Lung Cancer and the PTEN R233* Mutation

This material will help you understand:

- the basics of lung cancer
- the role of the PTEN gene in lung cancer
- if there are any drugs that might work better if you have certain changes in the PTEN 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 PTEN?
PTEN (pronounced “P-tĕn) is the name of both a gene and a protein. The PTEN gene contains the instructions for making the PTEN protein. PTEN is a tumor suppressor protein. In healthy cells, proteins are turned "on" or “off” as needed. PTEN turns off certain proteins. These proteins are usually in pathways. Proteins in pathways work together to do specific jobs within the cell.

Signals from outside the cell can also turn proteins "on" or “off” as needed. As the signal reaches proteins in the pathway, the proteins are turned on. When the signal stops, the proteins turn off.

The healthy cell image shows an example of how PTEN works. PTEN can stop the PI3K protein from turning on other proteins, even when the signal is present.

Figure 1A shows proteins and pathways activated, or turned on, by PI3K. When PI3K receives the signal, it can activate AKT1. AKT1 can then turn on other proteins and pathways. In Figure 1B, PTEN stops PI3K from turning on AKT1 and the other pathways. Turning on and off pathways is a normal function of cells.

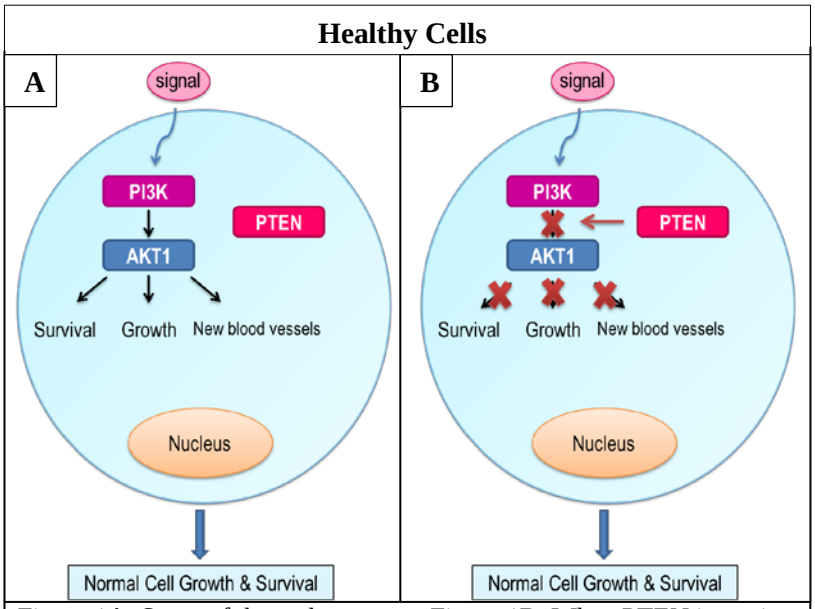


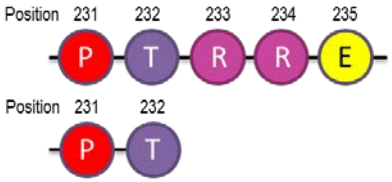
Figure 1A: Some of the pathways turned on by PI3K. The proteins pass the signal to activate each pathway.

Figure 1B: When PTEN is on, it stops PI3K from turning on AKT1 and the other proteins and pathways.

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 PTEN mutations in lung cancer?
About 1 in 20 non-small cell lung cancers (NSCLCs) have a mutation in the PTEN gene that changes the PTEN protein. PTEN mutations are usually in smokers with squamous cell carcinoma, a type of lung cancer.

What is the PTEN R233* mutation?
PTEN R233*is a specific variation in the PTEN protein. Proteins are long chains of amino acids. Full-length PTEN has 403 amino acids. In PTEN with no mutation, the amino acid at position 233 is an arginine, or R for short. PTEN with the R233* mutation has no amino acid at position 233. The protein stops after 232 amino acids. The cell does not make the rest of the protein



PTEN without mutation

PTEN with mutation

What is the effect of this mutation?
In cells with the R233* mutation, PTEN does not work. That means PTEN cannot stop PI3K from turning on AKT1. So, AKT1 is on more than it should be in these cells. This could cause cells to grow out of control and lead to cancer.

Are there targeted therapies for PTEN R233*?
At this time, it is unclear if any drugs target PTEN R233*. 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 PTEN 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.