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Genetic Aberrations Seen as Path to Stop Colon Cancer

By GINA KOLATA

More than 200 researchers investigating colon cancer tumors have found genetic vulnerabilities that could lead to powerful new treatments. The hope is that drugs designed to strike these weak spots will eventually stop a cancer that is now almost inevitably fatal once it has spread.

Scientists increasingly see cancer as a genetic disease defined not so much by where it starts — colon, liver, brain, breast — but by genetic aberrations that are its Achilles' heel. And with a detailed understanding of which genetic changes make a cancer grow and thrive, they say they can figure out how best to mount an attack. They caution that most of the drugs needed to target the colon cancer mutations have yet to be developed, but they say they are building the road map that they hope will lead them to new treatments.

The colon cancer study, published on Wednesday in Nature, is the first part of a sweeping effort that is expected to produce a flood of discoveries for a wide range of cancers. The colon cancer findings will soon be followed by studies of lung and breast cancers and, later this year, of acute myeloid leukemia. The effort, the $100-million-a-year Cancer Genome Atlas project, is being financed by two government agencies, the National Cancer Institute and the National Human Genome Research Institute.

The colon cancer results, based on a study of 224 tumors, show what may be possible.

"There are so many different ways that you can attack this tumor type," said Raju Kucherlapati, the principal investigator for the colon cancer project and a professor of genetics and of medicine at Harvard Medical School. "We have an opportunity to completely change the landscape."

Researchers caution, though, that although much is known about the genetic changes that occur in colon cancer, treatment has not caught up.

"It is going to take time, and it is going to take effort," said Dr. Charles Fuchs, a gastrointestinal cancer expert at Harvard who was an author of the study. But, he added: "I don't want to minimize the singular importance of this paper. It is transformative."

Researchers have studied colon cancer before and have identified mutations that seemed critical, but their work lacked the scope of the new project, and it provided more limited information on genetic changes, said Dr. Sanford Markowitz, a colon cancer and genomics expert at Case Western Reserve University. He said the new study was "like sending out Lewis and Clark."

Dr. Markowitz, like nearly every other leading scientist in colon cancer genomics, is an author of the new study.

About 150,000 Americans receive a diagnosis of colon or rectal cancer each year, and about 50,000 die annually from the disease.

Outcomes are excellent if the cancer is found and treated early, while it is confined to the colon. But they are dismal after it has spread, with only 5 percent of patients surviving for five years.

When it comes to treatment, Dr. Kucherlapati said, “nothing much has changed.”

For Dr. Kucherlapati, some of the most intriguing discoveries point to new treatment possibilities. For example, about 5 percent of the colon cancer tumors studied had extra copies of a gene, ERBB2, as do many breast cancer tumors. A drug, Herceptin, which greatly helps breast cancer patients with too many ERBB2 genes, might also help colon cancer patients with the same aberration. Scientists say they would like to put colon cancer patients with the mutation in clinical trials testing the effects of Herceptin.

Like previous studies, the new research found that about 15 percent of colon cancers had a mutation in a gene, BRAF, that is often mutated in melanoma, a skin cancer. A drug approved for melanoma blocks the function of that gene product, but it has not worked in colon cancer patients.

But these colon cancer patients often have an additional genetic aberration that can be attacked with a different drug, one that blocks the function of a cell protein, EGFR. Researchers would like to test whether treating colon cancer patients who have both the BRAF mutation and the EGFR aberration with the melanoma drug and the EGFR drug might halt the cancer.

The possibility of helping selected colon cancer patients with drugs that are already on the market “is actually thrilling,” Dr. Kucherlapati said.

The study also found gene pathways that had been previously identified in studies with small numbers of patients. One known as WNT was mutated in 95 percent of the colon cancer patients whose tumors were examined in the new study.

“To my knowledge, until this study it wasn’t really clear how pervasive aberrations of this pathway are,” said Dr. Todd R. Golub, a cancer genomics researcher at the Broad Institute of Harvard and M.I.T. and at the Dana-Farber Cancer Institute.

And that is good news, he said, because it rules out a situation in which every tumor has a totally different genetic pathway that is mutated, requiring 1,000 different drugs to attack 1,000 different tumors.

“We would never get on top of that,” Dr. Golub said. He was not an author of the study, but his colleagues at the Broad Institute were.

The hope now is that the genetic alterations driving those 1,000 different tumors are operating through

only a limited number of genetic pathways that can be targeted by a more manageable number of drugs.

Those drugs have yet to be developed, said Dr. S. Gail Eckhardt, the head of the division of medical oncology at the University of Colorado and an author of the study. But, she added, the work “confirms where some of the drug development should be going.”

“The Nature paper explains that it will not be simple,” she said, “but if we target smartly, it will lead to clinical benefits.”

It also shows why smaller studies could not provide a complete picture of the cancer’s genetic tricks, even though colon cancer has been a poster child for cancer genetics. Going back to the mid-1980s, Dr. Bert Vogelstein and his Johns Hopkins colleagues used what would now be considered outdated techniques to investigate the genetic changes that occur as a benign colon polyp becomes a deadly cancer. What he discovered — a sequence of genes that tended to be mutated — was confirmed in the new study, along with the finding of rarer genetic changes that he could not easily detect.

Dr. Vogelstein, who was not an author of the new study, said it was “a great study, a definitive study.”