CANCER EPIDEMIOLOGY

Claim of Higher Risk for Women Smokers Attacked

The established wisdom on smoking, gender, and lung cancer is straightforward: Male and female smokers are equally susceptible to the disease. More men die from the disease, but only because smoking has been common among men far longer. And if women were to match men cigarette for cigarette, they would match them in lung cancer mortality as well.

This widely accepted story gained a twist in September, when a study of Canadian smokers was published in the *American Journal of Epidemiology*. Entitled "Are Female Smokers at Higher Risk for Lung Cancer than Male Smokers?" the study concluded that smoking may be two to three times more hazardous for women than for men. The report prompted headlines in newspapers across the country. And two other studies, one published the same month in the *International Journal of Epidemiology*, appeared to bolster the idea that smoking is more dangerous for women.

But where there's smoke there may not always be fire. Other data—including large, ongoing studies by the American Cancer Society and the National Cancer Institute (NCI)—contradict the findings of the three recent studies. And other epidemiologists say the new results are the products of the misinterpretation of epidemiologic data. Says Richard Peto, co-director of the Cancer Studies Unit of Oxford University: "It's simply not true that females have bigger risks of smoking than males."

The researchers arguing for a higher risk for women, however, are far from convinced by this counterattack. Edith Zang of the American Health Foundation in New York, co-author on two of the studies, says that "people find it hard to accept because they have not been able to see it themselves. It's a real phenomenon."

Maybe, but just how real it seems depends on whom you ask. The *American Journal of Epidemiology* study, which ignited the controversy, was the work of Harvey Risch, a biomathematician at Yale University, and his collaborators at the University of Toronto and the Ontario Cancer Treatment and Research Foundation. Risch and his co-workers identified all lung cancers among women in southern Ontario between 1981 and 1985. For each of the 442 cases, they identified a randomly selected female control matched by age and area of residence, then identified 403 male lung cancer cases taken from the same hospitals, and randomly selected male controls. "Then," says Risch, "we looked at various measures of smoking, and different ways of characterizing smoking in all cases and related that to risks of getting lung cancer." What they found was that woman who smoked had a risk 27.9 times as great as nonsmoking women; in contrast, the risk for men who smoked regularly was only 9.6 times greater than that for male nonsmokers.

The results, although unusual, didn't stand alone; the *International Journal of Epidemiology* study stood right beside them. The investigators on that study, Randall Harris and Judy Anderson of the Department of Preventive Medicine at Ohio State University and Zang and Ernst Wynder at the American Health Foundation, compared more than 4000 lung cancer cases with more than 4000 controls and found that women were 1.5 to two times more likely to get cancer than were men. The finding extended work published last year by Zang and Wynder in the journal *Cancer*, in which they compared 3000 male and female lung cancer cases to 5000 nonsmoking controls in the New York area. "At every level of exposure to tar [the primary carcinogen in cigarettes], women had substantially higher risk of having lung cancer than men," says Zang

Just as clearly, however, these results contradict the latest findings from the American Cancer Society's second Cancer Prevention Study (CPS-II), which has been following more than a million Americans since 1982. The study has found that male smokers are dying twice as often from lung cancer as women smokers, although that's due to the fact that more men have been smoking longer. As the number of women smokers increase, as it's been doing since World War II, that gap should narrow. Moreover, says Michael Thun, director of analytic epidemiology for the American Cancer Society, an ongoing NCI study of lung cancer incidence and mortality corroborates this finding.

Not only are these results opposite to those obtained by Risch and the others, but the studies on which they're based are better suited to compare the absolute cancer risks of men and women, according to Thun, Peto, and other epidemiologists questioned by *Science*. In CPS-II and the NCI research, investigators select a group of individuals—both men and women—and establish which individuals are exposed to the risk factor and which are not, and then follow them for years to learn who develops which diseases and who doesn't. That provides an absolute measure of risk.

The studies of Risch and the others, known as case-control studies, can only provide what's known as a risk ratio—your risk of contracting the disease if you smoke compared to your risk if you don't. Risch and his colleagues derived risk ratios for women and men by comparing women smokers and nonsmokers, and male smokers and nonsmokers. So far so good, say their critics.

But then the researchers attempted to compare the two ratios, concluding that women have a greater absolute risk. That, says Ken Rothman, a Boston University epidemiologist and editor of the journal *Epidemiology*, is a meaningless exercise. One obvious problem is that the relative risk of lung cancer among female smokers may be higher then that of male smokers simply because male nonsmokers may have a higher incidence of lung cancer from occupational exposure to carcinogens. If the male nonsmoking baseline risk is higher, and if smoking results in an equal absolute risk of death for both men and women, then the women's risk ratio—smokers' lung cancer deaths to total lung cancer deaths—would be higher than the men's. Only with concrete evidence that the incidence of lung cancer in women nonsmokers is at least equal to the incidence in men nonsmokers could the researchers make a meaningful comparison of female to male risk. Even the larger CPS-II study hasn't produced numbers of nonsmokers' lung cancer deaths that are sufficient to make a statistically valid comparison.

Risch counters that his study—along with those of Harris, Anderson, Wynder, and Zang—generate such a high value for relative risk that some of the enhancement must be due to a smoking hazard that is greater for women than it is for men. But critics such as Thun and Rothman still disagree. That conclusion, they say, cannot be drawn from the data without information on the lung-cancer risks of nonsmokers. And the bottom line, says Peto, is that when it comes to lung cancer, the evidence for inequality between the sexes is uncompelling. "If women smoke like men," he says, "they'll die like men."

–Gary Taubes