

Study provides clues to prevent spread of ovarian cancer

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A drug that blocks production of an enzyme that enables ovarian cancer to gain a foothold in a new site can slow the spread of the disease and prolong survival in mice, according to a study by researchers from the University of Chicago Medical Center, but only if the drug is given early in the disease process.

In the April issue of the *Journal of Clinical Investigation*, the researchers show that an enzyme known as MMP-2 is necessary for ovarian cancer to attach itself to the sites where it tends to spread. Several drugs known as MMP inhibitors (for example, marimastat or prinomastat) inhibit the enzyme, dramatically reducing the tumor's ability to establish itself at sites beyond the ovary. But such MMP inhibitors, which were abandoned after they failed to extend survival in earlier clinical trials, have to be given before the cancer has spread.

"Our study suggests that MMP-2 inhibitors could have a significant impact on ovarian cancer but only if administered quite early, before the cancer has advanced beyond the ovary," said Ernst Lengyel, assistant professor of obstetrics and gynecology at the University of Chicago.

This approach could help women who receive surgical treatment while the disease is still limited to the ovary as well as those who have successful surgery to remove all evidence of local spread of the disease. In the earlier trial, marimastat was given to women with late-stage disease that had already spread.

The fifth leading cause of cancer death in women, ovarian cancer -- unlike breast, colon or lung cancer -- tends to spread within the abdominal cavity and not to distant organs. Carried by fluid, it most often spreads throughout the peritoneal cavity and to the omentum, a large fat pad draped over the small bowel.



Ernst Lengyel, assistant professor of obstetrics and gynecology at the University of Chicago

Lengyel and colleagues wanted to understand the many steps required for ovarian cancer to dislodge from its original site and establish itself elsewhere in the peritoneal cavity. They found that one of the key steps was production of MMP-2 by cancer cells that came in contact with the cells that line the peritoneal cavity.

When ovarian cancer cells make contact with the cells that line this internal cavity, they produce MMP-2 (an acronym for matrix metalloproteinase-2). MMP-2 alters two proteins--vitronectin and fibronectin--found on the surface of the cells that line the cavity. These alterations change those proteins in a way that enables the cancer cells to latch on to them better. Once attached, the cancer cells can multiply rapidly and invade.

By inhibiting MMP-2 activity early in the disease course, Lengyel and colleagues were able to prevent injected ovarian cancer cells from attaching to their target tissues in the peritoneum and omentum. This reduced the growth of new tumors by 68 percent, when measured four weeks after treatment.

The inhibitor nearly doubled survival time in mice that were injected with ovarian cancer cells. Those who received it survived an average of 63 days, compared to untreated mice, who survived only 36 days.

Brief and early intraperitoneal treatment with an MMP inhibitor, the authors conclude, may reduce peritoneal attachment, reduce metastases and significantly prolong survival.

The treatment has much less impact, however, once cancerous cells have attached and formed colonies. In several earlier trials, marimastat, an oral MMP inhibitor, was given for a prolonged period of time to women with late-stage disease that had already spread.

"MMP-inhibitors were given at the wrong time for too long, causing side effects," Lengyel said. Attachment is the first step for metastatic spread. MMP-2, the target of MMP inhibitors, plays a role in early cancer spread.

"Our study examines the initial step of ovarian cancer metastasis," the authors note, when cancer cells meet unprepared target cells. Other steps in this process, they suggest, may also provide additional treatment targets.

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