

What's at the Root of Ovarian Cancer? New Study May Have Found Part of the Answer

The discovery could spearhead the development of approaches for finding ovarian cancer at its earliest stages or preventing the disease.

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Researchers have discovered what appears to be a critical biological driver of the most common form of ovarian cancer. The discovery, they believe, could spearhead the development of approaches for finding ovarian cancer at its earliest stages or preventing the disease from taking hold in the first place.

Multiple studies have shown that high-grade [serous](#) ovarian cancer arises from [precancerous](#) growths called serous tubal intraepithelial carcinoma (STIC) lesions in the [fallopian tubes](#). These lesions can eventually [travel into the ovaries and transform into full-blown tumors](#).

In this new study, Lan Coffman, M.D., Ph.D., of the University of Pittsburgh School of Medicine, and her colleagues showed that STIC lesions appear to arise and turn into tumors in the ovaries with the assistance of a type of stem cell that they called high-risk [mesenchymal stem cells \(MSCs\)](#).

These high-risk MSCs—which have specific characteristics that appear to help their cancer-fueling capabilities—[were abundant in the tissue, or stroma, immediately underneath STIC lesions](#) in fallopian tube tissue samples from women without cancer. They were also sometimes present in normal tissue.

When the researchers implanted high-risk MSCs along with healthy fallopian tube cells into mice, some developed ovarian cancer, including, in some cases, metastatic cancer, the researchers reported March 14 in *Cancer Discovery*.

It's not yet clear if high-risk MSCs are the primary instigator that causes healthy fallopian cells to transform into high-grade serous ovarian cancer, Dr. Coffman said, but the group's findings support the idea that these cells are intimately involved.

"What we believe we're seeing is that [high-risk MSCs] are a supportive 'soil' for cancer initiation," she said.

Rogue MSCs and ovarian cancer

Approximately 70% of women diagnosed with ovarian cancer have the high-grade serous form of the disease. In most women, at the time of their diagnosis, the disease has already spread, or metastasized, to other parts of the body. Only about one-third of women with advanced high-grade serous ovarian cancer [live for 5 years or more after diagnosis](#).

These statistics have spurred researchers to try to find ways to identify high-grade serous ovarian cancer in its earliest stages, when treatments may be more effective.

The concern is especially acute for women with inherited [mutations](#) in the BRCA1 and BRCA2 genes, who have a 30- to 40-fold increased risk of ovarian cancer compared with women who don't have these mutations and for whom the only preventive option is surgical removal of their ovaries.

In earlier studies of women with advanced ovarian cancer, Dr. Coffman and her team found that a group of MSCs with specific traits, including producing an abundance of a protein called WT1, were [almost always present in and around ovarian cancer tumors](#). Because these cells appeared to help the tumors spread and resist the onslaught of chemotherapy and other treatments, the researchers called them cancer-associated MSCs.

Field effects and tumor formation

In their current study, the researchers analyzed tissue samples from the fallopian tubes of women without ovarian cancer who'd had their fallopian tubes removed for other health reasons, including those with BRCA1 or BRCA2 mutations who had undergone preventive surgery.

In samples in which STIC lesions were present, the researchers found large numbers of MSCs in the [stroma](#) that had strikingly similar features to cancer-associated MSCs. They also sometimes found these same high-risk MSCs, as they came to call them, in samples of healthy tissue, although in lower numbers.

In some STIC lesions, the high-risk MSCs appeared to have a blast radius—or “field effect”—in that they were often present in healthy tissue just outside of STIC lesions. This field effect may be how high-risk MSCs seed the spread of STIC lesions into the ovaries, Dr. Coffman said.

NCI's Joanna Watson, Ph.D., chief of NCI's Tumor Metastasis Branch, called the field effect finding “fascinating.” Although some studies have found evidence for field effects in other cancers, Dr. Watson said, this is the first time it has been documented in ovarian cancer.

Additional laboratory experiments showed that high-risk MSCs could damage [DNA](#) in healthy fallopian tube cells and help ovarian cancer cells grow and adhere to each other, a critical step for tumor formation.

Finally, no tumors formed in mice injected with tiny structures called organoids that contained high-risk MSCs from human tissue samples. But when the organoids also contained healthy fallopian cells, some of the mice developed ovarian cancer in the ensuing months, including metastatic tumors in the lungs and liver.

When the researchers analyzed the tumors that had formed in the mice, Dr. Coffman said, “they all had the genomic features of high-grade serous ovarian carcinoma.”

“Clearly, communication between stromal and epithelial cells is critical” to the development of ovarian cancer in these mice, Dr. Watson said. But which cells “start the conversation or what triggers it is unclear.”

Could the discovery of high-risk MSCs aid early detection, prevention?

Dr. Watson added that it will be important to do further studies using mouse models that should more accurately capture how high-risk MSCs behave in humans. Nevertheless, she said, the findings that these specific stem cells “promote and support cancer development in the fallopian tubes ... are quite convincing.”

Dr. Coffman and her colleagues are planning additional studies, including trying to identify molecular markers of changes in the stroma caused by high-risk MSCs or STIC lesions that could form the basis for a test used to detect ovarian cancer earlier than is currently possible.

For such a test, “blood [draws] would be the easiest,” Dr. Coffman said, or perhaps other “proximal fluids” that can be collected from the vagina or cervix using something similar to a [pap smear](#) or a tampon-like tool.

These sorts of early detection tests, Dr. Coffman said, could be targeted to women at highest risk of the disease, such as those with inherited BRCA1 or BRCA2 mutations.

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