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Deficiencies in repair of DNA identified in many types of solid tumors

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A new investigation of more than 48,000 stored tumor samples finds evidence of a key deficiency in a repair mechanism designed to keep DNA from being mutated and causing cancer.

The DNA repair deficiency, called homologous recombination deficiency, or HRD, has previously been studied in only a few cancers, but as researchers at Georgetown Lombardi Comprehensive Cancer Center report, HRD can be found in all of the cancer types the researchers studied, including prostate, breast, cervical, and endometrial cancers as well as two of the more deadly types: ovarian cancer and glioma, a type of brain cancer.

The researchers say the findings could play an important role in identifying which mutated genes, and which types of cancer, could be targeted to take advantage of the deficiency and ultimately help in treating the cancer. The abstract describing the work was released today. Additional details will be presented at the American Society of Clinical Oncology annual meeting next month in Chicago.

"We know that patients with BRCA mutations are at high risk for developing breast, as well as pancreatic, ovarian, prostate and other cancers, and we have learned over time that BRCA plays a very important role in DNA damage repair. But BRCA is just one of the many genes that encode important proteins in the DNA repair pathway known as homologous recombination," says the study's lead author, Arielle Heeke, MD, a clinical fellow at Georgetown Lombardi

Comprehensive Cancer Center.

"With ongoing studies of the homologous recombination pathway and its impact on cancer development, we may identify additional genes that, when mutated, allow for either improved response to specific treatments or conversely, portend more aggressive tumor biology, and this could greatly inform development of new cancer therapies," Heeke explains.

In this study, Lombardi researchers partnered with Caris Life Sciences, Inc. Caris performed the molecular profiling on 48,733 solid tumor samples to assess the prevalence of homologous recombination deficiency in about 20 different types of solid tumors. The investigators identified evidence of HRD-related mutations in 11.61 percent of them, with the highest concentration of mutations in endometrial cancer, gliomas, and ovarian cancers (38, 15 and 12 percent respectively). The most commonly mutated genes were found to be the ATM, PTEN, BRCA2, BRCA1, and ATRX genes.

"We do not yet know the clinical impact of many of these mutations. However, several clinical trials are currently underway to assess a type of therapy that inhibits a DNA repair enzyme known as PARP in tumors with HRD," said Heeke. "In fact, Lombardi has a clinical trial that will open this summer evaluating the use of a PARP inhibitor in patients with tumors with this key deficiency."

Heeke says the study would be open to people whose tumors have evidence of HRD like those found in this study, which includes bladder, breast, cervix, liver and bile duct, colorectal, endometrial, gastric/esophageal, head & neck, kidney, neuroendocrine, lung, ovarian, pancreas, prostate, sarcoma, and thyroid cancers, as well as gastrointestinal stromal tumors, glioma, melanoma and unknown primary cancers. The trial "Niraparib Plus Carboplatin in Patients with Homologous Recombination Deficient Advanced Solid Tumor

Malignancies" is not yet recruiting patients for enrollment.

"If, as we postulate, the combination of chemotherapy and PARP inhibition is successful in treating patients with HRD tumors, I expect that others will start exploring whether similar drugs or analogous therapies can make a difference in these diseases," Heeke concludes.

More information: Paper title: Prevalence of Homologous Recombination Deficiency Among All Tumor Types

Provided by Georgetown University Medical Center