New scientific model tracks form of ovarian cancer to origins in fallopian tube

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High-grade serous ovarian cancer (HGSOC), the fifth-deadliest cancer among American women, is thought by many scientists to often be a fallopian tube malignancy masquerading as an ovarian one. While most of the evidence linking HGSOC to the fallopian tubes has so far been only circumstantial, a new Dana-Farber Cancer Institute study suggests there is a direct connection, a finding that could aid in the development of better treatments for the cancer.

Dana-Farber scientists report in the Proceedings of the National Academy of Sciences they have developed a laboratory model that mimics the process by which fallopian tube cells may morph into cancer cells that appear to have come from the ovaries. Their demonstration that this process can happen in the lab is powerful evidence that it does happen in patients, throwing new weight behind the theory that HGSOC begins, in fact, in the fallopian tubes.

"The hypothesis of fallopian tube origin of high-grade serous ovarian cancer is based primarily on examinations of fallopian tubes surgically removed from women with a genetic predisposition to ovarian cancer," says Dana-Farber's Ronny Drapkin, MD, PhD, senior author of the new study. "Areas of the tubes adjacent to the ovary often had patches of cells that were predecessors of serous cancers. But to convincingly show that these cells are the source of high-grade serous ovarian cancer, we need to trace each step of the disease's development. Our model provides that kind of demonstration."

The origins of HGSOC have been so difficult to track down because of the insidious nature of the disease. Ovarian tumors often establish themselves without producing any warning symptoms. By the time the disease is discovered, the ovaries can be so overrun with cancer that adjacent sections of the fallopian tube are obscured, making them difficult to examine under a microscope. Late detection is one reason why ovarian cancer is notoriously difficult to treat. The American Cancer Society estimates that 22,000 women in the United States are diagnosed with HGSOC each year, and 14,000 die of it. Worldwide, the incidence approaches 200,000 women with 115,000 deaths each year.

In work published last year, Dana-Farber researchers created a laboratory model for studying the lining of the fallopian tubes. Using tissue from women who had had their fallopian tubes removed for reasons unrelated to cancer, the researchers established a model that mirrors the structure and function of normal fallopian tube tissue in the body.

For the new study, researchers removed secretory cells from the fallopian tube tissue model and "immortalized" them - altered the cells' genetic programming so they could divide indefinitely, much as cancer cells do. As the Cancer Genome Atlas Project has shown, ovarian cancers don't have a consistent pattern of gene mutations (other than in the p53 tumor suppressor gene). What they have, instead, are broad irregularities in the number of copies of key genes - too many, too few, or none at all. The gene most commonly missing from ovarian cancer cells is hRb, the one most often overduplicated is c-Myc. The Dana-Farber researchers made the immortalized cells mimic those abnormalities by shutting down hRb and sending c-Myc into overdrive.

Like true tumor cells, these "artificial" cancer cells proliferated rapidly and were able to leave their home tissue and grow elsewhere. When implanted in laboratory animals, they also gave rise to tumors that were

structurally, behaviorally, and genomically similar to human HGSOC.

"The model allows us to introduce other genetic abnormalities into these cells to see the effect on tumor growth and development," says Drapkin, who is also an assistant professof of pathology at Harvard Medical School. "Such studies will help us identify different types of high-grade serous ovarian cancer, as well as possibly discover biomarkers - proteins in the blood - that signal the presence of the disease. Ultimately, the model will enable us to test potential therapies to determine which work best in each type of the disease."

Provided by Dana-Farber Cancer Institute