Smoking and Breast Cancer

Cigarettes may cause more cases than the two so-called breast cancer genes combined

by Peter G. Shields, M.D.
National Cancer Institute

Christine B. Ambrosone, Ph.D.
National Center for Toxicological Research, Food and Drug Administration

Smoking has adverse health effects at any age. But new research shows that roughly half of all women are particularly prone to developing breast cancer in their 50s or 60s if they smoke.

By now, most people have heard the grim statistic of breast cancer: almost one in every eight women in the U.S. will develop the disease in her lifetime. This year alone, breast cancer will take the lives of roughly 45,000 American women.

For most women, the top risk factors for breast cancer are hormonal, such as start-

ing menstruation at a young age (before 12 years old), going through menopause late in life (after age 50), having few or no children and having a first full-term pregnancy at a late age. All these traits share one common feature: they contribute to a longer lifetime exposure to estrogen, which can spur the growth of breast cells into cancerous tumors. Estrogen levels rise at the onset of menstruation and decrease at menopause. Increasing physical activity and eating a diet rich in fruit and vegetables may decrease risk.

Family history also is an important risk factor for breast cancer. Because breast cancer is fairly common, many women have one or two relatives with breast cancer by chance. But some young women whose mother, grandmothers or sisters had breast (or ovarian) cancer carry an inherited susceptibility for the disease. Women from such high-risk families frequently carry mutations in the *BRCA1* or *BRCA2* gene. Mutations in these genes confer between a 40 and 90 percent lifetime risk of developing breast cancer. Although these familial cancer syndromes are devastating, they account for only about 5 percent of all breast cancer cases. The other 95 percent—the nonfamilial, or sporadic, breast cancers—are caused, in part, by the hormonal risk factors mentioned above and by some risk factors we are only now beginning to explore.

We believe that one important and preventable risk factor for breast cancer is cigarette smoking. Our research suggests that roughly half of all women are particularly sensitive to the carcinogens found in tobacco and so have a higher risk of breast cancer if they smoke cigarettes. Such women have a slow-acting form of a liver enzyme that normally detoxifies carcinogens. Because these women's "detox" enzymes act more slowly than the enzymes of other women, the carcinogens in tobacco last longer in their bodies, allowing the substances more time to cause cancer. For such women, every cigarette loads the dice in favor of breast cancer.

Conflicting Evidence

Epidemiologists have been intrigued for years by hints that smoking can cause breast cancer. But for every study that purports to show a link between smoking and breast cancer, others fail to demonstrate any association—and some even show that cigarette smoking decreases a woman's risk of breast cancer. This is surprising because smoking causes so many other cancers, such as lung and bladder cancer. The reason for the discrepancy might be related to a complicated interaction among unidentified chemicals present in cigarette smoke that might lower estrogen levels in the blood of some women, thereby lowering their risk of breast cancer. Smoking also appears to lower the age at which a woman goes through menopause, which would also lower breast cancer risk because estrogen levels drop at menopause.

Although many previous studies do not impli-

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cate smoking as a risk factor for breast cancer, it is still unclear why breast tissue should be resistant to the harmful effects of cigarette smoke. Cigarettes contain roughly 3,600 chemicals, many of which are carcinogens. These include aryl aromatic amines, polycyclic aromatic hydrocarbons, heterocyclic amines and *N*-nitrosamines. Studies of laboratory animals show that many of these chemicals spur cells in the milk ducts to become cancerous; other studies of breast tissue taken from women indicate that human breast tissue responds to the carcinogens in a similar way. We also know that carcinogens from cigarette smoke reach the human breast: breast milk from women smokers contains nicotine and can cause mutations in cells grown in the lab.

Many researchers concluded that if smoking does contribute to breast cancer, it is only a bit player. But we looked at the results of the previous studies from a different standpoint. In 1994 we hypothesized that the estrogen-lowering (and thus anticancer) effects of smoking and the cancer-causing effects of smoking are in a continual tug of war. In some women, the carcinogenic effects of smoking might be more pronounced, whereas for other women the estrogen-lowering effects of smoking might predominate. Accordingly, we set out to discover what dictates how a woman's breast cells respond to cigarette smoke.

The Liver Connection

To understand how cigarette smoke might be carcinogenic in some women but not others, we must first understand the critical role the liver plays in body chemistry. Once cigarette smoke is inhaled into the lungs, toxic substances in the smoke cross over into the bloodstream, where they are taken up into the liver. The liver is equipped with hundreds of enzymes for detoxifying potentially dangerous chemicals, such as those that might be inhaled or eaten. These enzymes break down toxic chemicals so they can be excreted through the kidneys (as urine), by the gastrointestinal tract (as feces), or by the skin (as part of perspiration). People whose detoxifying enzymes act more slowly than those of others end up exposed longer to carcinogens. In such people, the carcinogens have more time to travel throughout the body to reach virtually every cell—including, in women, those that line the milk ducts, where breast cancer originates.

We began our research on the breast cancer–inducing effects of cigarette smoking by examining the gene that prompts the body to make the enzyme *N*-acetyltransferase 2, also called NAT2. This enzyme, which is active mostly in the liver, normally breaks down aromatic amines, such as those found in cigarette smoke. The *NAT2* gene comes in different forms: some encode slow-acting versions of the enzyme, and others encode fast-acting ones. Using genetic tests, we can determine whether someone has a fast-acting form and is therefore what we call a rapid acetylator, or a slow-acting version and is therefore a slow acetylator.

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We focused on NAT2 for two reasons: the enzyme is known to affect how people respond to certain drugs, and it is also thought to determine whether some people develop specific cancers. For instance, in the 1950s and 1960s, several groups of researchers found that some people were more prone than others to developing side effects while taking the antituberculosis drug isoniazid. These researchers found that people who metabolized the drug slowly—slow acetylators—were more likely to develop liver complications than rapid acetylators.

Both the slow- and fast-acting forms of NAT2 have been associated with an increased risk for cancers of various types. A number of studies have shown that slow acetylators have a higher risk for bladder cancer than rapid acetylators, whereas rapid acetylators are more likely to develop colon cancer. NAT2 has different effects on different chemicals, depending on the structure of the chemical. Researchers now think that slow acetylators have more bladder cancers because they cannot detoxify aromatic amines, carcinogens that are known to cause the disease. On the other hand, scientists speculate that rapid acetylators have an increased risk for colon cancer because NAT2 can activate heterocyclic amines, dietary carcinogens that are formed in the cooking of meats.

Whether someone carries a slow- or fast-acting version of NAT2 depends on the genetic make-up of her parents. We know that the frequency of these genetic variants is more common in some races than others. Roughly 55 percent of all Caucasian and Latin-American women (and men) are slow acetylators. African-American women (and men) are slightly less likely to have the trait; roughly 45 percent of them have the slow-acting form. In contrast, only between 10 and 20 percent of Asians have slow-acting NAT2. People who are of Middle Eastern descent have the highest likelihood of being slow acetylators: between 65 and 99 percent of them share the trait.

A Look at Women Smokers

Our evaluation of NAT2 and its role in breast cancer related to smoking, which was reported in the *Journal of the American Medical Association* in 1996, included only Caucasian women. The participants came from a study conducted by our colleagues in the department of social and preventive medicine at the State University of New York at Buffalo. Altogether, we examined the *NAT2* genes of 631 women; 304 of them had breast cancer. About 53 percent of the women we studied had been or currently were smokers. As predicted, roughly half had the slow-acting form of the NAT2 enzyme.

When we analyzed our results, we initially found—as in previous reports—that smoking was not a risk factor for breast cancer. The women who were heavy smokers had the same rates of breast cancer as light or nonsmokers. And we saw similar breast cancer rates among both slow and rapid acetylators. But when we factored both smoking and being a slow acetylator into the equation, we made an important finding: postmenopausal women who had the slow-acting form of NAT2 and smoked more than 15 cigarettes a day were more likely to develop breast cancer than light smokers or nonsmokers who also had slow-acting NAT2. We also found that postmenopausal women who were slow acetylators and began smoking at an early age (age 17 or younger) had the highest risk of breast cancer. These findings indicate that a postmenopausal

woman with a slow-acting form could elevate her risk for developing breast cancer if she smokes, particularly if she begins smoking when young.

We want to emphasize that the link between slow-acting NAT2, smoking and breast cancer was found only in women who have already undergone menopause. We found that postmenopausal women who smoked more than a pack a day and were slow acetylators had roughly four times the risk of developing breast cancer as did nonsmoking postmenopausal women with the slow-acting version of NAT2. But this is the first of many epidemiological studies on the role of NAT2 and breast cancer; other studies will be needed to confirm our findings.

We still don't understand why we saw a higher risk of breast cancer among postmenopausal women smokers than among their premenopausal counterparts. It could be because estrogens play a greater role in some breast cancers, depending on whether a woman is still menstruating. Accordingly, the balance between estrogens and carcinogens might be tipped toward cancer in postmenopausal women. Smoking might also have less of an apparent effect on premenopausal women because many breast cancers among these women are probably caused by other genetic factors that have not yet been identified. The difference between premenopausal and postmenopausal women might also arise because postmenopausal women have smoked for a longer period, so it follows that they have had more opportunities for tobacco to harm them.

Time to Quit

If having a slow-acting form of NAT2 elevates a woman's risk of breast cancer if she smokes, should scientists develop a clinical test for the enzyme to convince women with slow-acting NAT2 that they should never smoke?

We hope that as more women learn that smoking may cause breast cancer, they will stop. Getting the word out is important because the rates of both smoking and smoking-related illness continue to rise among women in the U.S. But a test based on the *NAT2* gene would have little utility in helping women make decisions about their health. It would be foolhardy for a woman to conclude that if she is a rapid acetylator, it is acceptable for her to smoke. Also, because both rapid and slow acetylators are at risk for other types of cancers caused by smoking, knowing your *NAT2* genetic makeup would not assure that you would not develop some type of cancer.

Besides breast cancer, smoking also causes lung cancer [*see box below*], heart disease and emphysema. This means that women have many reasons not to smoke, regardless of whether they are slow or rapid acetylators. In addition, our results suggest that at least for breast cancer the number of cigarettes you smoke a day is a greater risk factor than the total number of years you have smoked. So even if you have smoked for a long time, quitting now can still reduce your risk of breast cancer. SA

PETER G. SHIELDS and CHRISTINE B. AMBROSONE have a long-standing collaboration studying the molecular epidemiology of cancer. Shields is chief of the Molecular Epidemiology Section in the Laboratory of Human Carcinogenesis at the National Cancer Institute. Ambrosone is a research epidemiologist in the Division of Molecular Epidemiology at the Food and Drug Administration's National Center for Toxicological Research in Jefferson, Ark.

Lung Cancer: Why Women's Risks Are Higher

Lung cancer is the most common cause of cancer death among both men and women, accounting for approximately 160,000 lives lost in the U.S. every year. According to American Cancer Society statistics, one in 12 men will develop lung cancer, and one in 19 women will have the disease.

Although fewer women than men die of lung cancer—it kills roughly 95,000 men and 65,000 women annually—women who smoke are in more danger of the disease than male smokers. Evidence suggests that for the same level of smoking, women have twice the risk of developing lung cancer as men do.

Why the difference? We have a few leads. The types of lung cancers that women suffer are frequently different from those seen in men. Women are more likely to suffer adenocarcinomas, whereas men get more squamous cell carcinomas. Both are dangerous lung cancers that are difficult to treat. But the gender discrepancy in lung cancer types suggests to us that a combination of genetics and a differing response to exposure to carcinogens plays a role.

Other clues also suggest a gender gap in the way women and men develop lung cancer. For example, both sexes tend to have different types of mutations in the *p53* gene. This gene normally serves as a brake to prevent uncontrolled cell growth; when it is mutated, cancer can result. Even though men with lung cancer tend to have more mutations in *p53* than women with the disease, women tend to have more of a mutation called a *G*-to-*T* transversion, which is thought to be caused by smoking. This type of mutation results when toxic chemicals damage guanine (*G*), one of the four units that make up DNA. When a cell with such damaged DNA tries to copy its genes before dividing, it can misread the damaged *G* as a thymine (*T*), another letter of the DNA alphabet. This case of mistaken identity can prevent *p53* from functioning normally, allowing a cell to grow out of control.

Several researchers have recently found that the risk of lung cancer from inherited genes also is different for men and women. As a result, women tend to have higher levels of so-called carcinogen adducts in their lungs than men do. These chemical compounds form when cancer-causing agents stick to DNA. Such carcinogen-DNA combinations increase the chances of mutations that can lead to cancer.

Hormonal differences between men and women undoubtedly contribute to the higher risk of lung cancer among female smokers. Women have higher levels of the hormones estrogen and progesterone than men do. Cells in the lung cancers of women are two times more likely than those of men to bear receptors for estrogen and progesterone, hormones that can stimulate tumor growth.

Considering the gender differences in lung cancer biology, it has been difficult to compare the lung cancer risks of men and women smokers. Because fewer women than men smoke on average, they develop lung cancer less frequently. So far studies examining the risks for lung cancer have not been large enough to explore the differences between men and women. But larger studies by us and others are now in progress. Perhaps within the next few years researchers will have a better understanding of the gender differences in lung cancer. We hope that knowledge will lead to better treatments for women—and men. *—P.G.S. and C.B.A.*