Linking of mutations in 12 genes to ovarian cancer may lead to more effective prevention

October 25 2011

More patients with ovarian carcinoma carry cancer-predisposing mutations, and in more genes, than previously thought.

A rapid experimental method for screening genomes has located mutations in 12 genes for inherited cancers of the ovary, fallopian tubes and peritoneum (the thin tissue lining the lower abdomen).

More than one-fifth of ovarian cancers arise in women with a familial predisposition, but relying on family history would have missed one-third of the cases, said Dr. Elizabeth Swisher, senior author of a paper on these findings published online ahead of print in the Proceedings of the National Academy of Sciences.

Swisher is an associate professor of obstetrics and gynecology at the University of Washington in Seattle. She directs the Breast and Ovarian Cancer Prevention program at the UW and the Seattle Cancer Care Alliance, and is an affiliate researcher at the Fred Hutchinson Cancer Research Center.

The results of her most recent study have far reaching implications beyond the important identification of mutations linked to ovarian and related cancers.

The speedy, low-cost genome analysis method her team developed could soon be applicable to patient testing for a broad range of all known breast, ovarian, colon, pancreatic and melanoma gene mutations. A

single test might be able to screen a patient for susceptibility to all these cancers.

Also, the great number of specimens that this method can analyze simultaneously could allow for large scale, population studies of cancer-causing mutations. Such studies would tell who is at risk for certain cancers and how to effectively target prevention.

The UW scientists named their sequencing method BROCA, after Paul Broca, a 19th century medical scientist who was among the first to describe inherited breast and ovarian cancer. BROCA, the researchers said, is highly sensitive and can find all classes of genetic mutations, including single substitutions, small insertions and deletions, and large rearrangements of genes.

"The BROCA test is not patented," the researchers said, and added that designs for its use in genetic studies are freely available.

At present, most tests for genes already known to be associated with breast and ovarian cancer, BRAC1 and BRAC2, are done by a lone company. The cost is about $4,000 for a non-comprehensive test accompanied by an additional test to find gene rearrangements.

As more cancer-susceptibility genes are found, it is not economical to test a person for one gene mutation, and then go back and test for another, then another. Gene-by-gene testing will eventually give way to a single test that accurately identifies all classes of those gene mutations that permit tumors to grow unchecked.

At present, the price for the BROCA chemicals is about $200. The costs are shrinking for running the genome analysis, due to the increasing number of samples that can be put through the multiple "lanes" in the sequencer.

Swisher and her team concentrated on ovarian cancer gene-detection in trying this sequencing method because ovarian cancer is one of the most deadly to affect a woman's reproductive system. It is difficult to diagnose in its early stages

Ovarian cancer and cancer of the peritoneum begin quietly. Eventually vague symptoms appear, but they mimic seemingly benign conditions, like bloating.

"Most women are not diagnosed until the cancer is has advanced to the point where the chances of a cure are small," Swisher said. "Women with early stage ovarian cancer have a better survival than those diagnosed with late stages, but current methods of detection are not effective."

The lack of effective early detection is why Swisher and her research team are looking for a more complete genetic picture of ovarian and related cancers. Learning the genetic mutations associated with these cancers could lead to tests to identify early on the women prone to these malignancies.

A quick, low cost, individual screening test for a variety of gene mutations linked to ovarian cancer would allow for effective preventive measures, the researchers said. For example, a woman whose genetic profile indicates high risk could consider an operation to remove her ovaries and fallopian types. This procedure has already been shown to decrease the overall death rate in women who have BRCA1 or BRAC2 mutations.

These particular mutations heighten the risk of ovarian as well as breast cancer. As this current study reveals, previously unknown mutations in other genes also occur in the population of women diagnosed with ovarian cancer.

New developments in cancer drugs that selectively wipe out cells containing certain genetic deficiencies is another major incentive for scientists to locate other mutations involved in ovarian cancer, Swisher noted. For example, the new drug class called poly-ADP-ribose polymerase (PARP) inhibitors is lethal to cells missing chemicals produced by normal BRAC1 and BRAC2 genes. The PARP drugs are showing efficacy in treating ovarian cancers in patients with mutations in these genes.

The UW scientists applied BROCA to analyze the DNA from a 360 women undergoing surgery between 2001 and 2010 at the University of Washington for cancer of the ovaries, peritoneum, or fallopian tubes, or who had cancer of the ovaries as well as the uterine lining. The women were enrolled at diagnosis. Neither age of onset of the cancer nor their family history were selection factors.

Among this group of women, the researchers found 85 mutations in 12 genes. Many were loss-of-function mutations. An example of loss of function is the inability of cells to produce chemicals to suppress tumors. As the scientists expected, women with a personal history of breast cancer had an extremely high likelihood of harboring an inherited mutation. Family history of breast, ovarian, uterine, and pancreatic cancer – but not colon cancer – were each associated with inherited mutations.

"An observation that has major implications for clinical practice was that nearly one-third of the women with inherited mutations had no prior personal history of breast cancer and no family history of ovarian or breast cancer," Swisher noted. This high proportion of unrecognized risk, she explained, is probably due to the combined effects of small family size, female cancer genes inherited from unaffected fathers, and the simple odds of a mutated gene being inherited or not inherited.

The researcher also found that the age when these types of cancer appear was not generally associated with the likelihood of having an inherited mutation, or with the gene in which a mutation was found.

There were no significant differences in survival rates between women who had one or more of the mutations identified in this study, and women who did not have these particular mutations.

What we found overall, the researchers noted, was that more than one in five cases of ovarian carcinoma were associate with a mutation in tumor suppressor genes. In their normal form, these genes act in a way that keeps tumors from growing.

The findings of this study, the researcher concluded, point to the need to develop comprehensive testing for inherited carcinoma for all women with ovarian, peritoneal or fallopian tube cancer, regardless of their age or family history. The researchers are moving clinical science forward to a time when expensive single gene testing for thousands of dollars will be replaced by testing many genes simultaneously at low cost.

More information: "Mutations in 12 genes for inherited ovarian, Fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing," *Proceedings of the National Academy of Sciences*.

Provided by University of Washington