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## LUNG CANCER IN NEVER-SMOKERS

**Heather Wakelee, MD**

Assistant Professor of Medicine, Division of Medical Oncology  
Stanford University  
Stanford Cancer Center

### **Introduction**

Smoking is the most common cause of lung cancer, but there are many people who develop lung cancer who have never smoked. Lung cancer in never-smokers is more common in Asia, particularly in women.<sup>1</sup> The causes of lung cancer in never-smokers are not well understood but there is ongoing research. We do know that lung cancer treatments can work differently in never-smokers. We also know that since fewer people now smoke, the rate of lung cancer in never-smokers is likely going to increase.

### **How many people get lung cancer as never-smokers?**

Usually the term “never-smoker” means a person who has smoked fewer than 100 cigarettes in their life. The information about how many people get cancer each year comes from cancer “registries” that have information about the type of cancer, age of the person with cancer and some other information, but not information about smoking. Because the cancer registries don’t have information about smoking, it has been hard to really know how many people with lung cancer do or do not smoke.

Around the world it is thought that about 15% of men with lung cancer are never-smokers and about 50% of women with lung cancer are never-smokers.<sup>2</sup> As mentioned earlier, more lung cancer in never-smokers is seen in Asia. In the United States we think that about 1 in 5 women with lung cancer are never-smokers and about 1 in 10 men with lung cancer are never-smokers.<sup>3</sup> About the same number of women each year get lung



# CAP Lung Cancer Medical Writers' Circle

cancer as never-smokers as get cervical cancer. For men, the number who get lung cancer each year as never-smokers is about the same number of men who get the blood cancer multiple myeloma.

An important question that people wonder about is whether the number of people who get lung cancer as never-smokers is increasing. At this time we don't really know, again because the cancer registries don't have information about smoking. A study in Swedish construction workers did show an increase rate of lung cancer in never-smokers in the 1990s compared to the 1970s.<sup>4</sup> Another study in the United States showed that more never-smoking women with lung cancer died of the disease in the 1980s and 1990s than in the 1960s, but this was not true for men.<sup>5</sup> We do not have other proof of an increase though, and some studies show no increase.<sup>6</sup> So at this time we cannot say if lung cancer in never-smokers is increasing or not.

## **Is lung cancer in a person who never smoked different than lung cancer in a person who has smoked?**

There are several known differences between lung cancer in smokers and never-smokers. The biggest difference is in the types of lung cancer that are the most common. While lung cancer in smokers is commonly a form of “non-small cell lung cancer (NSCLC)” called “adenocarcinoma”, other common types of “NSCLC-squamous cell carcinoma”, or “small cell lung carcinoma”. Squamous cell carcinoma and small cell lung cancer are very rare in never-smokers, who more commonly have adenocarcinoma.<sup>1,7</sup> Another type of lung cancer that is more often seen in never-smokers is called “bronchioloalveolar carcinoma (BAC)”.



# CAP Lung Cancer Medical Writers' Circle

It is also known that certain racial/ethnic groups are more likely to develop lung cancer as never-smokers. This is true for people of Asian ancestry and Hispanics.<sup>8,9</sup> Most of the risk is seen in women. We know that women with lung cancer are more likely to be never-smokers than men with lung cancer.<sup>3</sup>

Researchers have found that tumors from patients who have never smoked have different changes in the DNA than the tumors from smokers. Some of the changes are in a protein called the epidermal growth factor receptor (EGFR).<sup>10-15</sup> Many other changes in DNA are different between lung cancer tumors from smokers and never-smokers.

## **What causes lung cancer in never-smokers?**

We don't really know what causes lung cancer in never-smokers, but there are a few things that probably increase the risk and they are listed in Table 1. Secondhand smoke probably causes about 20% of lung cancer in never-smokers<sup>16,17</sup> Air pollution may cause about 5% of the disease.<sup>18</sup> Indoor air pollution like fumes from cooking oil and smoke from burning coal are known to increase lung cancer risk, particularly in Asia.<sup>19</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 (this can be tested with home kits). People who live in homes with high levels of radon are at a higher risk of lung cancer, whether or not they smoke.<sup>20,21</sup> Certain jobs expose people to toxic substances that can increase the risk for lung cancer like uranium, asbestos, chromium, and arsenic.<sup>22-24</sup> Arsenic can also be in drinking water in some areas (particularly Taiwan and Chile).<sup>25,26</sup> We don't know of any foods that increase the



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risk for lung cancer, but people who eat more fruits and vegetables may be at lower risk.<sup>27-29</sup>

Other lung damage, like from radiation therapy increases the risk of lung cancer. Researchers have also found that lung cancer may be increased in people who have a certain virus (human papillomavirus).<sup>30</sup> It is interesting that there is a virus in sheep that causes a disease like lung cancer, but no such virus has been found in people.

People with family members who have lung cancer have a slightly higher risk of getting lung cancer. We still have a lot to learn though about how big of a risk this is and what causes it.<sup>31-34</sup> There is some research that shows that estrogen may also play a role in causing lung cancer, particularly in never-smokers. This is still an area of controversy though.

## **How is lung cancer treated differently in never-smokers?**

People who develop lung cancer who have never smoked seem to do better than people who have a smoking history and get the disease. Some research studies have shown that never-smokers with lung cancer respond better to chemotherapy, but others have not shown this. For the most part, people with lung cancer are treated the same whether or not they have a smoking history. However, never-smokers with lung cancer do have a definite increase in benefit from the drugs erlotinib (Tarceva) and gefitinib (Iressa) compared to people who have smoked.<sup>12,35,36</sup> The tumors are more likely to shrink and on average people with non-smoking lung cancer live longer with these drugs than people with a smoking history. These drugs target a protein called the Epidermal Growth



# CAP Lung Cancer Medical Writers' Circle

Factor Receptor (EGFR). Changes in the EGFR protein that can cause lung cancer are seen more often in people with lung cancer who have never smoked.

At this time, people usually get the EGFR targeted drugs after receiving standard chemotherapy for a few months. So far, erlotinib (Tarceva) is only for people with advanced (metastatic, stage IV) lung cancer who have already had chemotherapy. Research is being done to see if it is a good idea for never-smokers with lung cancer to get erlotinib before chemotherapy or with chemotherapy, but we don't know the answers about that yet. People are also studying whether the drug may help prevent the cancer from coming back in people with early stage lung cancer that has been removed with surgery. That research trial is still happening. Recently, a drug called cetuximab (Erbix) was shown to help people with advanced lung cancer when given with chemotherapy. This drug also targets EGFR, but we don't yet know if it works better in people who are never-smokers. Research is also being done to see if other new drugs work better in people with lung cancer who have never smoked, but we don't have any answers yet.

## **Conclusions**

Lung cancer can happen to anyone, whether or not that person has smoked. We know a little bit about how lung cancer is different in people who have never smoked. We know that it is more likely in women, in people of Asian ancestry and Hispanics, and perhaps in younger patients. We know that the adenocarcinoma type of lung cancer is more common in never-smokers. Never-smokers are more likely to have changes in the EGFR protein. Some causes such as secondhand smoke, radon exposure, cooking fumes, family history and perhaps



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certain viruses have been identified. We know that patients with the disease have a better response to EGFR blocking drugs like erlotinib (Tarceva) and overall better survival than lung cancer patients with a smoking history. We still have a lot to learn though about why this disease happens and how it is different than other lung cancer. Ongoing clinical trials may help us find some of the answers. People who want to know more about this topic can look at recent reviews that have been written for doctors.<sup>1,7</sup>



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## REFERENCES-

1. Sun S, Schiller JH, Gazdar AF: Lung cancer in never smokers--a different disease. *Nat Rev Cancer* 7:778-90, 2007
2. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. *CA Cancer J Clin* 55:74-108, 2005
3. Wakelee HA, Chang ET, Gomez SL, et al: Lung cancer incidence in never smokers. *J Clin Oncol* 25:472-8, 2007
4. Boffetta P, Jarvholm B, Brennan P, et al: Incidence of lung cancer in a large cohort of non-smoking men from Sweden. *Int J Cancer* 94:591-3, 2001
5. Thun MJ, Henley SJ, Burns D, et al: Lung cancer death rates in lifelong nonsmokers. *J Natl Cancer Inst* 98:691-9, 2006
6. Peto R, Darby S, Deo H, et al: Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ* 321:323-9, 2000
7. Subramanian J, Govindan R: Lung cancer in never smokers: a review. *J Clin Oncol* 25:561-70, 2007
8. Ou SI, Ziogas A, Zell JA: Epidemiology study of never-smokers with non-small cell lung cancer (NSCLC): High percentages of Asian and Hispanic female never-smokers and the significance of Asian ethnicity. *J Clin Oncol* 26:425s (Abstr #8004), 2008
9. Epplein M, Schwartz SM, Potter JD, et al: Smoking-adjusted lung cancer incidence among Asian-Americans (United States). *Cancer Causes Control* 16:1085-90, 2005
10. Sonobe M, Manabe T, Wada H, et al: Mutations in the epidermal growth factor receptor gene are linked to smoking-independent, lung adenocarcinoma. *Br J Cancer* 93:355-63, 2005
11. Kosaka T, Yatabe Y, Endoh H, et al: Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res* 64:8919-23, 2004
12. Tsao MS, Sakurada A, Cutz JC, et al: Erlotinib in lung cancer - molecular and clinical predictors of outcome. *N Engl J Med* 353:133-44, 2005



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13. Pao W, Miller V, Zakowski M, et al: EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A* 101:13306-11, 2004
14. Pham D, Kris MG, Riely GJ, et al: Use of cigarette-smoking history to estimate the likelihood of mutations in epidermal growth factor receptor gene exons 19 and 21 in lung adenocarcinomas. *J Clin Oncol* 24:1700-4, 2006
15. Tam IY, Chung LP, Suen WS, et al: Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. *Clin Cancer Res* 12:1647-53, 2006
16. Wu A: Carcinogenic effects, in Shopland DR, Zeise L, Dunn A (eds): *Health Effects of Exposure to Environmental Tobacco Smoke*. Bethesda, MD, National Cancer Institute, 1999
17. Vineis P, Alavanja M, Buffler P, et al: Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst* 96:99-106, 2004
18. Vineis P, Hoek G, Krzyzanowski M, et al: Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health* 6:7, 2007
19. Kleinerman RA, Wang Z, Wang L, et al: Lung cancer and indoor exposure to coal and biomass in rural China. *J Occup Environ Med* 44:338-44, 2002
20. Krewski D, Lubin JH, Zielinski JM, et al: A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health A* 69:533-97, 2006
21. Darby S, Hill D, Auvinen A, et al: Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *Bmj* 330:223, 2005
22. Alberg AJ, Brock MV, Samet JM: Epidemiology of lung cancer: looking to the future. *J Clin Oncol* 23:3175-85, 2005
23. Gottschall EB: Occupational and environmental thoracic malignancies. *J Thorac Imaging* 17:189-97, 2002
24. Neuberger JS, Field RW: Occupation and lung cancer in nonsmokers. *Rev Environ Health* 18:251-67, 2003



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25. Chen CL, Hsu LI, Chiou HY, et al: Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan. *Jama* 292:2984-90, 2004
26. Ferreccio C, Gonzalez C, Milosavjlevic V, et al: Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology* 11:673-9, 2000
27. Wakai K, Ando M, Ozasa K, et al: Updated information on risk factors for lung cancer: findings from the JACC Study. *J Epidemiol* 15 Suppl 2:S134-9, 2005
28. Feskanich D, Ziegler RG, Michaud DS, et al: Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *J Natl Cancer Inst* 92:1812-23, 2000
29. Galeone C, Negri E, Pelucchi C, et al: Dietary intake of fruit and vegetable and lung cancer risk: a case-control study in Harbin, northeast China. *Ann Oncol* 18:388-92, 2007
30. Cheng YW, Chiou HL, Sheu GT, et al: The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. *Cancer Res* 61:2799-803, 2001
31. Wu AH, Fontham ET, Reynolds P, et al: Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. *Am J Epidemiol* 143:535-42, 1996
32. Brownson RC, Alavanja MC, Caporaso N, et al: Family history of cancer and risk of lung cancer in lifetime non-smokers and long-term ex-smokers. *Int J Epidemiol* 26:256-63, 1997
33. Gorlova OY, Zhang Y, Schabath MB, et al: Never smokers and lung cancer risk: a case-control study of epidemiological factors. *Int J Cancer* 118:1798-804, 2006
34. Bailey-Wilson JE, Amos CI, Pinney SM, et al: A major lung cancer susceptibility locus maps to chromosome 6q23-25. *Am J Hum Genet* 75:460-74, 2004
35. Thatcher N, Chang A, Parikh P, et al: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 366:1527-37, 2005
36. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 353:123-32, 2005



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Table 1: Potential Causes of Lung Cancer in Never-Smokers

Secondhand Smoke

Radon exposure

Other toxins (asbestos, chromium, arsenic)

Dietary factors (not enough fruits and vegetables)

Obesity

Air pollution (including cooking fumes)

Radiation therapy to the chest

Other lung diseases like “idiopathic pulmonary fibrosis”

Human papillomavirus

Other family members with lung cancer

Differences in ability to fix damage to DNA

Excess estrogen exposure