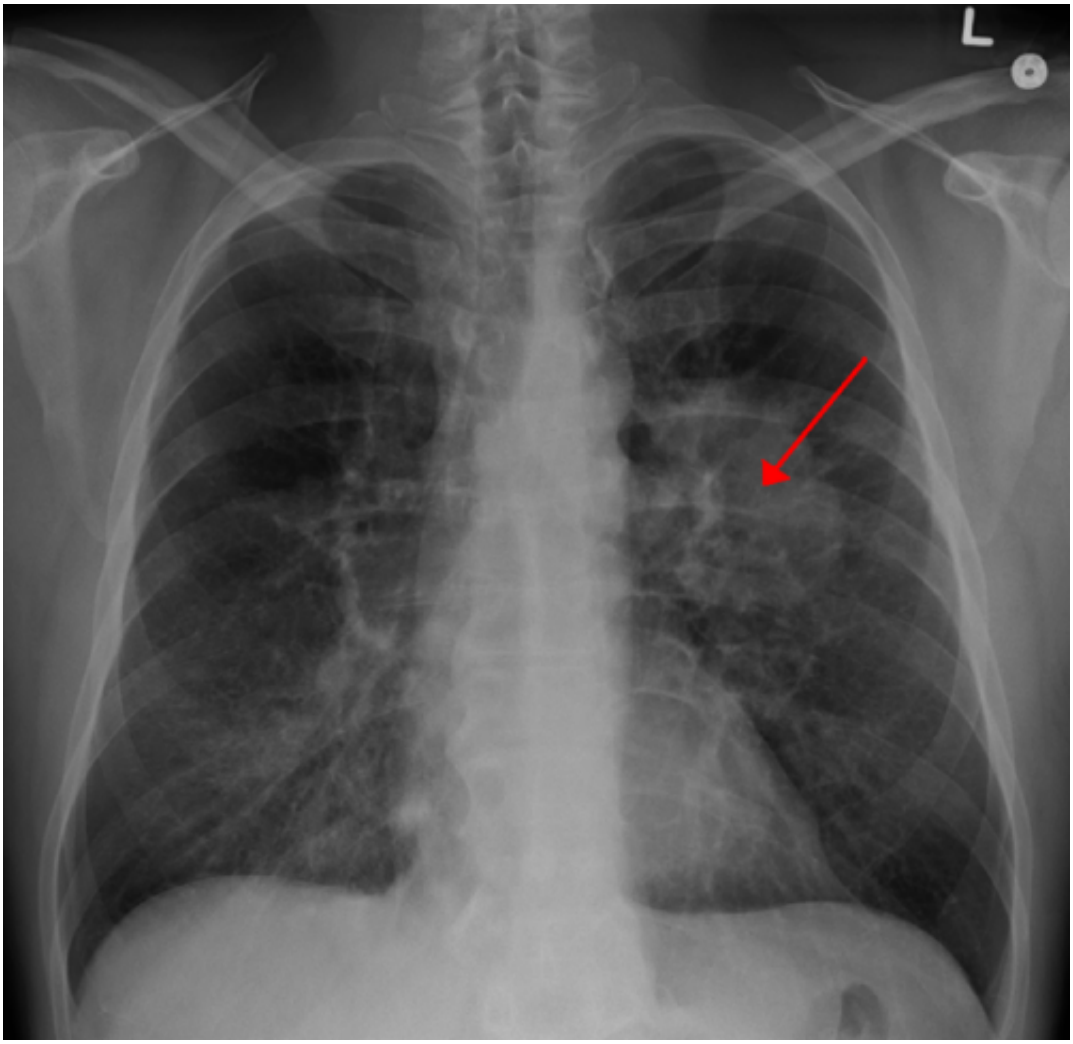

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

A joint study by University of Colorado Cancer Center and Memorial Sloan Kettering Cancer Center published in the *Journal of Thoracic Oncology* shows two distinct causes of HER2 activation in lung cancer: mutation of the gene and amplification of the gene. In patient samples of lung adenocarcinoma, 3 percent were found to have HER2 amplification and another 3 percent were found to have HER2 mutation. No samples were found to have both. These distinct causes of HER2 positivity imply the use of different targeted therapies to combat these related but possibly distinct diseases.

"The question we wanted to answer was if these two genetic alterations tend to be found together. The fact that they are not overlapped means that we must test lung tumors separately for both amplification and mutation of HER2 or risk missing patients who might benefit from HER2-targeted therapy," says Marileila Garcia, PhD, CU Cancer Center investigator and professor of Medicine at the CU School of Medicine.

The finding is counterintuitive in light of the opposite finding with the closely related gene EGFR, which is a genetic driver of about 10 percent of lung cancers in the United States and 35 percent of lung cancers in East Asia.

"These genes belong to the same family," Garcia says. "EGFR can also be called HER1."

In EGFR-associated non-small cell lung cancer, mutation and amplification are found together about 80 percent of the time.

"Because of this, a test for amplification is a surrogate test for mutation, and vice versa," Garcia says.

This study shows that the opposite is true in HER2, in which it appears amplification and mutation are not commonly found together.

Therefore, it also expands the potential number of patients carrying a HER2 dependent lung tumor.

The study also takes place in the context of the work exploring the role of HER2 in breast cancer. Approximately 20 percent of breast cancers harbor HER2 amplification, which make these breast tumors susceptible to treatment with anti-HER2 therapies including trastuzumab and lapatinib. These therapies, the first an antibody and the second of a class called tyrosine kinase inhibitors (TKIs), reduce the ability of a target gene to manufacture the protein it encodes. In fact, some oncologists are choosing to prescribe these and other targeted therapies approved to target HER2-associated breast cancer to patients with HER2-associated lung cancer.

"However, it may be that gene amplification is more susceptible to treatments based not on TKIs but on antibodies," Garcia says.

In other words, knowing that amplification or mutation is the cause of HER2-associated lung cancer may point to different treatment options.

Overall, "HER2-positive lung cancer may not be an adequate term," writes the paper. Instead, beneath identifying this gene's involvement, it may be useful to define the mechanism that creates this involvement.

"Whether the overexpression of HER2 in these lung cancers is due to mutation or to amplification may make help us conceptualize what we now call HER2 lung cancer as two related but distinct diseases," Garcia says.

More information: Bob T. Li et al. HER2 Amplification and HER2 Mutation Are Distinct Molecular Targets in Lung Cancers, *Journal of Thoracic Oncology* (2015). DOI: 10.1016/j.jtho.2015.10.025