Broken bones, the Pill, and *ovarian cancer*

Unexpected discovery may lower ovarian cancer risk

What do bone fractures, breast infections, the use of oral contraceptives, and gynecologic surgeries have in common? The answer: All these seemingly disparate occurrences may lower a woman's risk of developing ovarian cancer by inducing some degree of immunity against the disease.

This protection, as recently described by scientists in Dana-Farber's Women's Cancers Program, comes about because these events stimulate antibodies against a protein named epithelial mucin 1 – or MUC1 – that signals the body's defenses to attack the cancer. This protein might point the way to a much-needed vaccine to prevent ovarian cancer.

The connection between these varied events and protection against ovarian cancer "is a surprising, but credible association," comments Daniel Cramer, MD, ScD, director, Obstetrics and Gynecology Epidemiology, Brigham and Women's Hospital and Gynecologist and Co-Director of the Familial Ovarian Cancer Clinic, Dana-Farber Cancer Institute, who led the study published in the May 2005 issue of *Cancer Epidemiology, Biomarkers, and Prevention*.

The research connected the dots between two separate observations: One, that women with a history of some of the above experiences had a lower risk of ovarian cancer; and two, that ovarian cancer patients tended to survive longer if their blood harbored large numbers of antibodies against the MUC1 protein. The presence of the antibodies, which recognize and attack tumor cells that are heavily coated with MUC1, meant that patients had at some time mounted an immune response against the protein.

What does all this have to do with ovarian cancer? It turns out that MUC1 – though in a slightly different form – is overproduced by ovarian cancer cells (and other cancers, such as breast). It would make sense, then, that women with high levels of MUC1 antibodies, triggered previously by one or more of the events identified by Dr. Cramer, could be benefiting from those antibodies attacking ovarian cancer precursors, preventing them from becoming cancerous.

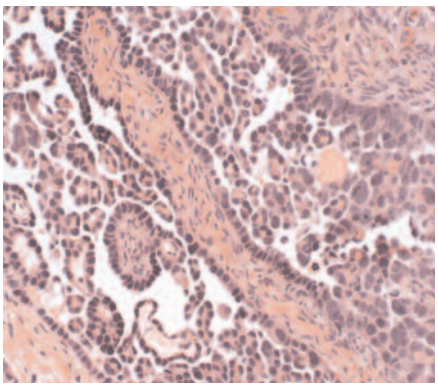
"The implications are profound," explains Dr. Cramer, "because this research may eventually offer new avenues for ovarian cancer prevention through vaccines to stimulate immunity against MUC1 and perhaps other proteins associated with ovarian cancer."

A new perspective

The link between MUC1 and ovarian cancer immunity began with a simple observation: Few of the women with ovarian cancer in Dr. Cramer's studies reported that they had experienced a mastitis (breast infection) while they were breastfeeding. In other scientific literature, Dr. Cramer found a case report of a pregnant woman with breast cancer who developed a mastitis and high levels of MUC1 antibodies and later became a long-term survivor. He contacted the author of the report, Dr. Oliveira Finn at the University of Pittsburgh, who agreed to measure MUC1 antibodies, including those from women who had mastitis.

The research showed that antibody levels were raised not only by mastitis, but also by factors as varied as oral contraceptive use; bone fracture or osteoporosis; pelvic surgeries including tubal ligation (or having one's "tubes tied"), cervical conization (also known as a cone biopsy of the cervix), and caesarian section; and, to a lesser extent, the use of an intrauterine device. Many of these events involved inflammation or injury and the repair of tissues that normally secrete MUC1 and might allow the protein to be shed into blood circulation, thus exposing it to recognition by the immune system. Women in the study who had ovarian cancer reported fewer of these events in their medical histories.

Dr. Cramer says the mechanism they observed might also explain the decreased risk for ovarian cancer associated with mumps documented in older studies, before the widespread use of mumps vaccination. Infection of MUC1-rich salivary glands by the mumps virus might, as in the case



Microscope view of a cancer on the surface of an ovary. The malignant cells occur on slender papillae (center) and as free-floating clusters. (Courtesy of Christopher P. Crum, MD, Division of Women's and Perinatal Pathology, Brigham and Women's Hospital).

MUC1 to the defense

MUC1

A form of MUC1 coats one side of cells that line glands of the breast, fallopian tubes, uterus, and other organs.

Inflammation

Inflammation or injury to glands releases MUC1 into the bloodstream, allowing it to be recognized by the immune system and anti-MUC1 antibodies to form.

of mastitis, trigger an anti-MUC1 response by antibodies.

"This model represents a foundation for a shift in how we think about ovarian cancer," explains Dr. Cramer. "Previously, we thought the cancer occurred because the ovary was not allowed to rest enough, which is why multiple pregnancies, birth control, and breast feeding are commonly thought to offer protection. We now see that this theory has some deficiencies." Furthermore, these findings may have implications beyond ovarian cancer and apply to other malignancies with high MUC1 expression, including uterine and breast cancer.

The team is already looking at next steps. They're undertaking studies in which blood samples are obtained and women are followed for years before the development of ovarian cancer. This will allow them to document directly that anti-MUC1 antibodies reduce risk, and to measure changes in antibody levels as women experience some of the events found to be associated with the antibodies.

"It will take time to confirm the results," says Dr. Cramer, "but this is an entirely new pathway that could ultimately lead to a clear strategy to prevent this disease."

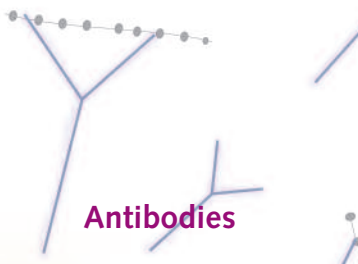
A broken bone may send powerful signals that either enhance MUC1 production or the immune processing of MUC1.

An ounce of prevention

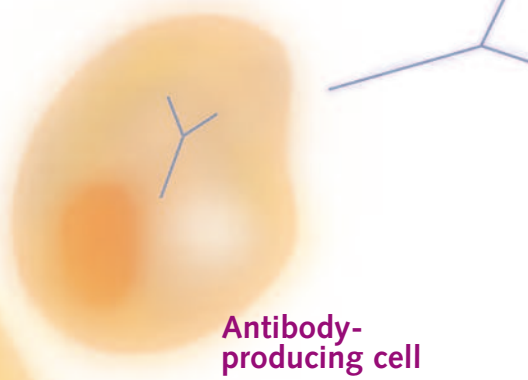
There's no need to wait for a vaccine to take preventive measures against ovarian cancer, which will be newly diagnosed in an estimated 22,220 women in the U.S. during 2005 and result in approximately 16,210 deaths. Incidence of the cancer typically peaks 15 years after ovulation stops.

"Ideally, ovarian cancer would be prevented from happening at all," says Ross Berkowitz, MD, director of Gynecologic Oncology Services at Brigham and Women's Hospital and Dana-Farber and one of the authors of the MUC1 study. "It is important to identify women at high risk and discuss precautionary measures available to them."

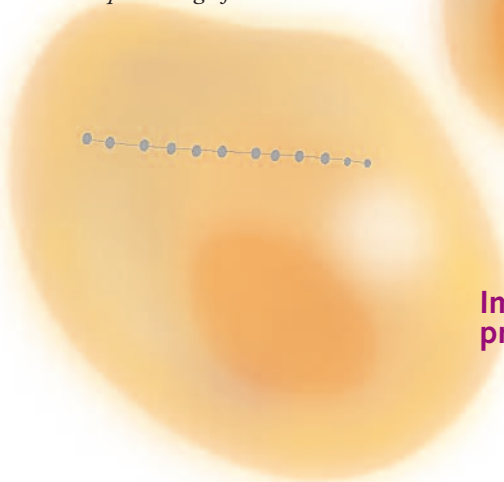
Ovarian cancer is not common: The average American woman's lifetime risk is only 1.5 percent. But among women who do develop the disease, about



Antibodies



Antibody-producing cell



Immune processing cell

5–10 percent have a strong genetic link as a root cause. And for those who inherited the *BRCA1* or *BRCA2* gene mutation, the lifetime risk jumps to 20–40 percent. Any woman who has a family history of ovarian cancer – mother, sister, daughter – should seek genetic counseling.

Until an effective screening tool is developed, the best preventive option for women at high risk is removal of the ovaries and fallopian tubes when childbearing is complete. For those with *BRCA* mutations, these measures reduce the risk of gynecological cancers (ovarian, fallopian tubes, and peritoneal) by more than 90 percent.

Even in women at average risk, tubal ligation lowers the risk by 30–50 percent. "There are a couple of theories about this," explains Dr. Berkowitz. "It is possible that sealing off the perineal cavity protects the ovaries; or tissue inflammation from the surgery may lead to the production of anti-MUC1 antibodies."

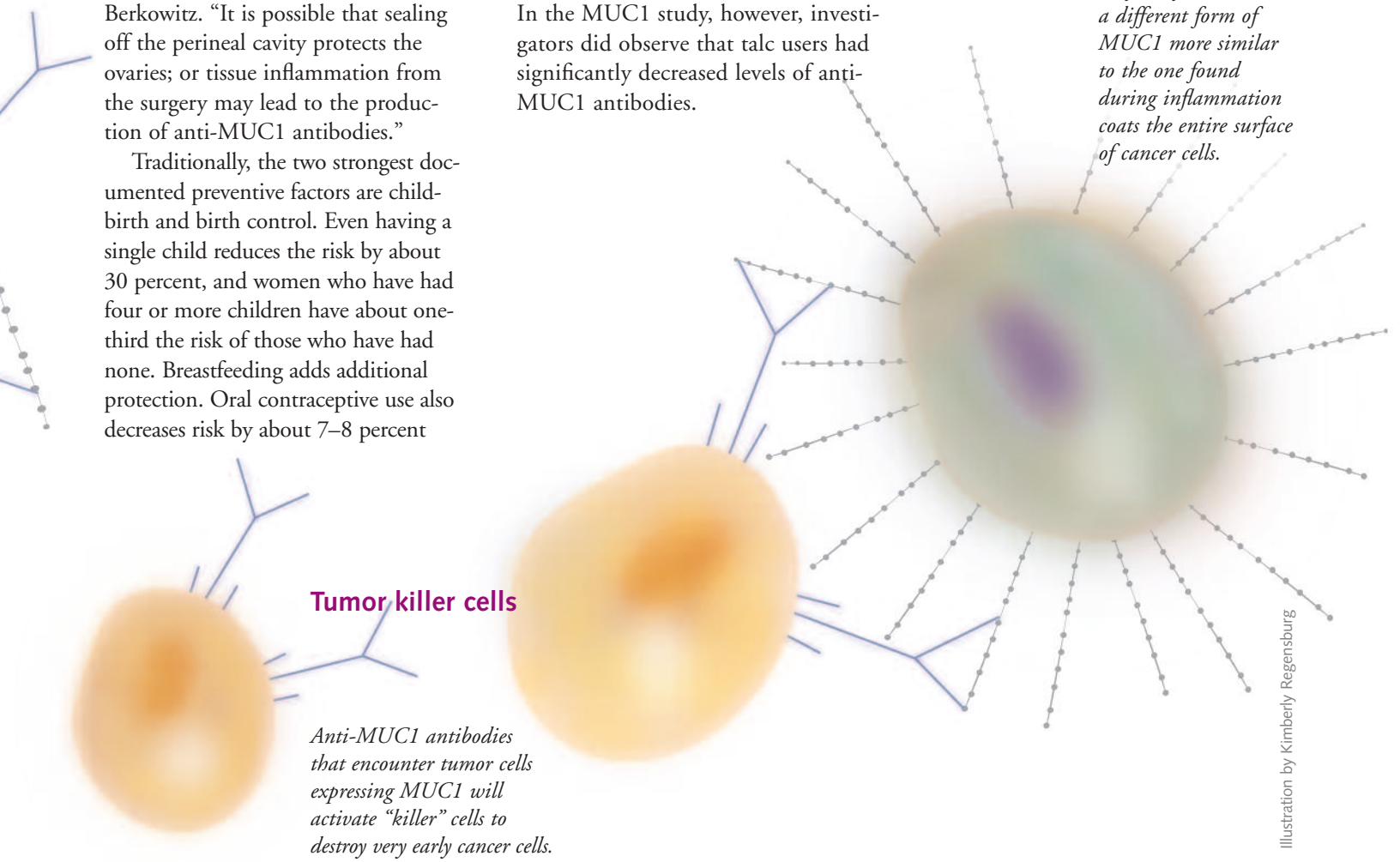
Traditionally, the two strongest documented preventive factors are childbirth and birth control. Even having a single child reduces the risk by about 30 percent, and women who have had four or more children have about one-third the risk of those who have had none. Breastfeeding adds additional protection. Oral contraceptive use also decreases risk by about 7–8 percent with each year of use, even for women who carry *BRCA* mutations.

Prevention also means avoiding known risk factors. Susan Hankinson, ScD, an epidemiologist at Brigham and Women's Hospital and a lead investigator on the Nurses' Health Study, notes that, unlike the birth control pill, hormone replacement therapy following menopause may increase the odds of developing ovarian cancer.

Use of talc in the genital area is another risk factor. Research by Dr. Cramer shows that women who use talc on their perineum (the skin around the vagina) have about a 30 percent higher risk of developing ovarian cancer. The association has been challenged because no relation between the amount of talc use and the increase in risk has been shown. In the MUC1 study, however, investigators did observe that talc users had significantly decreased levels of anti-MUC1 antibodies.

Still under investigation are early findings showing painkillers such as aspirin, ibuprofen (found in Midol and Advil), and acetaminophen (in Tylenol) may provide a risk reduction of about 30 percent. Drs. Cramer and Hankinson are studying this area further.

"We continue to lead the way in research into what can be done to reduce risk," says Dr. Berkowitz. "There are a number of things a woman can do to meaningfully reduce her risk, and these options should be discussed with her doctor. Women need not feel they are completely helpless against this disease." DS



Tumor cell

Very early in cancer, a different form of MUC1 more similar to the one found during inflammation coats the entire surface of cancer cells.

Tumor killer cells

Anti-MUC1 antibodies that encounter tumor cells expressing MUC1 will activate "killer" cells to destroy very early cancer cells.

Illustration by Kimberly Regensburg