Lung Cancer and the PIK3CA E545K Mutation

This material will help you understand:

- the basics of lung cancer
- the role of the PIK3CA gene in lung cancer
- if there are any drugs that might work better if you have certain changes in the PIK3CA 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 PIK3CA?
PIK3CA is the name of both a gene and a protein. The PIK3CA gene contains the instructions for making the PIK3CA protein. PIK3CA combines with another protein to form a PI3K protein complex. PI3K is short for "P-I-3-kinase." PI3K is part of several different pathways. Proteins in pathways work together to do specific jobs within the cell. The healthy cell image (Figure 1) shows examples of proteins and pathways activated by PI3K. PI3K helps control metabolism, new blood vessel formation, and cell growth and survival.

In healthy cells, signals from outside the cell turn proteins "on" or "off" as needed. As the signal reaches proteins in the pathway, the proteins are turned on. When PI3K receives the signal, it can activate AKT1. AKT1 can then turn on other proteins, such as IKK, mTOR, and NOS3. Each of these proteins in turn activates a different pathway.

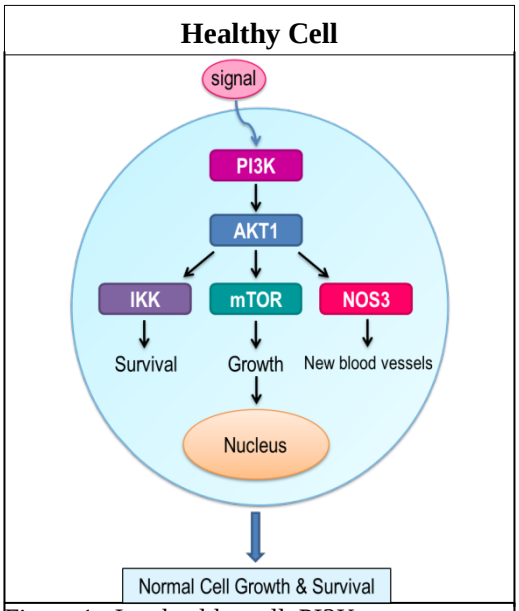
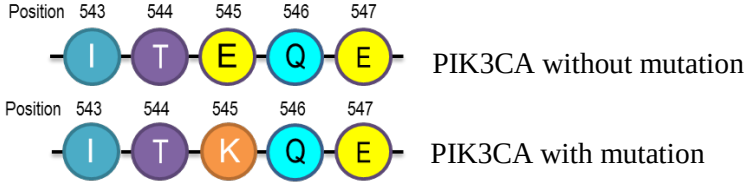


Figure 1: In a healthy cell, PI3K turns on AKT1 which turns on other pathways. The proteins pass the signal along to activate each pathway.

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 PIK3CA mutations in lung cancer?
About 1 in 50 non-small cell lung cancers (NSCLCs) have a mutation in the PIK3CA gene that changes the PIK3CA protein. PIK3CA mutations are most common in squamous cell carcinoma, a type of NSCLC. These mutations are found in smokers and nonsmokers.

What is the PIK3CA E545K mutation?
PIK3CA E545K is a specific variation in the PIK3CA protein. Proteins are long chains of amino acids. The PIK3CA protein has 1,068 amino acids. PIK3CA with no mutation at amino acid position 545 has a glutamic acid, or E for short. The amino acid at position 545 in PIK3CA with the E545K mutation is a lysine, or K for short.



What is the effect of this mutation?
PI3K is made up of PIK3CA and another protein. In cells with the E545K mutation, PI3K can always turn on AKT1. This can cause cells to grow out of control and lead to cancer.

Are there targeted therapies for PIK3CA E545K?
At this time, it is unclear if any drugs target PIK3CA E545K. 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 PIK3CA 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.

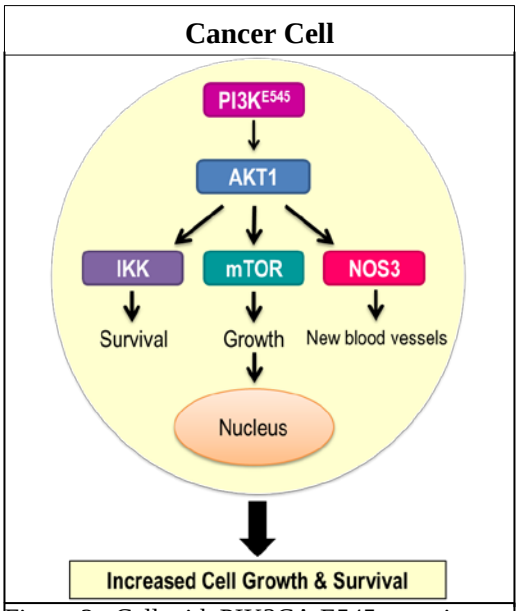


Figure 2: Cell with PIK3CA E545 mutation. PI3K is always on, even without any signal. This can lead to increased cell growth and survival.