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Discovery of gene fusion in ovarian cancer could lead to earlier diagnoses

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About 15 percent of cases of an aggressive, difficult-to-detect form of ovarian cancer contain a unique fusion between two neighboring, normally separate genes, say researchers at the Stanford University School of Medicine. Although gene fusions are known to occur in prostate and some blood cancers, they have been notoriously difficult to identify in solid tumors. This is the first recurrent gene fusion found for ovarian cancer.

The finding is important because it could give clinicians an edge as they scramble to develop a better screening test for serous ovarian cancer, which accounts for about 50 percent of all cases but about 80 percent of all deaths from this type of cancer. If further research shows that the protein product of the gene fusion circulates in the blood, it may be possible one day to detect in early stages of the cancer.

Furthermore, if the fusion protein — which marries a portion of a gene-regulatory protein related to the estrogen receptor and another of unknown function — initiates or contributes to cancer progression it could be a target for future therapies.

"This kind of genetic lesion — a chromosomal rearrangement involving pairs of genes located near one another on the same chromosome — can escape detection by any of the methods traditionally used to detect chromosome rearrangements in cancer," said biochemistry professor Patrick Brown, MD, PhD. "But I think these local rearrangements that have previously flown under our radar might actually turn out to be

among the most frequent genetic lesions in cancer."

Brown, a Howard Hughes Medical Institute investigator and a member of the Stanford Cancer Institute, is the senior author of the study, which will appear in the Sept. 20 issue of *PLoS Biology*. Research associates Julia Salzman, PhD; Robert Marinelli, PhD; and Peter Wang, MD, PhD, are co-first authors.

Gene fusions, where a portion of one gene is swapped with a portion of another, have been previously identified in other cancers. In particular, a fusion between two genes on chromosomes 9 and 22 (also known as the Philadelphia translocation) occurs in nearly all people with chronic myelogenous leukemia and is used to diagnose the disease. And recently, gene fusions involving a family of important regulatory genes have been found in a large fraction of prostate cancers.

Gene fusions are interesting because many proteins are modular — for example, containing discrete "domains" responsible for binding to DNA or other proteins. Hybrid proteins arising from such mix-and-match fusions may have unique functions that contribute to the development or progression of a cancer cell. Because these proteins are unique to the cancer cell, clinicians might also be able to also look for their presence in normal blood, which could be a more effective method than the current approach that uses other, less-sensitive markers for ovarian cancer that are also found in normal blood.

Early detection of serous ovarian cancer is particularly important. Every year about 14,000 women in the United States are killed by ovarian cancers, many of which are of the serous type. Serous cancers are especially deadly because they usually metastasize before they are diagnosed.

A previous study by Brown's lab indicated that it is necessary to be able

to detect tumors of this type of cancer when they are only about the size of a peppercorn in order to make a significant dent in mortality. This is about 200 times smaller than those detectable by the current diagnostic methods. Encouragingly, though, the previous analysis also indicated that it takes about four years before these tiny tumors metastasize and become life-threatening.

Building on their previous study, Brown, Salzman, Marinelli and Wang set out to find tumor-specific, recurrent (that is, the same fusion occurs in many cases of the tumor) biomarkers in 67 tumor samples collected by the Pacific Ovarian Cancer Research Consortium, the Fred Hutchinson Cancer Research Center and the British Columbia Cancer Agency. They focused on gene fusions because they can be highly detectable if the protein product circulates in the blood. But to do so, they had to rely on the latest in sequencing technology to "read" the RNA messages that carry protein-making instructions from the DNA to the cell's machinery.

"We began looking for biomarkers in ovarian cancer by using a recently developed technique called deep paired-end sequencing," explained Salzman. "This allowed us to catalogue all the RNA in a pool of 12 tumors and look for unusual combinations that don't exist in normal tissue. We identified several potential gene fusions, but one looked particularly interesting because it involved a protein called ESRRA, or estrogen-related receptor alpha."

The researchers took note because ESRRA has been linked in some cases to a poor prognosis in breast cancer. In the newly identified fusion, a portion of ESRRA's DNA-binding region is melded to the end of a neighboring protein of unknown function called C11orf20.

Pooling the tumors allowed the researchers to identify which potential fusion events occurred in more than one tumor sample. When they

analyzed individual tumors, they found the ESRRA-C11orf20 fusion in 10 of 67 patient samples — a prevalence of about 15 percent, and far greater than any previously identified in this cancer. A closer look at the DNA of two of the tumors showed that the gene fusion was the result of a chromosome rearrangement in the cancer cells, rather than occurring during the step in which DNA is transcribed into RNA.

"It's potentially the case that this fusion is an early event in the cancer," said Salzman, a statistician by training who developed a new algorithm to analyze potential fusion events in the messy background of the cancer cell. "If so, it's possible that it could be used as a biomarker for the cancer before it has become clinically apparent, or that we can learn more about what causes the cancer by studying what we expect will be a new protein product."

In addition to identifying and learning more about the putative fusion protein, the researchers plan to investigate whether the presence of the fusion correlates with the clinical outcome of the patients in which they occur. It will be important to determine whether the protein, which has not yet been identified, is detectable in circulating blood — a characteristic that would greatly aid its use as a screen for asymptomatic women.

More information: Salzman J, Marinelli RJ, Wang PL, Green AE, Nielsen JS, et al. (2011) ESRRA-C11orf20 Is a Recurrent Gene Fusion in Serous Ovarian Carcinoma. PLoS Biol 9(9): e1001156. doi:10.1371/journal.pbio.1001156

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