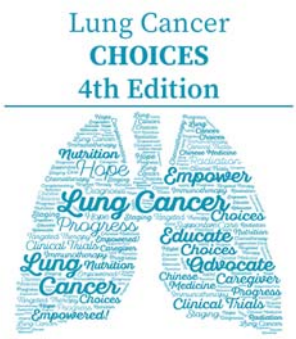

Chapter 10

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. Globally it is the leading cause of cancer death in men and the third leading cause in women.[1-2] 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, Hispanic populations, and women.[1] The causes of lung cancer in people who have never smoked are not well understood. Lung cancer treatment is similar for patients with early-stage disease regardless of whether they smoked. However, for patients with advanced disease (stage IV), many people who have never smoked will have mutations in their tumor, which allow them to respond to specific targeted treatments.

Never smoker: An adult who has never smoked, or who has smoked less than 100 cigarettes or cigars in his or her lifetime.

Frequency

The information about how many people develop cancer each year comes from cancer registries. These databases compile information about the type of cancer and the age of the person but often lack a smoking history. Therefore, it is difficult to know how many cases of lung cancer are attributable to tobacco use. Separate registries on smoking patterns are often used to estimate how many people in a population use tobacco. This information can be loosely correlated to the trends in lung cancer incidence from cancer registries to make estimates 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.[1] In the United States, approximately 1 in 10 men, and 1 in 5 women, with lung cancer are people who have never smoked.[3]

It is unknown whether the incidence of 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.[4] In the United States, more women who had never smoked died of lung cancer in the 1980s and 1990s than in the 1960s.[5] Lung cancer incidence rates have been declining overall due to the success of tobacco cessation programs. Recent data show that lung cancer rates have declined quicker among non-Hispanic men than women. Reversing a long-observed trend that more men develop lung cancer than women. Correlation with data from tobacco registries suggests that the relative increase in lung cancer among women in the US is not due to an increase in tobacco use.[6,7] However, these 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. Other reports have shown no increase in lung cancer in people who have never smoked.[8,9] 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.

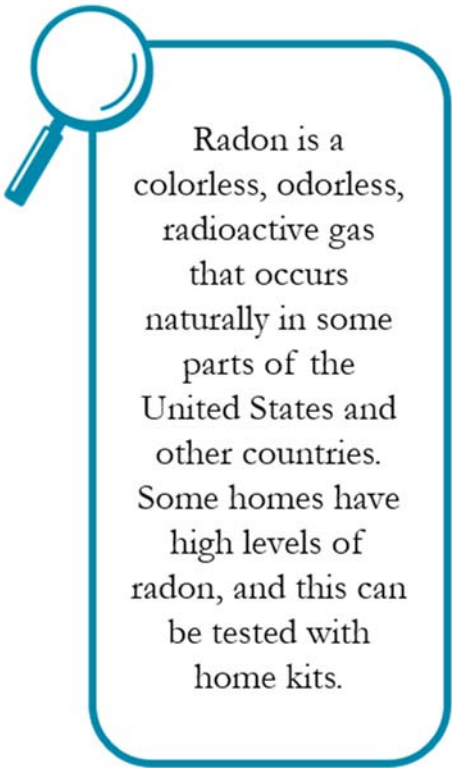
The Causes

The causes of lung cancer in people who have never smoked are unknown, but several factors may increase the risk. [10](Table 1)

Environmental exposures

Many environmental toxins have been implicated in increasing lung cancer risk. Secondhand smoke may cause 20% of the lung cancers in people who have never smoked.[11] Air pollution is thought to be responsible for 5% of cases of lung cancer.[12] Indoor air pollution, such as fumes from cooking oil and smoke from burning coal, may increase lung cancer risk, especially in Asia.[13]

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.[14-15] Jobs that expose people to toxic substances, such as uranium, asbestos, chromium, and arsenic, may increase the risk of developing lung cancer.[16-17] Arsenic may be present in drinking water in some areas such as Taiwan and Chile.[18-19] 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.[20-21]



Medical History

Chronic inflammatory diseases of the lung, such as pulmonary fibrosis or interstitial lung disease, can increase the risk of developing lung cancer.[22] Lung damage from prior radiation therapy (for example, people who received chest radiation for Hodgkin's Lymphoma) also increases the risk of developing lung cancer.[23] Lung cancer risk may be increased in people who have the human papillomavirus, but not everyone agrees with that risk.[24] At this time, there is no proof that human papillomavirus causes lung cancer.

Genetics

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.[10, 25-26] Research is being done to try to find what changes in the DNA (genes) may make individual families at higher risk for lung cancer. So far, we don't know any DNA changes that definitely link families to a higher risk of lung cancer. 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 papillomavirus (controversial)
Other family members with lung cancer
Differences in ability to fix DNA damage

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 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.[1, 27] However, people with a smoking history can also develop adenocarcinoma of the lung. 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.

Also, we know there are racial/ethnic and gender disparities in non-smoking lung cancer. Non-smoking lung cancer is more common in people of Asian ancestry and Hispanics[28,29] as well as in women.[30] 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, and rising.[3,6] The reason for these differences is not known although theories include a variation in biologic susceptibility to toxins or unequal reduction in workplace exposures.[7]

Non-smoking lung cancer is more common in people of Asian ancestry and Hispanics as well as in women.

In about half of the cases of non-smoking lung cancer, we can detect a genetic difference in the tumor, which not only caused cancer but also serves as a target for therapy. To help guide treatment and better understand the disease in each individual, testing for these DNA changes is now considered standard. Especially for patients diagnosed with non-small cell lung cancer or adenocarcinoma. For example, tumors from patients who have never smoked are more likely to have mutations in a protein known as the epidermal growth factor receptor (EGFR).[31-32] Tumors with specific changes in the EGFR protein are more likely to shrink when treated with drugs that attack the EGFR protein, such as osimertinib, erlotinib, gefitinib, dacomitinib, and afatinib. Another mutation that is more common in the tumors of people with no smoking history is in the Anaplastic Lymphoma Kinase (ALK) gene.[33,34] The drugs alectinib, brigatinib, crizotinib, lorlatinib, and ceritinib are used to treat lung cancer patients who have the ALK gene rearrangement.

There are other, less common, DNA mutations that are found more frequently in the tumors of patients with non-smoking lung cancer. In addition to EGFR, ALK, and ROS1, we now can look for changes in BRAF, RET, MET, HER2, and NTRK. We can offer specific "targeted" therapy when identified in tumors of patients with metastatic disease. In general, patients will have only a single major change in the DNA. For example, a patient with a change in the EGFR gene usually does not also have an ALK gene rearrangement. It is important that testing is done to look for EGFR, ALK, ROS1, BRAF and NTRK at a minimum in lung cancer patients who have never-smoked. There are many other gene changes in tumors of patients who have never smoked which have been identified, such as RET, MET, and HER2. As more "targeted" treatments are developed, it becomes even more critical that a tumor is tested for all the mutations that could allow for other treatment options.

"Surrender to what is. Let go of what was.
Have faith in what will be.
- Sonia Ricotti

Treatment of Lung Cancer in People Who Have Never Smoked

Early-Stage Lung Cancer (Stage I-III)

Treatment for people with early-stage non-small cell lung cancer who have never smoked is the same as treatment for smoking-associated lung cancer. For patients with tumors that can be removed with surgery, surgery is preferred therapy, followed by chemotherapy in some cases (depending on tumor characteristics). For people with stage III lung cancer that cannot be removed with surgery, treatment is a combination of chemotherapy plus radiation therapy, followed by a year of immunotherapy. Current research is evaluating whether EGFR targeted drugs such as erlotinib, osimertinib, or gefitinib may help prevent the return of cancer in people with surgically removed, EGFR mutant, early-stage lung cancer. So far, the studies have not supported this practice and therefore targeted agents are not given in early-stage disease, though this is an area of active investigation.

Treatment for people with early-stage non-small cell lung cancer who have never smoked is the same as treatment for smoking-associated lung cancer.

Advanced Stage Lung Cancer (Stage IV)

People who have never smoked and who have lung cancer are more likely to have changes in specific genes such as EGFR, ALK, or ROS1. These gene changes are not seen in the normal cells from a person with lung cancer, only in the cancer cells. In recent years, other genetic variations have been discovered including alterations in BRAF, RET, MET, NTRK, HER2, and others. For most people diagnosed with stage IV non-small cell lung cancer, the first treatment is chemotherapy plus immune therapy or immune therapy alone. 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 particularly important for all patients with advanced-stage lung cancer, especially patients who have never smoked, to have their tumor tested for the gene changes.

EGFR

Patients with metastatic lung cancer who have specific EGFR gene changes should receive osimertinib as the initial treatment. Osimertinib has been shown on average to control the tumor longer than chemotherapy, or the earlier EGFR therapies, and may even lead to living longer than starting other treatments.[35] For patients who are unable to receive osimertinib, treatment with erlotinib, gefitinib, dacomitinib, or afatinib, is preferred over chemotherapy. Studies have shown that they have a higher chance of shrinking the tumor for these patients.[36-37] In the patients who start on one of the earlier EGFR treatments such as erlotinib, gefitinib, dacomitinib, or afatinib, but who have tumor progression, testing for a resistance mutation called T790M is done to see if they would benefit from osimertinib prior to going on to chemotherapy.

The EGFR-targeted drugs are not generally added to chemotherapy, although this is an area of active investigation. A recent study looking at gefitinib alone versus gefitinib plus chemotherapy showed patients who received gefitinib plus chemotherapy had a longer time on treatment and improvement in overall survival compared with gefitinib alone.[38] However, gefitinib is rarely used as first-line therapy in the US anymore, so it is unclear how to apply this information. Studies looking at osimertinib plus chemotherapy are ongoing. Other studies have looked at whether to add chemotherapy to the targeted drug once it has stopped working. The recent IMPRESS trial showed that when chemotherapy has started, it is not beneficial to continue the targeted drug in the majority of patients.[39]

Adding other targeted agents to EGFR drugs has also been examined. For example, bevacizumab, a drug that reduces blood vessel formation in tumors, was looked at in combination with erlotinib. On average, patients who received both drugs together had their tumor controlled almost twice as long as patients who received erlotinib alone. Despite this, there was no difference between the two groups in how long patients lived with cancer.[40] Another blood vessel targeted therapy, ramucirumab, was also looked at in combination with erlotinib and showed that given together patients had a longer time of tumor control. We are still waiting to see whether this will increase survival.[41] Again, as erlotinib is being used less often to treat patients with EGFR mutant tumors, it is unclear whether this combination will be adopted. Trials looking at osimertinib in combination with bevacizumab are underway.

ALK

There are many targeted drug options for patients who have the ALK gene rearrangement (most common in lung cancer patients who have never smoked). Crizotinib was the only clinically available ALK+ targeted agent for several years but is no longer the preferred first-line therapy. The recommended first-line treatment for ALK+ lung cancer is alectinib based on data from the ALEX trial. The study showed improved disease control (almost three times longer) on alectinib compared to crizotinib and found that alectinib had fewer side effects.[42] In addition, alectinib does a better job of controlling and preventing cancer metastases to the brain compared with crizotinib. Other options for first-line treatment include brigatinib (off-label) and ceritinib. Brigatinib is approved for patients who have progressed on crizotinib but is not yet FDA approved for first-line treatment. That is likely to change soon, as a recent study comparing brigatinib to crizotinib showed that brigatinib did a better job controlling tumors (both in and out of the brain) than crizotinib.[43] Brigatinib and alectinib have not yet been compared head to head. Ceritinib has not been compared to crizotinib but was studied against chemotherapy. The ASCEND-4 study that showed that ceritinib did a better job of controlling disease compared with chemotherapy.[44]

There are many targeted drug options for patients who have the ALK gene rearrangement (most common in lung cancer patients who have never smoked).

After progression, treatment with another ALK targeted agent is preferred before chemotherapy. Options in the second-line setting depend in part on which drug patients received first. For patients who received crizotinib, second-line treatment is recommended with brigatinib, alectinib, or ceritinib. For patients who received one of the newer ALK drugs such as alectinib or ceritinib first-line, second-line option is lorlatinib.

ROS1

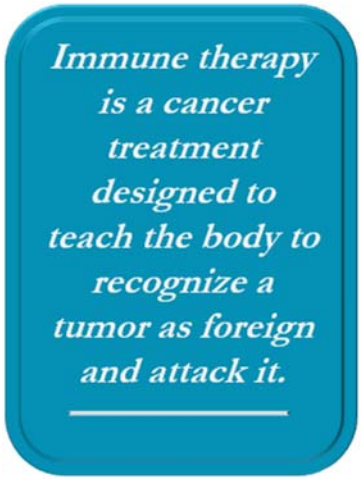
ROS1 rearrangements are also more common in patients who have never smoked. In early studies of crizotinib in patients with previously treated ROS1 positive lung cancer, the majority of patients had their tumor respond to crizotinib, and this response lasted on average about a year and a half. For this reason, crizotinib is preferred for the first-line treatment of ROS1 lung cancer.[45] Ceritinib also has some activity in ROS1 mutant tumors and is another option for first-line treatment.[46] Upon progression, options include lorlatinib, chemotherapy, or clinical trial. There are several agents currently under investigation including cabozantinib, entrectinib, and repotrectinib but none yet are FDA approved for this indication.

Other genetic changes

In addition to EGFR, ALK, and ROS1 we now can look for changes in BRAF, RET, MET, NTRK, and HER2 and can offer specific "targeted" therapy when identified in tumors of patients with metastatic disease. BRAF inhibitors approved for use in lung cancer are the combination of dabrafenib/trametinib. HER2 active drugs include TDM-1, afatinib, and trastuzumab. Multiple drugs are active for RET, including BLU-667, LOXO292, cabozantinib, and vandetanib. Cabozantinib is also active for METexon 14 splice site variations, as are tepotinib and crizotinib. Larotrectinib was recently approved for NTRK fusions.

Chemotherapy and Immune therapy

One theory as to how cancer can develop, and grow is that it acquires mechanisms to evade the body's immune system. Immune therapy is a cancer treatment designed to teach the body to recognize a tumor as foreign and attack it. Those drugs have been shown to work in lung cancer regardless of smoking history, but perhaps less so in patients with no smoking history. Patients with mutations in EGFR or ALK were excluded from many of the early immune therapy trials. It is unknown how well this group benefits from immune therapy, and there is some evidence to suggest their tumors do not respond as well. Efforts to get immune therapy to work in patients with limited smoking history are ongoing with multiple combination drug studies. For patients without targetable mutations, the preferred first-line treatment is a combination of chemotherapy plus immunotherapy. This combination has been shown to work in all patients regardless of smoking status.[47]



For patients with mutations in EGFR or ALK who have had growth of their cancer on targeted therapy, a 4-drug combination of chemotherapy plus bevacizumab (target against blood vessels) plus immunotherapy was found to have a small benefit in tumor control and the suggestion of possible improvement in survival.[48] However, the number of patients in the study with EGFR or ALK mutations who received this combination was small (111 patients). Additional data is needed to understand how to best use these treatments in patients who develop molecularly targeted mutations. Chemotherapy alone is another good option for patients with non-smoking lung cancer who have progressed on targeted therapy (in the case of having a targetable mutation) or on a chemo-immunotherapy combination. The combination of targeted therapy plus immunotherapy has been examined in several trials. Unfortunately, this combination has not been very effective and notably has a high rate of toxicity.[49] The most important point is that the best treatment cannot be chosen until all the information about a tumor is known. The results for immune therapy (PD-L1) often come back sooner than the results about EGFR, ALK, and the other potential tumor mutations. But in never-smoker lung cancer, the chance of a tumor having a mutation that can be treated is high. So, it is critical to wait to get the tumor mutation results back before starting treatment unless there is a medical reason that treatment must start sooner. Starting immune therapy (even with chemotherapy) can increase the risk of toxicity from some of the targeted treatments (like osimertinib), which can be a problem if that treatment is started before knowing about the tumor mutations.

Conclusion

Although lung cancer is 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 (lung cancer in people who have never smoked are more likely to be women, Asian, or Hispanic and potentially younger), and the type of lung cancer (adenocarcinoma is more common in people who have never smoked).

Some causes of lung cancer other than smoking have been identified, including secondhand smoke, radon exposure, cooking fumes, family history, and others. We know that patients with the disease who have never smoked 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 osimertinib or erlotinib. Patients with the ALK gene rearrangement usually respond well to alectinib, brigatinib, 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.[27, 50]

Notes

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