

## Lung Cancer in People Who Have Never Smoked

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### Introduction

Lung cancer is the leading cause of cancer death for both men and women in the United States, and globally it is the leading cause of cancer death in men and the second leading cause in women.<sup>1</sup> Smoking is the most common cause of lung cancer, but there are many people who have never smoked who develop lung cancer. Lung cancer in people who have never smoked is more common in Asia, especially women.<sup>1</sup> The causes of lung cancer in people who have never smoked are not well understood. Lung cancer treatments can work differently in people who have never smoked.

#### *Frequency*

People who have never smoked (“never-smokers”) are defined as people who have smoked < 100 cigarettes in their lifetime. The information about how many people develop cancer each year comes from cancer registries that have information about the type of cancer and age of the person, but no information may be available about smoking history. Therefore, it is unknown exactly how many people with lung cancer do or do not smoke. We can make estimates though about how many people with lung cancer have developed the disease without a smoking history.

Worldwide, approximately 15% to 20% of men with lung cancer, and 50% of women with lung cancer, are people who have never smoked.<sup>1</sup> In the United States, approximately 1 in 10 men, and 1 in 5 women, with lung cancer are people who have never smoked.<sup>2</sup> The number of men who have never smoked and who develop lung cancer each year is similar to the number of men who develop multiple myeloma, a cancer of the immune system. The number of women who have never smoked and who develop lung cancer each year is similar to the number of women who develop cervical cancer.

It is unknown whether the frequency of developing lung cancer is increasing in people who have never smoked. A study in Swedish construction workers who had never smoked showed an increased frequency of lung cancer in the 1990s compared with the 1970s.<sup>3</sup> In the United States, more women who had never smoked died of lung cancer in the 1980s and 1990s than in the 1960s.<sup>4</sup> However, there is no other evidence of an increased incidence of lung cancer in people who have never smoked, and some studies show no increase.<sup>5-6</sup> These types of studies are difficult to do because we do not have smoking information available in the same databases that capture information about the number of patients who develop lung cancer. There is a sense among doctors who treat lung cancer that the number of people with lung cancer who have never smoked is increasing. Studies are being done to try to get a better answer to that question, but at this time it remains uncertain.

### *Characteristics*

There are several known differences between lung cancer in smokers and people who have never smoked, including the specific type of cancer. Lung cancer in smokers frequently is often a type called “small cell lung cancer” or a form of “non-small cell lung cancer (NSCLC)” known as “squamous cell carcinoma”. Adenocarcinoma, a different type of NSCLC, is more common in people who have never smoked.<sup>1,7</sup> However, people with a smoking history can also develop adenocarcinoma of the lung and those who have never smoked are rarely diagnosed with squamous cell lung cancer or small cell lung cancer. The only way to know what kind of lung cancer it is for sure is to have a biopsy that is examined by a pathology doctor.

It is also known that lung cancer in people from certain racial/ethnic groups is more often seen in never-smokers than in other racial groups. This is true for people of Asian ancestry and Hispanics.<sup>8-10</sup> Most of the risk is seen in women. We know that the percentage of women with lung cancer who have never smoked is higher than the percentage of men with lung cancer who have never smoked.<sup>2</sup> The reason for these differences is not known. People are looking at air pollution as a cause of lung cancer in never-smokers.

Tumors from patients who have never smoked frequently have different changes in the DNA than the tumors from smokers, including changes in a protein known as the epidermal growth factor receptor (EGFR).<sup>11-16</sup> Tumors with specific changes in the EGFR protein are more likely to shrink when treated with drugs that attack the EGFR protein, (such as erlotinib, gefitinib and afatinib). Another change that is more common in people with no smoking history who develop lung cancer is with the Anaplastic Lymphoma Kinase (ALK) gene.<sup>17-18</sup> The drugs crizotinib, ceritinib and alectinib are used to treat lung cancer patients who have the ALK gene rearrangement.<sup>19</sup>

Other changes in DNA are frequently different between lung cancer tumors from smokers and people who have never smoked, and the major DNA change that is important for the cancer can be identified in approximately half of patients in research studies. Most commonly, patients have only a single major change in the DNA, and a patient with a change in the EGFR gene usually

does not also have an ALK gene rearrangement. Testing for these DNA changes is now considered standard for patients who have been diagnosed with non-small cell lung cancer, especially adenocarcinoma, to help guide treatment and better understand the disease in each individual. There are lung cancer patients who have never smoked who do not have any of these gene mutations. However, it is important that testing is done to look for EGFR, ALK and ROS1 at a minimum in lung cancer patients who have never-smoked. The number of other gene mutations or gene rearrangements that can lead to changes in treatment are rapidly growing. In addition to EGFR, ALK and ROS1 we now can look for changes in BRAF, RET, MET, and HER2 and can offer specific “targeted” therapy when identified in tumors of patients with metastatic disease. These gene changes can also be seen in patients with a smoking history who develop lung cancer, but they seem to be more common in patients without a smoking history.

### *The Causes*

The causes of lung cancer in people who have never smoked are unknown, but several factors may increase the risk (Table 1).<sup>20</sup> Second hand smoke may cause 20% of the lung cancers in people who have never smoked<sup>21-22</sup> Air pollution may cause 5% of cases of the disease.<sup>23</sup> Indoor air pollution, such as fumes from cooking oil and smoke from burning coal, may increase lung cancer risk, especially in Asia.<sup>24</sup>

Radon is a colorless, odorless, radioactive gas that occurs naturally in some parts of the United States and other countries. Some homes have high levels of radon, and this can be tested with home kits. People who live in homes with high levels of radon are at a higher risk of developing lung cancer, whether or not they smoke.<sup>25-26</sup>

Jobs that expose people to toxic substances, such as uranium, asbestos, chromium, and arsenic, may increase the risk of developing lung cancer.<sup>27-29</sup> Arsenic may be present in drinking water in some areas such as Taiwan and Chile.<sup>30-31</sup> Nutritional deficiencies may contribute to the development of cancer, and people who eat more fruits and vegetables may be at lower risk for developing lung cancer.<sup>32-35</sup>

Lung damage from radiation therapy may increase the risk of developing lung cancer. Furthermore, lung cancer risk may be increased in people who have the human papilloma virus, but not everyone agrees with that risk.<sup>36</sup> At this time there is no proof that human papilloma virus causes lung cancer. People with family members who have lung cancer have a slightly higher risk of developing lung cancer, but the magnitude and cause of this risk are unknown.<sup>20, 37-40</sup> Research is being done to try to find what changes in the DNA (genes) may make certain families at higher risk for lung cancer. So far we don't know any DNA changes that are definitely linked to a higher risk of lung cancer in families and we don't have a test to help people know if they are at risk. This research is ongoing.

**Table 1. Possible Causes of Lung Cancer in People Who Have Never Smoked**

Second hand smoke
Radon exposure
Other toxins (asbestos, chromium, or arsenic)
Dietary factors (diet deficient in fruits and vegetables)
Air pollution (including cooking fumes)
Radiation therapy to the chest
Other lung diseases such as idiopathic pulmonary fibrosis
Human papilloma virus (controversial)
Other family members with lung cancer
Differences in ability to fix DNA damage

## Treatment of Lung Cancer in People Who Have Never Smoked

People with lung cancer who have never smoked may live longer, but may or may not respond better to chemotherapy, than smokers with lung cancer. Basic treatment usually is similar for people with lung cancer whether or not they have a smoking history.

People who have never smoked and who have lung cancer are more likely to have changes in specific genes. Though we do not know what causes the changes, we do know that specific gene changes can be the driving force in a cancer. These gene changes are not seen in the normal cells from a person with lung cancer, only in the cancer cells.

The gene changes we know the most about that are more common in the lung cancer of people who are never smoked are in the genes Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK) and ROS1. In recent years more gene changes that can be the driving force behind lung cancer in never smokers have been discovered. There are specific treatments available for people with lung cancer with changes in some of these genes such as erlotinib, gefitinib or afatinib for EGFR gene mutations and crizotinib, ceritinib or alectinib for ALK gene changes.<sup>13-14</sup> Crizotinib is also active in ROS1. In addition to EGFR, ALK and ROS1 we now can look for changes in BRAF, RET, MET, and HER2 and can offer specific “targeted” therapy when identified in tumors of patients with metastatic disease. Specific BRAF inhibitors approved for use in melanoma including vemurafenib or the combination of dabrafenib/trametinib are active with many BRAF mutations. HER2

active drugs include afatinib and trastuzumab. Multiple drugs are active for RET including cabozantinib and vandetinib and cabozantinib is also active for MET exon 14 splice site variations, as is crizotinib.

For most people diagnosed with stage IV (also called metastatic or advanced stage) non-small cell lung cancer the first treatment is chemotherapy. Chemotherapy can also work very well for patients with tumors with specific gene mutations; however, if we find the gene mutation before chemotherapy is started we usually start with a drug “targeted” to treat the gene mutation. It is very important for all patients with advanced stage lung cancer, especially patients who are never-smokers where it is more common, to have their tumor tested for the gene changes.

Patients with metastatic lung cancer who have specific EGFR gene changes should receive erlotinib, gefitinib, or afatinib as the initial treatment, even before the typical chemotherapy regimen, based on studies that have shown that they have a higher chance of shrinking the tumor than chemotherapy for these patients.<sup>13,41-42</sup> People who start therapy with a “targeted” drug also have a longer time before the cancer starts to regrow and new treatment is needed. Chemotherapy can be further delayed with the approval of osimertinib for patients who have tumors with EGFR mutations who have initially responded to an EGFR drug and then became resistant due to a resistance mutation called T790M in EGFR. For ALK positive tumors we now have 3 drugs approved which can be used in sequence and many others are in development.

Erlotinib is not usually added to chemotherapy because the results of combining chemotherapy and erlotinib or gefitinib are not better than giving the chemotherapy alone as the first course of treatment. Recent studies looked at whether or not to continue the “targeted” drug after it stops working as well. Usually at that time chemotherapy is started and the question was whether the targeted drug should be continued when chemotherapy is started. The recent IMPRESS trial showed that it is not good in the majority of patients to continue the targeted drug when chemotherapy is started. We now also have 3<sup>rd</sup> generation EGFR targeted drugs like osimertinib that work for the majority of patients (especially if the T790M mutation has developed) when the initial drug (erlotinib, gefitinib or afatinib) stop working. Current research is also evaluating whether erlotinib or gefitinib may help prevent the return of cancer in people with early stage lung cancer that has been removed with surgery. So far the studies have not proven that erlotinib or gefitinib after surgery leads to improved chance of cure. There are studies being done in Asia and the United States though to explore that question.

For patients who have the ALK gene rearrangement (most common in lung cancer patients who have never smoked), the drug crizotinib is now available to be given either after completion of chemotherapy in patients with metastatic non-small cell lung cancer, or before the chemotherapy is started.<sup>42</sup> We know that crizotinib works better than chemotherapy as the first treatment in patients with the ALK gene rearrangement in their tumor.<sup>43</sup> In 2014 the drug ceritinib (LDK378) was approved in the United States for patients with tumors with

ALK gene rearrangements whose tumor was growing after the use of crizotinib.<sup>44</sup> Alectinib was approved in 2015 for patients after crizotinib and there are studies to determine if it is better to start with alectinib instead of crizotinib. There are now many other drugs being developed for use in ALK+ lung cancer.

Other mutations that can be the driving force behind lung cancer and offer other treatment options if they are found are also being investigated.

Many other gene changes that can lead to lung cancer have been discovered in the past few years as outlined above.<sup>43-44</sup> Some of these are also known to be cancer causing in other cancers like melanoma (BRAF mutations) and many have other targeted therapy available (HER2 mutations) as outlined above. Regardless of smoking status, the gene mutation profile of a lung cancer is now important for deciding on the best treatment. The gene mutations that have specific therapies are more common in cancer in never smokers.

Many of the exciting developments in lung cancer starting in 2015 are related to immune targeted therapy. Those drugs have been shown to work in lung cancer regardless of smoking history, but perhaps less in patients with no smoking history. Efforts to get immune therapy to work in patients with limited smoking history are ongoing with multiple combination drug studies. At this point it is standard to offer immune therapy such as nivolumab or pembrolizumab to patients who have previously received chemotherapy and have developed progression of disease.<sup>45-47</sup> The use of these drugs as first line therapy in selected patients is likely to become standard soon. How to best utilize these treatments in patients who develop lung cancer as never-smokers, and in patients with molecularly targeted mutations, is under investigation.

## Conclusions

Lung cancer can happen to anybody, whether or not that person has ever smoked. Though, overall, lung cancer is very similar in patients whether or not they have a history of smoking, there are some differences. These include the types of people with the disease (never-smokers with lung cancer are more likely to be women, Asian, or Hispanic and potentially younger), and the type of lung cancer (adenocarcinoma is more common in never-smokers).

Some causes of lung cancer other than smoking have been identified, including second-hand smoke, radon exposure, cooking fumes, family history, and others. We know that patients with the disease who are never-smokers are more likely to have mutations in the EGFR gene, ALK gene rearrangements or other gene changes in the tumor that can change treatment plans. Patients who have specific EGFR gene changes have a better response to EGFR blocking drugs like erlotinib and afatinib, and patients with the ALK gene rearrangement usually respond well to crizotinib, alectinib or ceritinib. Further research will provide more information about the cause of this type of lung cancer and how to best treat patients with this illness. People who want to know more about this topic can look at recent reviews that have been written for doctors.<sup>7,48</sup>

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