

LUNG CANCER IN KENTUCKY *Policy Brief*

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The causes of lung cancer

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Cigarette smoking is a well-established cause of lung cancer. In fact, an estimated 87% of all lung cancers can be attributed to cigarette smoking alone.¹ Although it is by far the leading cause of lung cancer, the disease has several other causes. Of the roughly 3,900 lung cancers that will develop this year in Kentucky, about 500 are not attributable to *active* cigarette smoking. Granted, a portion of these 500 lung cancers are still directly or indirectly related to tobacco use from cigars, pipes, and secondhand cigarette smoke, but several other risk factors act independently or synergistically with tobacco to cause lung cancer. Occupational and environmental exposures, such as asbestos, arsenic, secondhand smoke, and radon, also increase the risk of lung cancer. In this issue we examine several risk factors and their contribution to lung cancer. But to understand better how risk is calculated we will first review some basic concepts of epidemiology.

Epidemiology overview

Epidemiology is the study of how diseases are distributed in populations and of the risk factors that influence this distribution. A *risk factor* is a behavior, exposure or other characteristic that increases the likelihood of developing a disease or condition. The effect of an exposure on *disease burden* – that is, the number of people in a given population with the disease – will depend on several factors, including how common the exposure is, how common the disease is, and how strong the relationship between them is.

The strength of the association between a risk factor and a disease can be measured in several ways. The *relative risk* or *RR* quantifies this association as a ratio between the disease risk among individuals *exposed* to the risk factor under study and among those *unexposed* to the risk factor under study (see Box 1).

Because the RR is a ratio, where the risk to the unexposed group is the denominator, a value greater than 1 means that the exposed group has a greater likelihood of developing the disease than the unexposed group. A value less than 1 means that the exposed group has a lower likelihood of developing the disease than the unexposed group. RRs less than 1 are appropriately called *protective factors*.

Different exposure levels often result in a dose-response relationship. For instance, those who smoke a pack a day or more have about twice the risk of developing lung cancer

(RR=13) than those who smoke half a pack a day (RR=6).² Similarly, a dose-response relationship can vary with duration of exposure. A person smoking a pack a day for 30 years is at higher risk of developing lung cancer than one who has smoked a pack a day for 10 years. (Intensity and duration are sometimes combined into one measure – pack-years – to quantify smoking exposure.)

Few people are exposed to just a single risk factor; more commonly, they are exposed to multiple factors. The effect of combined exposures can vary widely. If a person has two risk factors sometimes the effect can be *additive* (RR₁=3, RR₂=5; RR_{TOTAL}=8), sometimes the resulting risk can be *greater than the sum of the individual risks* (RR₁=3, RR₂=5; RR_{TOTAL}=10), and sometimes it can have a *multiplicative effect* (RR₁=3, RR₂=5; RR_{TOTAL}=15). Such variation is often called an *interaction* or an *effect modification*.

Epidemiologists further distinguish between two major kinds of risk factors: those that are *modifiable* and those that are *unmodifiable*. Age, sex, race, and genetics are all unmodifiable. Some evidence suggests that, given the same smoking patterns, women have a higher susceptibility to lung cancer than do men.³ Similarly, African-Americans seem to have an increased risk of lung cancer relative to other races. Genetics also plays a role since only 10% to 15% of those who smoke develop lung cancer.³ And, among those who do not smoke, the risk of getting lung cancer increases with the number of first-degree relatives (parents, children, and siblings) with cancer, after controlling for exposure to secondhand smoke.³

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$$\text{Risk of lung cancer among smokers} = \frac{100 \text{ lung cancers}}{1000 \text{ smokers}} = 0.1$$

$$\text{Risk of lung cancer among nonsmokers} = \frac{10 \text{ lung cancers}}{1000 \text{ nonsmokers}} = 0.01$$

$$\text{Relative risk} = \frac{0.1 \text{ (risk to exposed group)}}{0.01 \text{ (risk to unexposed group)}} = 10$$

Interpretation: Smokers are 10 times more likely to develop lung cancer than are nonsmokers.

Box 1. Calculating relative risk from a hypothetical study on smoking and development of lung cancer.

Modifiable risk factors, in contrast, are those that can be controlled, such as smoking behavior or exposure to asbestos and radon. Our discussion focuses on these modifiable or external risk factors for lung cancer.

Risk factors

Tobacco: Cigarettes

In addition to lung cancer, cigarette smoking also causes cancers of the oral cavity, pharynx, larynx, esophagus, urinary bladder, renal pelvis, and pancreas,² as well as increases the risk of cardiovascular disease. The overall average RR for lung cancer from cigarette smoking is 10, meaning that smokers are 10 times more likely to develop lung cancer than are nonsmokers. However, a clear dose-response relationship has been established, where risk increases linearly with the number of cigarettes smoked. Duration of smoking plays an even bigger role in developing lung cancer. The International Agency for Research on Cancer noted that the relationship between lung cancer and smoking depends more on the duration of smoking than on the frequency.⁴ A three-fold increase in cigarettes smoked per day, for example, may lead to a three-fold increase in the incidence of lung cancer. But a three-fold increase in duration of smoking might produce a 100-fold increase in the incidence of lung cancer.⁴

An estimated 87% of all lung cancers are from cigarette smoking alone,¹ and if that figure is applied to Kentucky it means that 3,414 of the 3,924 lung cancers diagnosed in 2000 would have been prevented if cigarette smoking had been completely eliminated. This leaves about 13% or roughly 500 annual lung cancers in Kentucky that may be attributable to exposures other than active cigarette smoking (Figure 1).

Tobacco: Cigars

Cigar use has increased dramatically in recent years. While occasionally depicted as a harmless alternative to cigarettes, cigars are not a safe substitute.⁵ Cigar smoking is an established cause of lung cancer. In fact, cigar smokers are twice as likely as nonsmokers to develop lung cancer (RR = 2).⁵ As with cigarettes, a dose-response relationship is evident between cigars and lung cancer – as the number

smoked per day increases so does the risk of lung cancer. But the risk associated with cigars is lower than that for cigarettes because cigar smokers typically inhale less deeply and smoke less often than do cigarette smokers. This reduced depth of inhalation is mainly what makes the cigar-lung cancer association weaker than that for cigarettes.⁵ But once differences in the level of inhalation and quantity of tobacco smoked per day are accounted for, the risk of lung cancer may be similar for both cigarette and cigar smokers.⁵

Tobacco: Environmental tobacco smoke

Environmental tobacco smoke – ETS or secondhand smoke as it is often called – also causes lung cancer.^{1,6} In June 2002, the International Agency for Research on Cancer declared ETS a known human carcinogen to which there is no safe level of exposure.⁷ This is the first time an international group has made such a conclusion about secondhand smoke, although about ten years earlier the U.S. Environmental Protection Agency and National Cancer Institute announced the same conclusion. Nonsmokers exposed to ETS have approximately a 20% increased risk of lung cancer (RR = 1.2).⁶ Or, to put it another way, an estimated 2% of all lung cancers in the United States can be attributed to secondhand smoke.¹ This translates to about 80 new cases in Kentucky each year, or 16% of the estimated lung cancers diagnosed in nonsmokers.

Other modifiable or external factors

A number of other lung carcinogens have been identified. Most of these carcinogens occur in certain places of work, so they are generally restricted to particular groups of individuals. (In the United States many of these exposures are now controlled or regulated, so the risks from them have been reduced greatly.) Exposure to other carcinogens can be both occupational and environmental, with a few being mainly environmental. Some of these distinctions, however, are arbitrary. Secondhand smoke is generally considered an environmental carcinogen, but for flight attendants it has been an occupational risk for years and for many restaurant workers it still is occupational. We will discuss three non-tobacco lung carcinogens – radon, asbestos and arsenic.

Radon

Radon is an invisible, odorless, and tasteless gas that exists naturally in the environment, and is considered the second leading cause of lung cancer in the United States, though still distantly trailing smoking. This radioactive gas is produced by the decay of uranium in rocks and soil, so the highest exposures have occurred among uranium miners. Radon can enter homes, however, through cracks in the foundation. Radon's distribution varies regionally but not systematically – two neighboring homes can have entirely different concentrations of the gas.

People exposed to residential radon have a 14% higher risk of developing lung cancer than those who are unexposed

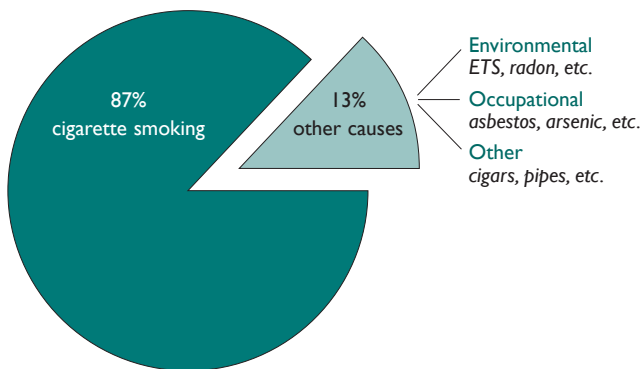


Figure 1. A breakdown of lung cancer's major causes.

(RR=1.14).⁸ A dose-response effect is also evident, as rising radon concentrations lead to increasing lung cancer risk.^{8,9} The National Research Council estimated that about 10% of lung cancers are from indoor radon exposure, contributing between 15,400 and 21,800 of the total estimated 157,400 annual lung cancer deaths in the United States. But because of a synergistic effect, the risk radon poses is much higher among smokers than among nonsmokers. The majority of the 15,400 to 21,800 radon-related lung cancer deaths are among smokers, with 2,100 to 2,900 among nonsmokers.

Since Kentucky has high smoking rates, the carcinogenic effects of radon exposure will be increased. And based on largely voluntary radon testing in the state, areas with high radon levels have been clearly documented. Unfortunately, most people do not know the radon levels in their homes or about their amplified cancer risk if they also smoke.

Asbestos

Asbestos is a group of naturally occurring fibers that have been mined since the 1880s. It is used commercially in North America and found in more than 5,000 products.¹⁰ Asbestos-containing products themselves pose no health risk as long as the asbestos is not disturbed. But asbestos tends to break easily into a dust that can be inhaled or swallowed.¹⁰ People who are exposed occupationally to asbestos fibers are five times more likely to develop lung cancer (RR=5) than those who are not exposed.¹ Those who become ill from asbestos tend to be exposed regularly, usually at their occupation.¹⁰

As with radon, the effect of asbestos on lung cancer risk is much higher among smokers. The figures are alarming: While the RR of smoking is around 10, and about 5 for asbestos alone, the combination can yield an RR of 50.¹ In other words, if you have had significant exposure to asbestos and smoke cigarettes, your risk of getting lung cancer can be 50 times higher than the risk faced by the general nonsmoking, non-asbestos exposed population.

Arsenic

Arsenic inhalation, mostly in occupational settings such as in copper smelters, also causes lung cancer. Recent evidence indicates that elevated concentrations of arsenic in drinking water also can increase risk of lung cancer.¹¹ In some populations around the world, particularly in South America and Asia, the number of lung cancers attributable to arsenic

exposure is high because the water that many people drink has high concentrations of arsenic. In the United States such exposures are less common, although some areas are more affected than others, particularly in the western states. As with radon and asbestos, smokers have a substantially higher risk of lung cancer if they also inhale or ingest arsenic.

Other carcinogens

A number of other exposures are known or suspected lung carcinogens – from metals such as beryllium, cadmium, chromium, nickel, and uranium, to radiation, to organic compounds such as polychlorinated biphenyls or PCBs, trichloroethylene or TCE, diesel, and dioxin.

Conclusions

Lung cancer is a common, highly fatal cancer. Along with cigarette smoking, a number of other risk factors increase the likelihood of developing lung cancer, but the number attributable to cigarette smoking is much higher than for any other cause. (A summary of major lung cancer risk factors and their RRs is given in Table 1.) Moreover, since active smoking acts synergistically with some common lung carcinogens, smoking greatly increases the risk of developing lung cancer. Secondhand smoke is also carcinogenic, so the burden of lung cancer from all major causes would be reduced among nonsmokers if we lowered our smoking rate. Exposure to the less common or less potent lung carcinogens accounts for about 10% of all cases, but they lead to 500 lung cancers a year in the Commonwealth. These cases also could be substantially lowered if smoking were eliminated or reduced because of the potentiating or synergistic effect smoking has when combined with other lung carcinogens.

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Table 1. Relative risk for lung cancer from common carcinogens.

Risk factor	Relative risk for lung cancer
Cigarettes	10
Cigars	2
Secondhand smoke	1.2
Residential radon	1.14
Asbestos	5

FROM THE GOVERNANCE BOARD

To raise awareness about lung cancer and to improve survival of Kentuckians with lung cancer, the Kentucky General Assembly of 2000 established a 20-year initiative to combine the efforts of the University of Kentucky and the University of Louisville to become national leaders in lung cancer epidemiology, diagnosis, and treatment. The resulting Kentucky Lung Cancer Research Program funds research grants for faculty at the University of Kentucky and University of Louisville. Typically, grants receive two years of funding, with a third year contingent on research progress as reported in annual progress reports. More information about the KLCR Program can be found at <http://kentuckylungcancer.org>.

In the second cycle of research applications the governance board of the KLCR Program funded 14 projects. We congratulate these scientists for their leading role in lung cancer research in Kentucky.

Researcher at UK	Project title
Thomas Burke	Anti-topoisomerase I aerosols for lung cancer therapy
Edward Hirschowitz	Detection of tumor markers in peripheral blood of non-small cell lung cancer patients
David Kaetzel	PDGF as a gene therapy target in lung cancer
Heinz Kohler	Second-generation antibody against HER-2/neu: Preclinical studies on lung cancer cells
Guo-Min Li	Alterations of DNA mismatch repair genes in lung cancer
Jeffery Moscow	Drug transport genes as novel targets of lung cancers
Daniel Noonan	Targeting retinoic acid treatment of lung cancers
Stephen Zimmer	EIF-4E and metastasis in lung cancer

Researcher at UofL	Project title
Steven Ellis	LAMR1, a potential lung cancer tumor suppressor gene in chromosomal region 3p21.3
Carolyn Klinge	Interaction of carcinogens with estrogen receptor beta
Thomas Mitchell	T-cell function in nicotine-treated mice
John Trent	Design of nucleolin inhibitors
Vaclav Vetvicka	Inhibition of procathepsin D secretion in lung cancer treatment
Wolfgang Zacharias	Tumor microenvironment as determinant of protease-mediated malignancy in lung cancer

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