

Lung Cancer in Women on the Rise

BY SHIRLEY S. WANG

As doctors have substantially brought down the rate of lung cancer in men over the past three decades, they face a stubborn riddle: Why does it continue to grow among women?

A new study offers an intriguing possibility that the answer may involve estrogen.

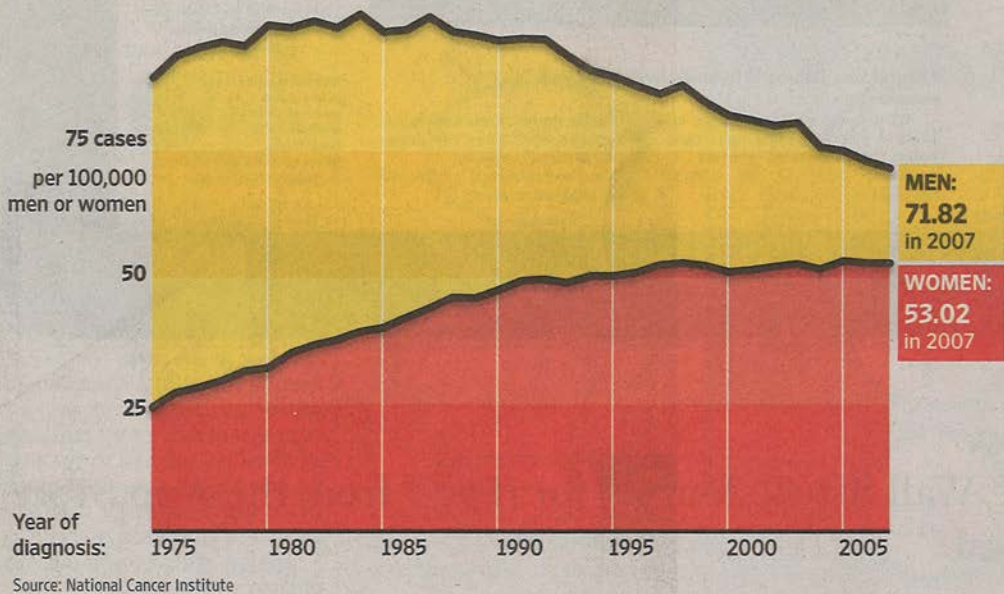
Lung cancer is the leading cancer killer of both women and men. And overall, it still kills more men than women: Some 71,000 deaths are projected in women and 86,000 in men in 2010. That's a much higher casualty rate than the No. 2 killer, breast cancer, with about 40,000 deaths expected, according to the American Cancer Society.

Experts don't agree on whether women are naturally at greater risk for lung cancer or more vulnerable to the effects of tobacco smoke than men. Still, there are striking gender differences in cancer rates. For instance, women who have never smoked are far more likely than men who have never smoked to get lung cancer, according to data from the National Cancer Institute.

The diagnostic trajectory among women is concerning. Researchers are trying to understand why it is rising and what can be done to change it.

"Unless we start seeing a turnaround for women," says Brenda Edwards, associate director of the surveillance research program at the National Cancer Institute, "there will be as many women diagnosed with lung cancer in the next few years as

As Rates Fall for Men, More Women Get the Disease



men."

The rate of new cases of lung cancer has dropped for men to 72 in 100,000 males in 2007 from 89.5 in 100,000 in 1975. In women, however, the number of cases has more than doubled to 53 in 100,000 females in 2007 from 24.5 per 100,000 in 1975, according to the National Cancer Institute.

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The hormone estrogen is a possible culprit. Certain forms of estrogen are known to help create genetic mutations in cells and contribute to tumor formation in the breast. Recently, researchers found out that lung cells in both women and men also make estrogen, raising the possibility that the hormone

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Lung-Cancer Rate Is On the Rise in Women

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contributes to lung-cancer development.

Margie Clapper and her colleagues at Fox Chase Cancer Center, a major research center in Philadelphia, set out to examine what would happen to the lung cells of female animals that were exposed to tobacco smoke. They wanted to identify early genetic changes in the cells—before tumors formed—that could be targeted in the future.

The goal is that one day these early genetic changes could be disrupted, preventing lung cancer from developing in the first place, says Dr. Clapper, co-leader of the cancer prevention and control program.

After placing female mice in smoke-filled chambers six hours a day, five days a week for three, eight or 20 weeks, they looked to see how material produced by genes differed in the lung tissue of animals that were exposed to smoke and those that weren't.

Researchers found differences in 10 genes around an enzyme called cytochrome P450 1b1, which is known to break down estrogen and tobacco smoke. The 1b1 enzyme activates cancer-causing agents in tobacco and converts estrogen to a more active form that appears to cause DNA mutations. Estrogen may, in essence, be adding fuel to the fire that occurs when lung cells are exposed to tobacco smoke.

The findings, published last week in the journal *Cancer Prevention Research*, "reinforce the role that estrogen is clearly a player and we need to look at it more closely," Dr. Clapper says.

Since only female mice were used in the study, it isn't clear how male mice—whose lung cells also produce estrogen—would react differently.

Dr. Clapper says that this estrogen pathway could be particularly harmful for women because they have higher levels of estrogen in their blood before menopause, and some may take drugs that boost estrogen, including hormone-replacement therapies or birth control pills.

The lab is now looking at what happens when hormone levels are boosted in mice that already have lung tumors, and also what hormones might do to

damage cells even in a non-smoke environment.

The study "points to directions that we could take to either prevent or treat lung cancer," says Jill Siegfried, a pharmacology and chemical biology professor at the University of Pittsburgh who wrote a commentary, which accompanied Dr. Clapper's paper, on why the research is important. The research "also provides some public health information for women to understand what tobacco smoke is doing to their lungs and how it could interact with their natural hormones."

Some cancer researchers say that the rise in lung cancer cases in women is simply due to differences in men's and women's smoking patterns.

Women as a group started smoking later than men and are slower to quit, and smoking is

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known to be the biggest contributor to lung cancer, says Michael Thun, a researcher and former head of the surveillance and epidemiology group at the American Cancer Society. The rise in cases seen now for women is just a result of the rise in women's smoking from decades ago, he says.

Others say that while smoking patterns explain part of the trend, recent evidence suggests that women are more susceptible to lung cancer than men.

One in five women diagnosed with lung cancer has never smoked compared with one in 12 men, says Tracey Hyams, director of the Connors Center for Women's Health and Gender Biology at the Harvard-affiliated Brigham and Women's Hospital in Boston.

Three times as many female never-smokers are diagnosed with lung cancer compared with male never-smokers, according to a report recently published by Dr. Hyams's group.