Genomics to reshape endometrial cancer treatment

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Scientists at Washington University's Genome Institute have shown that adding genomics-based testing to the standard diagnostic workup for endometrial cancer could change the recommended treatment for some women. Credit: Robert Boston, Washington University in St. Louis

The most in-depth look yet at endometrial cancer shows that adding genomics-based testing to the standard diagnostic workup could change the recommended course of treatment for some women.

The new research, involving nearly 400 women with endometrial cancer, is published May 2 in the journal *Nature*. The endeavor is part of The Cancer Genome Atlas project, funded by the National Institutes of Health (NIH).

The study also indicates that some endometrial tumors are genetically similar to subtypes of ovarian cancer and deadly basal-like breast cancer. Future clinical trials should evaluate whether some endometrial cancers could be treated with drugs typically used for the other cancers, says project co-leader Elaine Mardis, PhD, co-director of The Genome Institute at Washington University School of Medicine in St. Louis. The other co-leader is Douglas A. Levine, MD, of the Memorial Sloan-Kettering Cancer Center.

A second Cancer Genome Atlas paper will be published May 1 in the *New England Journal of Medicine*. That research, also led by Washington University, describes finding virtually all the major mutations involved in acute myeloid leukemia.

While gynecologic oncologists have long recognized two subtypes of endometrial cancer, one more aggressive than the other, the new data reveal four novel subtypes and also suggest that the frequency of mutations in a tumor could be used to help guide treatment decisions.

"We are entering an era when tumors can be evaluated from a genomics standpoint, not just by looking at cancer cells under a microscope," Mardis says. "This more comprehensive approach provides a clearer picture of the way particular endometrial cancers will behave and will be important to gynecological oncologists who treat this disease."

As part of the new research, a consortium of researchers analyzed tumors from 373 women with endometrial cancer using different technologies to look for defects in DNA, RNA (a close chemical cousin

of DNA) and proteins.

Their analysis indicates that about 25 percent of women with endometrial cancer who are thought to have a favorable prognosis based on pathology reports instead have a more formidable form of the disease, based on underlying genetic changes, and should be treated aggressively.

Clinically, endometrial cancers fall into two categories: endometrioid and serous. Endometrioid cancers generally are associated with excess estrogen, obesity and a favorable prognosis. In contrast, serous endometrial cancers are more common in older women and generally have poorer outcomes.

After surgery to remove endometrial cancer, women with the endometrioid subtype typically are treated with radiation therapy to kill remaining cancer cells, while those with serous tumors receive a more aggressive treatment – chemotherapy.

Doctors distinguish between the two tumor subtypes by evaluating cancer cells under a microscope. But categorizing some tumors is difficult, and pathologists don't always agree.

Looking closely at endometrioid tumors classified as high-grade, meaning they are more likely to grow quickly and spread, the investigators showed that many share genetic features with serous tumors. These include frequent mutations in TP53, a tumor suppressor gene, as well as extensive copy number alterations, which refer to a cell having too many or too few copies of a gene.

"This highlights the benefit of digging deeper to find the genetic drivers of cancer growth," Mardis says. "Even though high-grade endometrioid and serous endometrial cancer are different from a pathological

standpoint, they are genetically very similar and may require a similar course of treatment."

With a complete analysis of the tumor samples, the investigators identified four novel genomic-based subtypes of endometrial cancer, which set the stage for developing new ways to diagnose and treat the disease. The subtypes are based, in part, on the frequency of mutations in the tumors.

"The Cancer Genome Atlas' multidimensional approach to collecting genomic data, including clinical and pathology information, have made these findings possible," says Harold Varmus, MD, director on the National Cancer Institute. "Without the integrated characterization of so many tumor samples, correlations between histology and genomic data may not have been observed or potential clinical outcomes identified."

Interestingly, one subtype features an exceedingly high mutation rate in the POLE gene and, in this respect, is similar to an "ultramutated" subtype of colorectal cancer. But, surprisingly, patients with these kinds of tumors generally have good outcomes.

"Having many, many mutations sounds like a bad thing," Mardis explains. "But these patients can't fix the mistakes in their tumor DNA, so their cancer cells mutate themselves into oblivion before they have the opportunity to spread to other locations in the body. The good news for these patients is that their outcomes are excellent, and they don't need aggressive treatment."

Women with serous tumors frequently had mutations in one of two genes that potentially could be targeted with existing targeted therapies. Those with ERBB2 alterations, for example, may be effectively treated with Herceptin, a drug typically used in women with breast cancer who have the same mutation. Additionally, women whose endometrial tumors

have PIK3CA mutations may benefit from drugs that inhibit the gene. Those drugs are now in phase II clinical trials.

According to the authors, the new findings provide a roadmap for future clinical trials for endometrial cancer.

"Each tumor subtype may warrant separate clinical trials because of marked genomic differences, which are indicative of different drivers of endometrial cancer," Mardis says. "Developing therapies for each subtype may improve outcomes for many women with endometrial cancer and parallel what has been accomplished in breast cancer."

Endometrial cancer is the fourth most commonly diagnosed cancer among U.S. women. About 50,000 cases will be diagnosed in 2013, and an estimated 8,000 women will die from the disease. For a majority of patients diagnosed with aggressive, high-grade tumors that have spread, the five-year survival rate is about 16 percent, though chemotherapy has been associated with improved survival, and new targeted agents are being tested.

More information: Levine DA, Mardis ER and The Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. *Nature*. May 2, 2013.

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