

But is it ready for prime time?

Hot, new technology shows promise for determining breast-cancer risk

Although they have received a great deal of attention in the press, mutations in the BRCA1 and 2 genes are responsible for only a small percentage of breast-cancer cases. Since breast cancer is a genetic disease, science needs to look for variations in other genes to explain what causes the disease in the majority of the women and men who get it. A recent advance in genetics may help solve the riddle by looking for tiny differences in a person's overall genetic makeup, or genome, said Jessica Everett, M.S., who is a genetic counselor at Cincinnati Children's Hospital Medical Center.

"The big hot thing that people are talking about are common changes in the genome that are called single nucleotide polymorphisms, or SNPs (pronounced snips)." A person's genetic makeup is derived from his or her DNA, a long chain of chemical compounds, known as nucleotides or base pairs. These nucleotides come in just four varieties, designated by the letters A, T, G and C. Everett explained, "A SNP is just a change in the DNA sequence of one letter. When we say they are 'common,' we mean that if we looked at 100 people, probably 99 of them would not have the change, but one would."

Scientists currently know of at least 10 million different kinds of SNPs that can occur in humans, she said. "That accounts for the reason we look and behave differently from one another." It also affects a person's susceptibility to diseases like breast cancer. She explained, "There is a lot of buzz around the idea that some these little variations may individually have a small impact on a person's breast cancer risk, but when you add those particular SNPs together, that may be enough to have a big influence on the individual's risk for breast cancer."

Although it seems straightforward, the determination of an individual SNP's impact on breast-cancer risk is anything but, Everett said. "The way this kind of study works is that researchers gather a group of women who have breast cancer and a group of women who do not, and then look at a particular SNP location." Perhaps they find that the SNP is present more often in the women who have breast cancer by a ratio of 9 percent to 5 percent. "The idea is there may be some type of connection there. Maybe they're finding that genotype (form of the gene) in women with breast cancer, because it is somehow related to why they got breast cancer." However, she cautioned, "This doesn't necessarily tell us there's a direct cause and effect. It only tells us that it seems there might be something going on here."

The relationship between a certain SNP and cancer risk becomes thornier because different SNPs can act against each other or can cooperate with one another. "We know that individual genes certainly don't act independently of each other, so looking at variation in one SNP is not even going to come close to getting at the complexity of the situation."

She pointed to a study of SNP interactions as an indication of the difficulties in determining the importance of certain SNPs to breast cancer. The researchers in the study considered only 10 of the different SNPs that might be related to breast-cancer risk. When they looked at the number of genotypes that could arise from combinations of two or three SNPs among those 10, they counted more than 16,000 different genotypes, she said. "And that doesn't even get close to understanding how all 10 of them interact together."

The task is daunting, but studies of SNPs are making important inroads, she said. "We're now at the stage where we can genotype a person at probably 90 different SNPs and have the result in a couple of days. We can do this quickly, we can do it easily, and it's relatively inexpensive." This is also presenting a problem, she noted. "Because we can do it quickly, easily and inexpensively, and because we're dealing with consumers who want to know their risk and how they can do something to change it, we're starting to run into situations where companies are coming to market with risk-prediction tests based on SNP associations. What we need to think about as scientists, researchers, health care providers and health care consumers is: Is this really ready for prime time?"

One currently available test is an example. It claims to determine an individual's five-year and lifetime breast-cancer risks by screening for 90 SNPs in 78 genes, she said. "They send you back a piece of paper that says your five-year risk for breast cancer is (for example) 12 percent and your lifetime risk for breast cancer is 30 percent, so good luck," Everett recounted. Unfortunately, she said, clinicians don't really have good, clear recommendations to give women based on these kinds of risk numbers. "The first thing that comes to my mind when I find these kinds of tests for sale on the internet is whether it's OK for us to offer tests to patients outside of a research setting when we don't know if they are clinically relevant. My argument would be that that is irresponsible, but I'm certainly not the only one having a voice on the issue."

Ethical questions aside, the research is continuing at a fast pace. Everett commented, "Cancer is a genetic disease. Cancer happens because things go wrong with genes, and it's this kind of SNP testing that really shows a lot of the promise." She added, "Coming at this from a clinical perspective, my big question is always about what we are going to do differently. How is this going to be clinically relevant, and at that point, are we ready to talk to patients about doing this particular kind of testing?"

Summary of Ms. Everett's presentation at the November 2005 BCERC Scientific Symposium:
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