New Studies Fan Controversy Over Gender Risk in Lung Cancer

When the Surgeon General’s Report on Smoking and Health was released 40 years ago, smoking was largely viewed in the context of men’s health—so many men were dying from lung cancer and associated diseases that scientists debated whether the lower numbers of female smokers were resistant to the tobacco scourge. But now tobacco use has taken its place as a serious health threat for women and is being seen as a “contemporary epidemic” in women in the United States and many other countries.

Today in the United States, 40% of American women report a history of smoking. Lung cancer incidence has dipped in men but not in women, and the disease killed almost 69,000 women in 2003—many more than breast and all other gynecologic cancers combined. In fact, mortality from smoking has increased 600% in the past 50 years.

So the risk that tobacco use poses to women is not disputed. But what is a subject of disagreement among researchers is the question of whether women are more susceptible to developing lung cancer than men, given the same history of smoking. A spate of case–control studies in the early 1990s pointed to an increased risk among women, but larger cohort studies did not find that same association. In the last several months, a number of published studies have again fallen on both sides of the issue.

What is most at stake are the funds to explore the answer to this question and all its associated ramifications, such as screening and prevention strategies. If a true association is found, then research dollars should be devoted to uncovering the mechanisms that contribute to that risk and to exploring new targeted treatments.

“Research dollars are precious, so we need to focus studies on phenomena that really exist,” said Michael Thun, M.D., chief epidemiologist for the American Cancer Society, who co-authored an article in the June 2 issue of the Journal of the National Cancer Institute that found no lung cancer risk differences between men and women in two large cohorts. “Studying why women respond differently than men to treatment for lung cancer is potentially valuable, because a sex difference exists. But studying why women have a higher risk than men of developing lung cancer from smoking is not informative because the premise is false.”

Differences in Biology Versus Risk

Researchers agree that non–small-cell lung cancer, the predominant class of lung cancer, appears to have important biologic differences between the sexes. Adenocarcinomas comprise a larger fraction of all lung cancers in women than men. Tumors from female patients have shown reduced DNA repair capacity compared with tumors from males, and some research suggests that estrogen signaling in women may play a role in the development of lung adenocarcinoma.

Some treatments have been shown to be more effective in women than in men, such as use of gefitinib (Iressa), which appears to be more effective in younger, nonsmoking women with lung adenocarcinomas, including bronchioloalveolar cancers. And women fare better overall than men when treated for lung cancer.

But lung cancer can differ biologically between men and women without evidence that either gender is at higher risk of developing the disease. The controversy about women being more—or even less—susceptible to the carcinogenic effects of cigarette smoke began in the early 1990s with several reports from case–control studies. A 1993 study of 800 Canadians, for example, found that, compared with nonsmokers, the odds ratio of developing lung cancer for those with a 40–pack-year history was 27.9 in women and 9.6 in men. That study, led by Yale epidemiologist Harvey Risch, M.D., Ph.D., was followed by a 1996 American Health Foundation study of almost 4,000 patients and control subjects that found that female smokers had a 1.5-fold higher risk of developing lung cancer than did male smokers. But other large cohort studies, such as several conducted by the American Cancer Society, found either no gender differences or that men had a greater risk of developing lung cancer than women.

Recent studies have continued, if not intensified, the debate.

Claudia Henschke, M.D., Ph.D., did not think that gender differences would matter that much when she undertook a large study using low-dose computed tomography (CT) to screen for lung cancer. Other factors, such as age and smoking history, just seemed more relevant.

So she said she was more than a little surprised when her results showed that women smokers in her study had twice the risk of lung cancer compared with...
men of the same age who smoked the same amount. “I wasn’t expecting the result, but that is what the data very strongly showed,” said Henschke, a professor of radiology at Weill Cornell Medical Center in New York, and lead investigator on a study published in the January issue of Lung Cancer.

Henschke and her colleague Olli Miettinen, M.D., Ph.D., analyzed data from the New York Early Lung Cancer Action Project, which is following thousands of men and women age 40 and older who had a history of cigarette smoking to determine which risk factors, when combined with the size and texture of lung nodules found on the CT scans, could predict lung cancer development. The investigators looked at two different cohorts totaling 2,490 patients and found that women were 2.7 times more likely than men to have lung cancer.

Henschke rejects suggestions that the results were skewed because women in the study may have been underreporting their use of tobacco or that enrollment in a screening trial does not offer a valid comparison of disease incidence. Although she said she does not have a hypothesis for why such gender differences exist, Henschke noted that it may be analogous to the increased risk associated with alcohol in women—the likely result of a number of factors ranging from body size to genetic differences.

**No Consensus**

The debate was further highlighted, but not answered, in a review in the April 14 issue of the Journal of the American Medical Association. The article, written by researchers at Memorial Sloan-Kettering Cancer Center in New York and Northwestern University in Chicago, concluded that important differences exist among men and women with lung cancer, noting that “undertaking sex-specific research in lung cancer is crucial.” The question of susceptibility has not been answered, said co-author Peter Bach, M.D., a pulmonologist and epidemiologist at Memorial Sloan-Kettering. “I think we are a long way from a definitive answer, as none of the studies examining this question were designed to address it,” he said. Still, he added, “it might be reasonable to conclude that we put more editorial emphasis on the possibility of differences than the equally or sometimes more likely possibility of similarity.”

Bach added that “the research community needs to think about these problems and pursue an efficient agenda.” The question that needs to be answered, he said, is whether biology relates to differences in risk, differences in treatment, or both. “Our point is exactly that heterogeneity has been observed,” he said in an interview. “Whether it is important or irrelevant remains the open—but to us, very important—question.”

The latest study to weigh in on the debate is the largest to date, an analysis of two hefty cohort studies, the Nurses’ Health Study of women and the Health Professionals Follow-up Study of men, published earlier this month in the Journal of the National Cancer Institute.

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**United States Signs International Tobacco Treaty**

Activists working to control the tobacco industry worldwide have offered tepid praise to Health and Human Services Secretary Tommy Thompson for his signing of the international tobacco treaty, the Framework Convention on Tobacco Control (FCTC), on May 10 in Washington.

“We welcome his signing, but if the administration does not follow through, the action will be little more than an obvious public relations gesture,” said Judith Wilkenfeld, director of international programs at the Campaign for Tobacco-Free Kids.

The treaty, developed by the World Health Organization (WHO) and agreed to last May by all 192 member nations, would impose a total advertising ban on tobacco products and mandate large warning signs on cigarette packs. Although the WHO has set a deadline of June 29 for nations to sign the treaty as they promised—which is what 107 countries had done by the time Thompson signed—penning a name on the treaty is largely a symbolic act.

The treaty will become international law only after 40 nations have ratified it, and by late May, 12 nations had done so. In the United States, ratification would come only after the Senate and the President agree to the treaty, which may actually have little impact because the U.S. Constitution would overrule the advertising restrictions.

Wilkenfeld expects the treaty will be signed by many more nations than is required. “With its 27 nations, the European Union is getting ready to ratify it, so it is moving along much faster than expected,” she said.

But Wilkenfeld and Kathryn Mulvey, another longtime supporter of the FCTC, say they predict the United States will not adopt the treaty, even though ratification would earn the United States—and, presumably, its multinational tobacco companies—“a seat at the table” among those who will work out how the treaty would be implemented.

Both Wilkenfeld and Mulvey pointed to other treaties that were signed but not implemented, such as the Convention on the Rights of the Child, and the Convention on Biological Diversity, among others. “The U.S. government has fought the FCTC every step of the way, even while they’ve publicly claimed to support it,” said Mulvey, executive director of Infact, a corporate accountability group. “We are not holding our breath for the U.S. to ratify the treaty.”

—Renee Twombly

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The researchers, primarily from Harvard Medical School in Boston, analyzed new prospective data and also reviewed previously published prospective analyses, and they found that women do not have a greater susceptibility to lung cancer than men.

From 1986 through 2000, 955 and 311 lung cancers were identified among more than 60,000 women in the Nurses’ Health Study, and more than 25,000 men in the Health Professionals Study, yielding among current smokers an incidence rate of 253 cancers per 100,000 person-years in women and 232 per 100,000 in men. For former smokers, there were 81 cancers per 100,000 person-years among women and 73 per 100,000 among men. Adding an analysis of other large cohort studies suggested a trend toward increased susceptibility in men, said co-author Thun, from the American Cancer Society.

He and his colleagues argue that, given these results, “there does not seem to be either the need for, or a point to, pursuing biologic or other explanations for a hypothetical greater susceptibility to lung cancer among women.”

Thun argues that the central question should shift to, “What we can learn about gender differences in response to therapy that can improve the therapy?” That is the way we must now frame the question.”

Risch, the Yale researcher who was among the first to find a gender difference in risk of developing lung cancer, is exasperated by the debate and has left this field of research. “The disease is so serious, why are we still competing to see if absolute risk is greater, or relative risk, or risk in general?” he asked.

“The mortality and morbidity toll on our society is so bad in both men and women from this epidemic,” Risch said, “but because so much money is involved, everyone is blinded from the real issue, which is our social responsibility to help people stop smoking.”

—Renee Twombly