

FEATURE STORY

No Smoking

BY KATY HUMAN

What's to blame for lung cancer in people who never smoked, and what that means for treatment and survival.

After feeling achy and winded for a few months in 2005, Angie Lee-Ow finally visited her doctor. Fluid filled Lee-Ow's right chest, clouding her X-ray and hiding a 3.5-centimeter tumor.

Soon after her chest fluids were drained, Lee-Ow was diagnosed with lung cancer—adenocarcinoma. She never had a cigarette in her life.

The tumor lurking in her right lung had spread into her chest, shoulder bones, and lymph nodes. "It was like getting slammed with a Mack truck," Lee-Ow says. "I never smoked, I had no health problems, I did all the normal screening—mammograms and Pap smears. Shocking would be an understatement."

Lee-Ow, 56, lives in Sacramento, California, and is one of about 25,000 never-smokers (defined as having smoked fewer than 100 cigarettes in a lifetime) who are diagnosed with lung cancer every year in the United States. Estimates from the American Cancer Society state close to 214,000 people will be diagnosed with lung cancer in 2007—making never-smokers, two-thirds of whom are women, 10 to 15 percent of newly diagnosed lung cancer patients.

"It's not like everybody who smokes gets lung cancer, and this—lung cancer in never-smokers—is the flip side of that," says Heather Wakelee, MD, a thoracic oncologist at Stanford Comprehensive Cancer Center in California. "Why do these people get lung cancer at all?"

Actress and singer Dana Reeve, who died of lung cancer at age 44 in 2006 and never smoked, brought national attention to the issue. Now, in a series of recent journal articles and clinical trials, Dr. Wakelee and other researchers are beginning to unravel the disease, which often plays out quite differently than lung cancer in current or former smokers. Many researchers hope understanding the differences between lung cancer in smokers and never-smokers will lead to better treatments for both.

What's the Difference

In people who never smoked, lung cancer is most often a type called adenocarcinoma, a cancer that usually arises from cells on the periphery of the lung. For some types of adenocarcinoma, prognosis seems to be a bit better than in other types of lung cancer. In smokers, lung cancers are more evenly divided among adenocarcinomas and squamous cell carcinomas, which arise from thin, flat cells lining the lung's airway. Both are non-small cell lung cancers—more common, slower to grow, and somewhat less likely to spread than small cell lung cancer.

Although many clinicians say they're seeing more and more cases of lung cancer in never-smokers, researchers have not been able to definitively say it's increasing. "It's hard to get solid numbers, because most of the databases that track lung cancer didn't actually keep good records about smoking history," says Jill Siegfried, PhD, a lung cancer researcher and pharmacologist at University of Pittsburgh Medical Center. "In the past, clinicians just assumed everybody smoked."

Still, tantalizing evidence from a handful of studies across the globe hint the disease in never-smokers is on the rise. Even if that trend fails to hold up in further research, the current incidence of lung cancer in never-smokers is quite significant. "Clinicians need to know this," Siegfried says. "If a never-smoker comes in with a chronic cough or other symptoms, you cannot assume that just because they never smoked, they can't have lung cancer."

Nancy Rackear, 52, of Pompano Beach, Florida, got regular screenings since her mother, father, and all four grandparents had various types of cancer. At 47 and at her sister's urging, Rackear asked for a chest X-ray, although she had no symptoms of lung trouble.

Her doctor was concerned about the image, and three specialists reading a follow-up PET (positron emission tomography) scan had different interpretations: One saw a suspicious tumor, another suspected metastatic lung cancer that was headed to her brain, and a third thought there was no way she had lung cancer, just a thyroid problem. "He said, 'There isn't any reason for you to have lung cancer,'" Rackear says.

Rackear herself couldn't accept she might have lung cancer. "I couldn't believe that I would have to go through surgery to prove to everyone that they were wrong, but I also knew I couldn't live with not knowing definitively."

She did go ahead with surgery, and Rackear's surgeon discovered a 5-centimeter tumor that was just about to perforate the lung. He removed the left upper lobe. "I was lucky," Rackear says.

The Search for Reasons

Patients who never smoked say they have spent uncountable hours wondering

what caused their lung cancer. Lee-Ow worried most about environmental factors. “But you stop asking why, because it will drive you crazy,” she says.

Molecular changes play a key role in lung cancer in never-smokers. Certain types of mutations contained only in tumor tissue (not inherited) make some patients much more responsive to life-extending medications called epidermal growth factor receptor (EGFR) inhibitors, one of which is Tarceva[®] (erlotinib), a drug approved for lung cancer in November 2004. Ironically, the same EGFR mutation may make these never-smokers more likely to get lung cancer.

View Illustration: A Host of Factors

A Host of Factors

Midway through chemotherapy, Lee-Ow learned her cancer cells had the mutation, which she considered good news. “I learned that having the profile of being a non-smoking Asian woman might give me a better chance of responding to Tarceva,” says Lee-Ow, who was relieved to know there was a back-up plan—one she eventually needed.

“It’s potentially hormonal, too,” Siegfried says. Researchers have found estrogen receptors in lung tumors of never-smokers—more receptors in women than in men. (In breast cancer, estrogen encourages cancer cells to proliferate.)

“This could potentially drive lung cancer in women, and it might be more important if you don’t smoke,” Siegfried says. Smoking loads up the lung with so many mutation-triggering carcinogens that other pathways to lung cancer may be harder to discern. Those other pathways, which could explain lung cancer in never-smokers, may involve a very low background rate of mutation.

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—Angie Lee-Ow

Siegfried and other scientists have also searched for a role of human papillomavirus in lung cancer. The virus is a known cause of cervical cancer in women, and a similar virus is linked to a pulmonary cancer in sheep. Siegfried says HPV has been found in one of about 300 lung tumors of never-smokers in patients of Asian ethnicity, but rarely in the tumors of white or Western patients.

Other risk factors have emerged in epidemiological studies, including long-term exposure to radon. The Environmental Protection Agency estimates radon—a radioactive gas that occurs naturally in many places—causes lung cancer that kills more than 20,000 smokers and never-smokers combined each year. However, research continues regarding the precise amount of risk and the

specific number of lung cancer deaths attributable to radon.

The California Environmental Protection Agency calculates secondhand smoke, also called passive smoke, kills 3,400 annually in the United States. Dr. Wakelee says some researchers still disagree about the secondhand smoke evidence, but it could help explain why women never-smokers are more likely than their male counterparts to get lung cancer: “More men smoke, so women never-smokers may be more likely to be exposed to passive smoke,” Dr. Wakelee says.

Evidence also suggests lung cancer is triggered by certain types of air pollution—“small particles in the air” that can penetrate deep into the lungs and affect both smokers and never-smokers. Lung cancer in never-smokers has also been linked to workplaces that expose workers to asbestos and other toxic substances, such as cadmium, nickel, chromium, benzene, and formaldehyde.

Finally, genetics plays a strong role in the development of lung cancer in never-smokers, as it does for other types of cancer. National Institutes of Health researchers have identified a lung cancer susceptibility region on chromosome 6, which could eventually lead to the discovery of a gene or genes responsible for the disease.

People inherit various versions of other genes that help the body build detoxifying enzymes. Some of those varieties are known to be better than others at breaking down the carcinogens in tobacco smoke, and could also help deal with toxins in secondhand smoke or air pollution.

Treating Non-Smokers

Lee-Ow’s first-line treatment was fairly typical for patients who present with advanced, unresectable non-small cell lung cancer: carboplatin and Taxol[®] (paclitaxel) for three months to kill as many cancer cells as possible. Her primary tumor shrank and the fluids receded.

Soon after starting therapy, Lee-Ow lost her hair, experienced low blood counts, and lost some feeling in her hands and feet (a condition known as neuropathy). Chemotherapy was followed by Erbitux[®] (cetuximab) administered every week intravenously as part of a clinical trial. Erbitux—Lee-Ow nicknamed the drug “Erbi”—is an EGFR inhibitor that prevents cancer cells from proliferating.

Her cancer responded to the drug for eight months, “which is a pretty good response time, before the fluid in my right chest began to increase again.”

Lee-Ow immediately started on Tarceva, which is taken orally and generally has fewer side effects than chemotherapy. Side effects of Tarceva are similar to those of Erbitux, including a painful rash that some people cannot tolerate, even if the drug appears to be working. It can also make open wounds more susceptible to infection.

Lee-Ow’s rash went away after a few months, but she still gets deep fissures in the skin on her fingers and feet. “They’re like really deep paper cuts that don’t heal,” Lee-Ow says. “But it’s worth it.”



Angie Lee-Ow, with her husband Raymond and daughter Pamela, was diagnosed with lung cancer although she never smoked. Photo by Anne Williams

Since she started Tarceva in April 2006, Lee-Ow's chest fluids have nearly disappeared, the primary tumor is stable, and it appeared nearly silent in recent PET scans that indicate tumor activity levels.

Rackear's lung cancer was caught early, had not spread and was localized enough to be surgically removed. Under normal circumstances, Rackear says she would have followed up with an oncologist, and might have been given chemotherapy. However, she returned home after surgery to a letter saying her employer was going out of business, and her health insurance would be terminated.

"So I never made that appointment with an oncologist," Rackear says. Three months post-op, with new insurance papers in hand, she consulted with a local thoracic oncologist. He discussed her case with well-known Indiana University oncologist Lawrence Einhorn, MD. Given that Rackear was a never-smoker with no metastases, and with successful surgery three months ago, Dr. Einhorn's recommendation: "No chemo. Just monitor it," Rackear says. "I was given a new life."

Patients who have never smoked tend to have slightly better survival rates than smokers or former smokers, says Adi Gazdar, MD, a molecular oncologist at the University of Texas Southwestern Medical Center in Dallas. "It could be because they have healthier lungs or because they're healthier in general, and it could be because smoking activates a different pathway" leading to lung cancer, Dr. Gazdar says.

He's impressed with the success of Tarceva and related drugs, including Iressa[®] (gefitinib), which are far more effective in never-smokers than in smokers. Former and current smokers in a phase III clinical trial did no better on Iressa than on placebo, but never-smokers had a reduced risk of death. A recent study of Tarceva reported the response rate at close to 25 percent for never-smokers, and less than 4 percent for smokers and former smokers, probably reflecting more cases of tumors containing the EGFR mutation among never-smokers, rendering these tumors more sensitive to drugs like Tarceva.

Other therapies are in the pipeline for never-smoking lung cancer patients,

including Sutent[®] (sunitinib), an oral drug already approved for advanced kidney cancer and gastrointestinal stromal tumors. Sutent blocks the activity of multiple tyrosine kinases that are involved in cancer growth. “[Other drugs] target EGFR kinases specifically. Sutent is also a kinase inhibitor, but it is more broad-reacting, which may be good or may not,” Dr. Gazdar says. “It could have unpredictable effects.” Another kinase inhibitor approved for kidney cancer, Nexavar[®] (sorafenib), is undergoing testing for all lung cancers.

As research into the intricacies of treating never-smokers continues to reveal new insight, Lee-Ow feels fortunate. “The five-year survival rate for lung cancer (all stages) has not changed significantly in the past 30 years, but that doesn’t include people like me who have responded to these new therapies,” she says. “I intend to be among the long-termers.”