Research breakthroughs may lead to colonoscopy alternative: NetWellness

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By Special To The Plain Dealer

For men and women combined, colon cancer stands as the leading cause of cancer-related deaths in the United States. Given this reality, researchers across the globe work to make advancements in the detection, diagnosis and treatment of this disease.

A leading example of this work can be found in the Markowitz laboratory at the Case Western Reserve University School of Medicine. The laboratory research can be separated into three broad categories: inheritance and colon cancer, the effect of mutations on colon cancer defense, and advancements in colon cancer screenings.

Inheritance and colon cancer

The research focus of the Markowitz laboratory concerns cancer inheritance; the genetic risk for developing colon cancer. By identifying inherited risk, tests can be created to recognize individuals at high risk for colon cancer who can benefit from screening to detect colon cancer and precancers in early stages when there is a better chance of the disease being cured. A growth is considered to be precancerous when cells are undergoing abnormal changes that, left untreated, could lead to cancer. As the process continues, these cells may develop changes that are definitive for cancer.

Along with other CWRU faculty members, the lab led a study to determine if there was a genetic (inherited) marker in families for colon cancer. A genetic marker is an alteration in DNA that may indicate an increased risk of developing a specific disease. By finding these markers, researchers are able to trace a certain trait (like colon cancer) from person to person within families.

This particular study involved families in which two or more siblings who at age 65 (or younger) developed colon cancer or large precancerous polyps. This "colon cancer sibling study" gained exposure with the help of CBS Evening News anchor Katie Couric and recruited families from across the country.

In 2003, researchers discovered that many of the people who had developed colon tumors inherited the same abnormal region on a specific chromosome, chromosome 9. (A chromosome is a single piece of coiled DNA that contains many genes, which determine a person’s inherited characteristics.)

By 2009, the team was able to identify that certain people who developed colon cancer inherited a nonworking form of a specific gene in this region named the GALNT12 gene. Research to date suggests that this defective gene may result in defective colonic mucins and inflammation of the inner wall of the colon, giving rise in turn to colon...
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cancer. Many genes other than GALNT12 have been shown to affect the creation of mucins in the intestines. Therefore, this discovery is only the tip of the iceberg and more research is under way.

How mutations limit cancer defense

Like brakes on a car, the role of tumor suppressor genes is to slow and even stop abnormal cells from dividing. When left unchecked, the fast division of these defective cells leads to cancer. Mutations (abnormal DNA) in special genes that prevent tumors from developing (tumor suppressor genes) remove one tool of the body’s defense to cancer. Finding the culprit attacking the tumor suppressor genes is an important way to identify how cancer is brought on and how it can be treated.

Since 1995, one of the initiatives of the laboratory has been the discovery of mutations that wipe out the body’s normal ability to keep colon cancer from forming. Research conveyed that more than one-third of human colorectal cancers showed mutations in a particular gene, called TGF-beta Receptor 2 (RIL). One role of RIL is to turn on another gene, named 15-PGDH, which in turn keeps tumors in the colon from forming. Similar to a domino effect, when RIL does not work properly, 15-PGDH is not present. This is now believed to be one key cause of colon cancer.

By knowing how a cancer starts, more specific and targeted therapies can be discovered. Research shows that the levels of 15-PGDH in the colon determine how effective existing drugs will be in people with colon cancer. In some cases drug therapies may be the best option, but the lab is now working on developing gene therapies for those who lack 15-PGDH in their colon. Medications are being investigated by the Markowitz Lab to increase or reactivate the effective functioning of this gene as a new treatment for colon cancer.

From lab bench to bedside

Currently, colonoscopies remain the physician’s best tool for the early detection of colon cancer in patients. However, many patients remain fearful of the test, due to its uncomfortable, laxative-based preparation and its cost (when not covered by insurance). In an effort to give patients another colon cancer screening option, researchers at CWRU have developed an alternative, marketed as Colisure. In 2009, the American Cancer Society added DNA testing to its colon cancer screening guidelines.

Through research, it was discovered that abnormal DNA is produced by colon cancer, and could be identified from the stool of colorectal cancer patients. Regardless of the location of the cancer in the colon, the test detected 77 percent of stage I and stage II colorectal cancers.

Using a stool sample that is taken at home, this noninvasive test identifies DNA markers for colon cancer. Though not covered by some insurances, the $250 cost of this test is much less than that of a colonoscopy, which can cost more than $3,000 when not covered by insurance or when insurance is unavailable. Colisure is now available for order by doctors and more testing is under way to improve the sensitivity of the test. This stool DNA test should be considered in cases where colonoscopies are not feasible, for reasons such as financial and medical concerns.

Also in 2009, collaboration between researchers at CWRU and Johns Hopkins University showed that a colon cancer blood test proved promising. By detecting genetic cancer markers in a colon cancer patient’s blood, nearly half of early-stage colon cancer cases were detected in studies. Further studies are planned to improve the sensitivity of the test. Its use as a detection tool for early recurrences of colon cancer following initial surgery is also being investigated.

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