Attention Turns to Lung Cancer in Nonsmokers

When Dana Reeve, the 43-year-old wife of Superman star Christopher Reeve, died of lung cancer in March, commentators often asked two questions: Why do nonsmokers, who make up 10%–15% of all lung cancer patients, develop the disease? And who exactly is at risk?

Some in the media chalked it up to bad luck—the same bad luck experienced by 17,000–26,000 American nonsmokers who get lung cancer each year. And in some sense they’re right, as the etiology of most lung cancers in nonsmokers remains unknown.

“For nonsmokers, the risk factors are not very well understood,” said Olga Gorlova, Ph.D., assistant professor of epidemiology at the University of Texas M. D. Anderson Cancer Center in Houston.

The National Cancer Institute’s Physician Data Query (PDQ) database lists secondhand smoke and indoor exposure to asbestos, radon, arsenic, chromium, nickel, tar, and soot as risk factors. Other proposed risks include pipe, cigar, and marijuana smoking; air pollution; and, in Asia at least, chronic exposure to household kitchen smoke. But the NCI does not break down how many cases are caused by each. One recent study estimated that secondhand smoke causes 3,000 cases of lung cancer among nonsmokers each year. But that still leaves most cases unaccounted for.

New research is now helping clear the smoke. A study from Gorlova and colleagues suggest that many nonsmokers who develop lung cancer appear to carry a genetic predisposition. And, in this issue of the Journal (see p. 691), researchers for the first time estimate the lung cancer death rate among nonsmokers in a large cohort: 17.1 per 100,000 for men and 14.7 per 100,000 for women. Those figures place lung cancer among nonsmokers, if considered as a distinct disease, in the cancer top 10.

“If 10% of lung cancers are in nonsmokers, that would make it the eighth most common cancer type, in terms of fatalities,” said Michael Thun, M.D., an epidemiologist at the American Cancer Society in Atlanta and first author on the report. “If the figure is closer to 15%, then it is the sixth most common cause of cancer death.”

Genetic Risk

An ambitious project headed by Margaret Spitz, M.D., chair of epidemiology at M. D. Anderson, is focused on developing a mathematical risk model for lung cancer. In the 1990s, the Gail model for breast cancer made a splash, giving women and their physicians a tool to estimate their risk by inputting simple figures—age, age at first period, number of children, and so on. “Our goal is to make a Gail model for lung cancer,” said Matthew Schabath, Ph.D., a postdoctoral researcher at M. D. Anderson, who presented a preliminary model at the American Association for Cancer Research annual meeting, held in Washington, D.C., in April.

Spitz said that the model, as it stands, applies most readily to smokers, 20% of whom will develop lung cancer. However, the team is modifying the formula to make it more applicable to nonsmokers. In particular, they’re focusing on inherited risk.

“These patients don’t have the major risk factor, smoking, yet they develop lung cancer,” said Gorlova. “So it’s logical to think they might have a predisposition. That’s exactly what we observed.”

At the AACR meeting, Gorlova presented data showing that first-degree relatives of nonsmokers with lung cancer had a 25% increased risk for any type of cancer, compared with a control group. The heritable risk was strongest among children of nonsmoking lung cancer patients, who had a twofold
greater risk of developing any cancer than children of control subjects.

“The findings really underscore that there is an inherited genetic component,” Gorlova said.

Perhaps most striking, data from 316 nonsmoking lung cancer patients and 2,465 of their first-degree relatives suggests that early-onset lung cancer in nonsmokers heralds a family propensity for early onset cancers in general. Parents, siblings, and children of nonsmoking lung cancer patients had a 44% higher risk for developing early-onset cancers—those diagnosed before age 50—than that of relatives of the control group. In another measure of subjects who developed cancer, relatives of nonsmokers with lung cancer were diagnosed roughly 10 years earlier than were relatives of the control group, which included nonsmokers without lung cancer. The team is now combing tissue and blood samples to find the specific genes involved.

The team is also pursuing other risk factors to fold into the formula. In the April 1 issue of the International Journal of Cancer, it reported data from 280 nonsmokers with lung cancer and 242 matched control subjects. Secondhand smoke and dust exposure, especially in the workplace, topped the list of risk factors; exposure to substantial amounts of both more than tripled the risk. The diagnosis of a relative with any type of cancer at age 50 or younger also increased risk. Finally, Gorlova said that the team found evidence that exposure to pesticides may increase risk, a finding she is in the process of submitting for publication.

**Sex Differences?**

From 1959 to 1972 and again starting in 1982, the American Cancer Society surveyed 2.2 million Americans, asking a variety of questions about health and known cancer risk factors. These Cancer Prevention Studies, which track participants until death, offer a huge epidemiological database. In this issue of JNCI, Thun and colleagues for the first time mine that data to determine death rates from lung cancer among nonsmokers. Overall, though, the rate remained steady. “There’s been a vocal constituency arguing that environmental pollutants have caused an increase in one cancer or another. And they hold up lung cancer in never smokers as sort of a sentinel indicator,” said Thun. “Our study doesn’t support that idea.” Instead, the increase in the death rate for women likely stems from increased awareness of the disease among older women and their physicians, he said. “There are autopsy studies showing that many women in the past died from undiagnosed lung cancer.”

Thun hopes that his study renews public debate about funding for lung cancer, which draws substantially fewer research dollars per patient than other major cancers. “I think there are two things going on here. The first is that the survival rate from lung cancer is so low that there isn’t an advocacy group left,” said Thun. “And second, there’s always been a kind of blame-the-victim attitude about lung cancer. Well, not only should we not blame smokers—nobody ever sets out to get addicted—but now, with the death of Dana Reeve, people are more aware that many nonsmokers die from lung cancer, too.”

—Brian Vastag