Variations on a Theme

Interplay of genes and environment elevates cancer risk

By KATHLEEN FACKELMANN

A young woman named Donna starts to fill out a life insurance form. She answers all sorts of health questions, including some on diet. One asks how often she eats red meat. Her reply: at least 7 times a week.

A visiting nurse takes the completed form and tells her the company will need a blood sample to go along with her application. Donna rolls up her sleeve and watches as the nurse fills several tubes with the crimson liquid.

Two weeks later, Donna gets a letter in the mail from the insurer. Her application has been denied.

The blood sample revealed that she has inherited a common genetic variation, one that is harmless except to meat lovers. Donna's carnivorous habits have put her at high risk of developing cancer.

Geneticists seem to capture headlines at a dizzying pace as they mine the human genome. Last year, they uncovered a gene that, when flawed, ratchets up the risk of breast and ovarian cancer. A mutant form of another gene has been linked to the near certainty of developing colon cancer.

Yet scientists know that such disease-causing supergenes account for only a fraction of all cancer cases. The fictional example described above represents a far more common genetic tie to cancer. In such cases, an otherwise harmless genetic variation can predispose an individual to cancer, but only in conjunction with external factors, such as diet.

It turns out that some genes, like ice cream, come in several varieties. At birth, some people get the plain chocolate form, while others get the mint chocolate chip version. Either way, scientists don't regard these gene variations — called polymorphisms — as flaws.

But there's a hitch. Scientists suspect that certain polymorphisms may boost the chance of developing cancer. Unlike the nearly immutable risk conferred by the supergenes, these polymorphisms raise the specter of cancer only in the presence of specific environmental hazards.

For example, one team now presents evidence that smokers with a particular polymorphism run a high risk of breast cancer. A second group shows that a common genetic variant can boost, for some people, the chances of developing a deadly brain cancer. The scientists aired these findings in March at the American Association for Cancer Research meeting held in Toronto.

"I'm thrilled that we're showing there's a clear gene-environment interaction," says Peter G. Shields of the National Cancer Institute in Bethesda, Md. "That is something that hasn't really been proven until the last few years."

Knowledge of an inherited susceptibility might spur people to avoid carcinogens that raise their risk, the researchers say.

Take smoking, for example. Shields, along with Christine B. Ambrosone of the State University of New York at Buffalo, has evidence that a genetic variation in a gene called NAT may put smokers in jeopardy of breast cancer.

The NAT gene contains the blueprint for the enzyme N-acetyltransferase. Cells rely on this enzyme to detoxify carcinogens, including the hazardous chemicals found in tobacco smoke. NAT comes in several varieties, each one responsible for a slightly different version of the enzyme.

The researchers knew that previous epidemiological research had failed to find a consistent link between breast cancer and smoking. Those negative findings had always puzzled Ambrosone and others, because they knew that tobacco smoke contains certain chemicals, called aromatic amines, that damage the DNA in breast cells. Such DNA injury is the first step leading to cancer. Moreover, other scientists had discovered that these amines cause breast tumors in rodents.

The laboratory studies suggest that "these are powerful mammary carcinogens," Ambrosone says. So why had previous epidemiological studies failed to forge a solid connection between breast cancer and smoking?

Perhaps only a subgroup of smokers would prove at risk, the researchers speculated. To test that hypothesis, Ambrosone's team collected information on 159 postmenopausal women who had breast cancer and who had participated in a large study conducted from 1986 to 1991. For comparison, the team looked at 203 women who did not have cancer at the time of the study. The researchers culled data on smoking, diet, alcohol use, and other factors that might influence cancer risk.

Researchers also had access to blood samples from the study participants. That's where Shields and his colleagues came in. Using polymerase chain reaction, a technique that ampli-

Illustration by Dan Skripkar

fies segments of DNA, they looked for variations in the NAT gene.

They then classified each volunteer as either a slow or a fast acetylator. Slow acetylators have a version of the NAT gene that leads to an enzyme that is less efficient at detoxifying carcinogens, including the aromatic amines in cigarette smoke.

When the team analyzed breast cancer risk on the basis of genotype, they found the increased risk in one group: smokers who produce the slower enzyme.

Indeed, the analysis suggests that slow acetylators who smoke more than 15 cigarettes a day (this study's definition of heavy smoking) are eight times more likely to develop breast cancer than nonsmokers with the same genetic heritage.

Ordinarily, the NAT enzyme can prevent DNA damage caused by aromatic amines by changing these carcinogens into a form that the body can excrete. But the slower the process of excretion, the greater the likelihood that some DNA foul-ups will occur.

Once its DNA is injured, a cell may lose control over its growth and turn malignant.

Ex-smokers who are slow acetylators appear to have a higher risk of breast cancer than women who have never smoked. What's more, the team's data show that women who begin smoking early in life, possibly in their teens, face the greatest cancer threat. "Carcinogenesis is a long, slow process," Ambrosone says.

Yet slow acetylators who do not smoke face no excess threat of breast cancer, the research indicates.

That finding may help explain why previous epidemiological studies revealed no link between smoking and breast cancer. When researchers lumped slow and fast acetylators together, the cancer risk never emerged. But when they zeroed in on a specific group of smokers, the jeopardy surfaced, Shields says.

"If we can categorize women by specific [genetic] susceptibilities, then we can identify new risk factors," he adds.

What's the difference between inheriting a polymorphism and inheriting a mutation in a breast-cancer-causing gene, such as BRCA1?

Geneticists believe that women born with a mutant BRCA1 face an 85 percent chance of developing breast cancer at some point in their lives (SN: 9/24/94, p.197). Environmental factors may play a role, but in most cases the defective gene by itself confers that elevated cancer risk.

In contrast, the slow version of NAT does not by itself increase cancer risk, even though it causes changes in the enzyme. But should a polymorphism be considered a defect?

Shields points out that "in some populations, slow acetylation is 20 percent; in other populations it's 80 percent — so who's got the mutation?" He speculates that the polymorphism in the NAT gene may have evolved to serve some unrecognized beneficial purpose.

Rapid acetylators may face their own cancer demons, says Shields. For example, they are at risk for colon cancer because they can unleash the toxicity of heterocyclic amines, potential carcinogens found in cooked meats (SN: 4/23/94, p.264).

NAT isn't the only example of a polymorphism's link to cancer.

Enter the GST gene, which codes for an enzyme called glutathione S-transferase. This gene and its enzyme help the body get rid of cancer-causing chemicals that are known to be active in the brain.

John K. Wiencke and Margaret Wrensch of the University of California, San Francisco, and their collaborator Karl T. Kelsey of Harvard University speculated that variations in GST might play a role in a mysterious, deadly brain cancer called glioma. Glioma causes progressive mental deterioration, blindness, deafness, and convulsions.

The team knew that many people — 50 percent of whites in the United States and about 30 percent of African Americans — inherit a polymorphism of GST. But rather than representing a simple variation in the GST gene, this polymorphism results in an absence of the gene altogether, Wiencke points out.

Scientists consider it a completely normal difference in genetic heritage. People who lack GST don't experience problems — unless they encounter a specific chemical that needs to be quenched. The researchers wondered if such individuals would then face a heightened threat of brain cancer.

To find out, they collected information on 147 people from Northern California who had been diagnosed with glioma. For comparison, the team gathered data on 118 controls who did not have brain cancer.

The team's analysis revealed a risk associated with this polymorphism, but only for young women. About 80 percent of the women who had developed gliomas before age 40 had no GST gene.

Researchers have no real clue as to the causes of such tumors. "It's a very difficult and puzzling disease," Kelsey says. That enigma added significance to the dramatic finding.

"We were thrilled at our results," Wiencke says.

Yet the team stresses that their results are only preliminary and must be confirmed. "To my mind, the first thing to do is to replicate and see if this finding is real," Wrensch says.

Many questions remain unanswered. For example, the group has no idea why young women appear at risk. Does this indicate a sex-based difference, perhaps a hormonal involvement in this kind of brain cancer? "We're trying to explain that [finding]," Kelsey says.

And unlike the NAT-smoking link, no environmental toxin predisposing some people to gliomas has surfaced yet. GST genes detoxify a whole host of carcinogens, and the researchers have yet to focus on a particular one.

They plan to isolate some environmental suspects soon. "We've got a gene that is leading us to something," Wiencke says.

Whereas cancer-causing supergenes run in only a few families, polymorphisms are part of everyone's genetic heritage. You're either a slow or a rapid acetylator. You either have GST or you haven't. In most cases, such polymorphisms cause no harm. In fact, scientists argue that when high percentages of the population inherit such a variation, it may be a sign that the altered form confers some as yet unknown advantage.

But the flip side is that polymorphisms may pose a cancer threat to certain people — those exposed to a specific carcinogen. Smokers who've inherited the slow version of NAT run the risk of developing breast cancer. Without the smoke, there's no threat.

Scientists are just beginning to unravel the complex interplay among genetic variations, cancer, and the environment. Studies will continue to fill in the details of how such polymorphisms bring on a malignancy.

If successful, researchers may someday print out a map of an individual's genome, including the variations in genes that help detoxify carcinogens. "That would be the fantasy," Shields says. "To actually sit down with a person and say: Look, you have this genetic makeup. Your risk from smoking is much higher [than average]."

"If you could find genes that are important in carcinogenesis and understand what in the environment they're interacting with . . . then you'd have a handle on what to modify in the environment," Wrensch says.

Some scientists believe that such knowledge would provide people with powerful incentives to protect themselves.

Others believe that Donna's fictional story may become reality. Will insurance companies deny coverage to people who indulge a habit sure to skyrocket their odds of developing cancer? Will employers require workers to take a genetic test that assesses their body's ability to detoxify certain chemicals?

"This is a controversial and difficult area," Kelsey says. "I believe that some of these variant genes will in fact increase risk. Once that is well accepted and well shown, then we have to make social decisions on how to deal with that." □