Researchers develop test to ID aggressive ovarian cancers early

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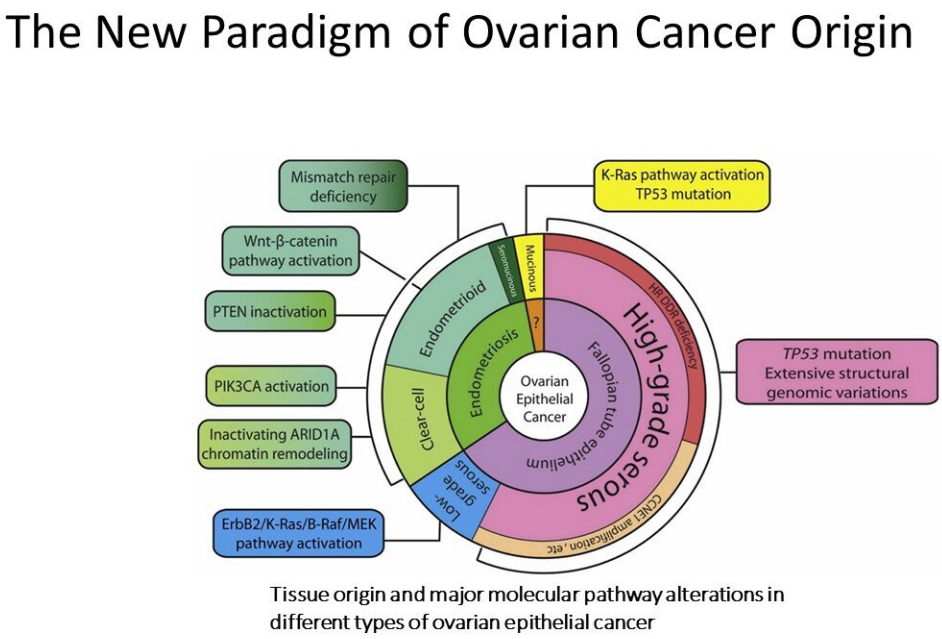

This graphic depicts the biology of serous tubal intraepithelial carcinomas (STICs), lesions believed to be the main precursors of ovarian high-grade serous carcinoma (HGSC), the most common form of ovarian cancer in women Credit: Ie-Ming Shih (author) and Lydia Gregg (artist)/JHU

Researchers at the Johns Hopkins Kimmel Cancer Center and the Department of Gynecology and Obstetrics at the Johns Hopkins University School of Medicine have developed an algorithm to identify

high-risk precancerous lesions on the fallopian tubes. Known as serous tubal intraepithelial carcinomas (STICs), these lesions are thought to be the main precursors of ovarian high-grade serous carcinoma (HGSC), the most common form of ovarian cancer in women.

The algorithm, called "REAL-FAST" (RealSeqS-based algorithm for fallopian tube aneuploidy pattern in STIC), identified five distinct groups of precancerous lesions in fallopian tubes, two of which were identified as potentially aggressive and frequently associated with recurrent HGSC. The results provide the first molecular evidence that STICs have unique identifiable genetic features.

The pilot study, published in *Clinical Cancer Research*, was led by Yeh Wang, M.D., Ph.D., a pathology resident under the direction of Ie-Ming Shih, M.D., Ph.D., Richard W. TeLinde Distinguished Professor and professor of gynecology and obstetrics at the Johns Hopkins University School of Medicine.

Although women at an increased or average risk of developing ovarian cancer often undergo salpingectomy, a procedure to surgically remove both fallopian tubes to reduce the risk of developing ovarian cancers, current clinical practice does not include a detailed examination of potential precancerous lesions, meaning many women face an uncertain future, Shih says.

"This is a high-risk setting—these patients need more immediate diagnostic approaches," says Christopher Douville, Ph.D., assistant professor of oncology at the Johns Hopkins University School of Medicine and one of the lead study authors. "This test is about identifying precursor lesions before they progress to cancer."

However, not all STICs are molecularly equal, Douville says, and identifying aggressive STICs early is challenging. Due to the small size

of the lesions, current evaluation methods equate to trying to find a needle in a haystack. Shih, Douville, and their team set out to develop a tool that could detect and stratify STICs according to key genetic alterations and mutations.

The researchers used a technique called Repetitive Element AneupLoidy Sequencing System, or RealSeqS, to sequence 150 DNA samples and analyze the level of aneuploidy, the presence of missing or extra DNA chromosomes, in STIC versus HGSC and normal-appearing samples.

Initial results showed that while normal-appearing samples had low levels of aneuploidy, STICs had significantly more non-random genetic alterations, even when they appeared structurally normal, including whole and partial deletions of chromosome 17 in the signatures of the tumor suppressor p53 proteins.

The authors suggest that the loss of chromosome 17 offers a potential explanation for the concurrent inactivation of both the TP53 and BRCA1 genes, which are both located on chromosome 17 and represent the most important tumor suppressors known to be involved in the development of HGSC. This could explain why germline mutations involving the BRCA1 gene, and not BRCA2 (found in chromosome 13), are associated with a high risk of HGSC.

Based on these findings, the researchers then built the REAL-FAST algorithm to classify samples into distinct molecular groups independent of their structural characteristics. REAL-FAST identified five groups, including a STIC subgroup with unique chromosome alterations that are associated with increased proliferation and abnormal growth.

Further validation of REAL-FAST for detecting STICs and HGSCs demonstrated that the test accurately detected the presence of cancer 95.8% of the time and correctly ruled out cancer where it did not occur

97.1% of the time.

Together, the findings suggest that only some STICs progress to HGSC and that this progression is associated with a non-random increase in chromosomal abnormalities.

"The analysis of the RealSeqS data provides a basis for answering fundamental questions pertinent to the earliest events of HGSC development," says Douville. "Although it can easily take a decade to translate research to clinical practice, Dr. Shih feels this research could make a rapid impact on patient care by providing clinicians with diagnostic alternatives with quantitative answers."

Though REAL-FAST requires further validation of its utility in a clinical setting to correlate the molecular data and patients' outcomes, the authors believe that a clearer understanding of how HGSC develops will soon lead to better diagnostics and improved outcomes for the thousands of women diagnosed with cancer every year.

More information: Yeh Wang et al, Aneuploidy Landscape in Precursors of Ovarian Cancer, *Clinical Cancer Research* (2023). DOI: 10.1158/1078-0432.CCR-23-0932

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