patients, the ACS will continue to promote participation in these trials.”

LESS LETHAL SMOKING STILL A PIPE DREAM

The notion of tobacco harm reduction—that there may be a “safer” way to smoke—is one that holds great appeal for smokers unwilling or unable to kick the habit and for the tobacco companies that profit from it. But two recent studies add weight to the argument that quitting is still the only certain way to reduce the health risks of tobacco.

The first, published in *BMJ* (2004;328:72–80), compared lung cancer risk among smokers of high-tar, regular-tar, and reduced-tar cigarettes. Researchers from the Massachusetts Institute of Technology and the ACS found that low-tar and very low-tar cigarettes were no less harmful than those with regular or medium-tar levels.

“The data underscore that terms like ‘light’ and ‘ultra light’ are misleading because they imply less health risk but do not correspond to less hazardous cigarettes,” said coauthor Michael J. Thun, MD, MS, Vice President of Epidemiology and Surveillance Research at ACS.

Nearly 1 million men and women (non-smokers, former cigarette smokers, and current cigarette smokers) participating in the ACS Cancer Prevention Study II were analyzed. The tar rating of the brand of cigarette smoked in 1982 was compared with mortality from cancer of the lung, trachea, or bronchus over the next six years. Cigarettes were categorized as “very low tar” (0 to 7 mg tar per cigarette), “low tar” (8 to 14 mg tar per cigarette), “medium tar” (15 to 21 mg tar per cigarette), or “high tar” (22 mg or more per cigarette). The statistical analyses controlled for factors including age, race, education, marital status, diet, occupation (including asbestos exposure), and cardiovascular or respiratory comorbidities.

As expected, people who never smoked had virtually no risk of lung cancer. Those who smoked high-tar brands (which typically are unfiltered) had the highest risk; compared with current smokers of medium-tar cigarettes, their hazard ratios were 1.44 for men and 1.64 for women.

But lung cancer risk among people who smoked low-tar or very low-tar cigarettes was indistinguishable from that of smokers of medium-tar brands. Hazard ratios were 1.17 and 1.02 among men smoking very low-tar and low-tar brands, respectively, and 0.98 and 0.95, respectively, among women. None of these values were significantly different from the hazard ratio for smokers of medium-tar brands (set at 1.0 for this statistical analysis).

The way people smoke is the likeliest explanation for the findings, Thun said. The tar and nicotine content listed on cigarette labels is based on measurements from a smoking machine, but studies have shown “there’s a very poor correlation between machine-measured yield and what people are actually taking in,” he explained.

People who smoke reduced-tar cigarettes don’t necessarily lower the amount of chemicals they inhale because they tend to inhale deeper, hold the smoke longer, and puff more often than smokers of regular-tar brands. They also tend to smoke more and may, inadvertently or not, cover ventilation holes in the cigarette filter that are designed to dilute the smoke with air.

Compensation in smoking behavior is also the most likely explanation for the findings of a second study examining the effect of smoking fewer cigarettes on the level of carcinogens in the body. Researchers from the University of Minnesota Cancer Center Transdisciplinary Tobacco Use Research Center reported in the *Journal of the National Cancer Institute* (2004;96:107–115) that smoking fewer cigarettes did not result in a proportional reduction in metabo-
lites of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

“The reduction was just not as great as you would have expected based on how much [the study participants] had cut back,” said lead researcher Stephen Hecht, PhD.

Hecht and colleagues enrolled more than 150 people who smoked, on average, 23.7 cigarettes a day. The study involved gradual cigarette reduction using nicotine replacement therapy and brief counseling sessions. At each stage of the program, urinary levels of the NNK metabolites 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and NNAL glucuronides (NNAL-Gluc) were measured. The reductions in these biomarkers did not keep pace with the reductions in cigarettes.

Cutting cigarette consumption by 53% led to a reduction of only 29% in NNAL and NNAL-Gluc. Cutting cigarettes by 75% caused only a 37% drop in the chemicals. Even people who cut back to just 2.6 cigarettes a day, a reduction of 90%, lowered their levels of NNAL and NNAL-Gluc by only 46%.

Although these reductions in carcinogens were statistically significant, for most smokers the effect was modest and transient, Hecht said. As the study went on, NNAL and NNAL-Gluc increased again in many participants, even though they were still smoking fewer cigarettes. Compensatory smoking is probably the reason.

Thun and Hecht said their findings support the notion that giving up cigarettes entirely is the best bet for reducing the health risks caused by tobacco. In the first study, quitting reduced lung cancer risk substantially; people who gave up smoking before age 35 had almost the same lung cancer risk as nonsmokers, but even those who quit after age 55 saw a substantial reduction. Hecht has done previous research showing that levels of NNAL and NNAL-Gluc gradually decrease and eventually become undetectable in people who quit smoking.

Moreover, no product or strategy designed to reduce the harm from smoking has yet been shown to work, Hecht said.

“I still think cessation is the way to go, clearly,” he said. “We don’t have conclusive evidence that anything else works.”

VACCINE TRIALS SHOW ACTIVITY IN KIDNEY AND LUNG CANCER

The recent successes of two therapeutic cancer vaccine trials have focused attention on the recent progress and future potential of harnessing the immune system’s power to fight cancer.

In a study published in the Journal of the National Cancer Institute (2004;96:326–331), researchers from Baylor University Medical Center at Dallas and colleagues reported results of a Phase I/II multicenter trial involving 33 patients with Stage II or IV nonsmall cell lung cancer. The vaccine caused complete responses in three patients lasting six months, 18 months, and 22 months. In seven other patients, the disease did not progress for a period ranging from five months to 28 months, while an eighth patient experienced a 30% reduction in the size of the lung nodule.

The vaccine, called GVAX (Cell Genesys, Inc., San Francisco, CA), was made from autologous tumor cells genetically modified to secrete human granulocyte-macrophage colony-stimulating factor, a protein that stimulates the lymphocytes to attack the cancer cells.

Lead researcher John Nemunaitis, MD, said this was the first time immune therapy alone has been shown to be effective against metastatic nonsmall cell lung cancer. Nemunaitis, Director of the Mary Crowley Medical Research Center at Baylor and Director of the US Oncology Phase I research program, called the results promising for patients with this disease, which is frequently resistant to chemotherapy.