Lung Cancer and ERBB2 Exon 20 Insertion Mutations

This material will help you understand:

- the basics of lung cancer
- the role of the ERBB2 gene in lung cancer
- if there are any drugs that might work better if you have certain changes in the ERBB2 gene

What is lung cancer?

Lung cancer is a type of cancer that starts in the lungs. It is the number one cause of cancer deaths in the world. Doctors name lung cancers based on how lung cells look under a microscope. There are two main groups of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Most people with lung cancer have NSCLC. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are types of NSCLC.

What causes lung cancer?

Cancer is a result of changes in our genes. Genes contain the instructions for making proteins. Changes in genes, called mutations, may result in changes in proteins. These changes may cause cells to grow out of control which could lead to cancer.

The biggest risk factor for lung cancer is exposure to cigarette smoke. But, not all lung cancers are due to smoking. Other risk factors include exposure to radon gas, asbestos and pollution.

What are the most common current treatments for lung cancer?

Doctors may treat lung cancer using one or more of these options:

- **Surgery** – operation that removes as much of a cancer tumor as possible.

- **Radiation** – treatment that uses high-energy beams to kill cells in the area where the cancer is growing.

- **Traditional chemotherapy** – drugs that kill growing cells. All cells grow. Cancer cells usually grow faster than most healthy cells. So, these drugs kill more cancer cells. But because these drugs kill healthy cells too, this can cause unwanted side effects.

- **Precision medicine therapy** – treatments that target proteins involved in cancer. These therapies mainly kill cancer cells and not healthy cells. This also means you may have fewer side effects. Two types of precision medicine therapies are:

    - **Small molecule therapy** – mainly acts on cells with specific protein changes. Small molecule therapy uses drugs to target those proteins. Genetic testing can tell if your cancer cells have protein changes that can be targeted. Small molecule therapy is a type of targeted therapy.

    - **Immune-based therapy** – works with your body's defense system to fight cancer. These can mark cancer cells so they are easier for your immune system to find.

Can I pass on mutations found in my cancer cells to my children?

You cannot pass on mutations found only in your cancer cells to your children.

How well does cancer drug treatment work?
After a while, your cancer cells may stop responding to the drug(s). This means your cancer may start to grow again. Your doctor will do regular checkups to watch for this. If the cancer starts to come back, your doctor can try another drug or treatment.

What is ERBB2?
ERBB2 is the name of both a gene and a protein. The ERBB2 gene contains the instructions for making the ERBB2 protein. The ERBB2 protein used to be called HER2. It is a member of the ERBB family of proteins. These proteins are a group of human epidermal growth factor receptors. Receptors are proteins that are often in cell membranes. The cell membrane is the outside surface of a cell. Receptors have three basic parts. One part is outside the cell, one part crosses the cell membrane, and one part is inside the cell. Receptors receive signals from outside the cell. These signals may tell the cell to grow, divide, or die. These signals are turned on and off as needed.

In healthy cells, ERBB2 pairs with another ERBB receptor. When the receptors pair, the outside parts can receive a signal. This activates, or turns on, the parts of the proteins inside the cell.

When the inside parts are on, the receptors can turn on other proteins. These other proteins are usually in pathways. Proteins in pathways work together to do specific jobs within the cell.

ERBB2 can turn on different cell growth and survival pathways. ERBB2 pairs with different ERBB family members to turn on different pathways. The healthy cell image shows the proteins in a pathway turned on by a pair of ERBB2 proteins (Figure 1A). RAS, RAF, MEK and ERK are proteins in this growth pathway. When the signal reaches ERK, it turns on genes in the nucleus that help cells grow. When the signal stops, the ERBB2 proteins turn off and separate (Figure 1B).

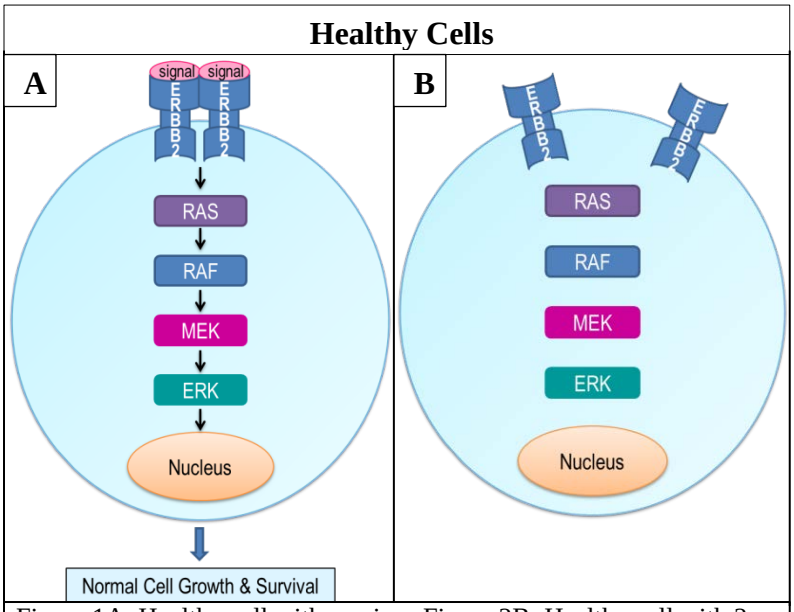


Figure 1A: Healthy cell with a pair of activated ERBB2 receptors and the proteins in the pathway they turn on.

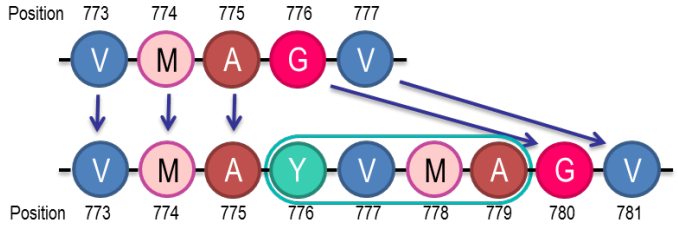
Figure 2B: Healthy cell with 2 ERBB2 proteins. The receptors are not on, so they cannot pair to turn on this pathway.

How do mutations in proteins affect pathways?
If a mutation affects one or more proteins in a pathway, the proteins may not be able to be turned on or off as expected. This can cause cells to grow out of control and lead to cancer.

How common are ERBB2 mutations in lung cancer?
About 1 in 25 non-small cell lung cancers (NSCLCs) have a change in the ERBB2 gene that changes the ERBB2 protein. ERBB2 mutations are most common in nonsmokers with adenocarcinoma, a type of NSCLC. But, ERBB2 mutations can happen in all types of NSCLC, regardless of smoking status.

What are ERBB2 exon 20 insertion mutations?
ERBB2 exon 20 insertions are specific variations that change the ERBB2 protein. An exon is a section of a gene. The ERBB2 gene has 27 exons. Each exon makes a piece of the ERBB2 protein. Proteins are long chains of amino acids. The ERBB2 protein has 1,255 amino acids. The inside part of the protein starts at amino acid 720 and goes to the end of the protein chain. Exon 20 makes amino acids 770-831.

ERBB2 proteins with insertion mutations have extra amino acids added. Most exon 20 insertions occur between amino acids 775 and 781. The image below is an example of an ERBB2 exon 20 insertion, A775-G776InsYVMA. The amino acids in the green oval are only in ERBB2 with this mutation.



ERBB2 without mutation

ERBB2 with mutation

What is the effect of these mutations?
These mutations are in the part of ERBB2 that is inside the cell. When the inside part is on, ERBB2 can turn on other proteins. In most cells with these mutations, the signal is not needed. The inside part of ERBB2 is always on. This means cells with these mutations could grow out of control, which can lead to cancer (Figure 2).

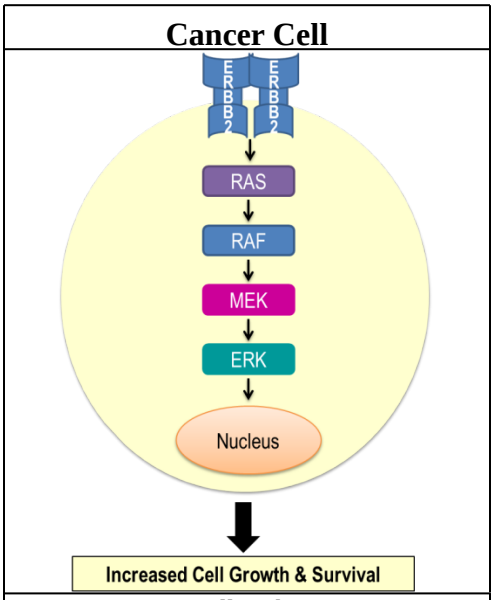


Figure 2: Cancer cell with an ERBB2 exon 20 insertion. ERBB2 is always on (no signal needed) so cells may grow out of control.

Are there targeted therapies for ERBB2 exon 20 insertions?
At this time, it is unclear if any drugs target ERBB2 with exon 20 insertions. But, scientists are working on new potential therapies all the time. So, you should talk to your doctor about your treatment options.

What if I have a different mutation in ERBB2 or "no mutation"?
Your cancer cells might have mutations in this gene or in other genes that were not tested. Your genetic test results will still help your doctor determine the best treatment for you.