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New DNA Sequences Hone In On Breast, Ovarian Cancer Risk: Mayo Clinic

ROCHESTER, Minn. — Researchers at Mayo Clinic Cancer Center have identified new DNA sequences associated with breast cancer — the most common cancer among women, with an average risk of developing the disease of 10 percent — and ovarian cancer, the most common cause of death from gynecological cancers in the U.S. The findings, which appear in three studies in the journals *Plos Genetics* and *Nature Genetics*, will help reveal the underlying causes of these diseases and help researchers build better risk models to support new prevention strategies.

In the first study, published in the journal *PLoS Genetics*, researchers studied variations across the genomes of 14,351 BRCA1 mutation carriers and found two new DNA sequences that are associated with breast cancer risk and two new DNA sequences associated with ovarian cancer risk. One sequence associated with ovarian cancer is the first known BRCA1-specific risk sequence for the disease. The researchers were then able to use their results to estimate the risks of both cancers for each BRCA1 mutation carrier. These new results may soon be incorporated into clinical management of patients.

"Women with mutated copies of the BRCA1 or BRCA2 gene have markedly increased but highly variable risks of breast and ovarian cancer," says Fergus Couch, Ph.D., a Mayo Clinic investigator who co-authored the study. "To put this into perspective, a woman with a BRCA1 mutation has about a 65 percent lifetime risk," says Dr. Couch. "Risk models will help her make decisions by indicating if her true risk is liable to be closer to 90 percent — in which case she may choose prophylactic surgery — or closer to 40 percent — in which case frequent monitoring may be most appropriate."

The second study, published in the journal *Nature Genetics*, focuses on women susceptible to estrogen receptor-negative (ER-negative) forms of breast cancer. Dr. Couch's team discovered four new DNA sequences that were associated with ER-negative breast cancer but not ER-positive breast cancer. The discovery was based on integrated results from three genome-wide association studies of 6,514 ER-negative breast cancer patients and 41,555 healthy controls.

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"Women have a worse prognosis if their tumors are ER-negative because these cells grow more rapidly," says Dr. Couch. "They also have fewer treatment options." He says the new DNA sequences will yield new information about the biology of the disease which could eventually help researchers develop new treatments.

About one fourth of all breast cancers are ER-negative, with a higher proportion in younger women and women of African ancestry. ER-negative breast cancers are more aggressive and unresponsive to anti-estrogens compared to ER-positive breast cancers, which generally have a better prognosis and are often responsive to anti-estrogen therapy.

The third study, also published in *Nature Genetics*, reports the findings of the largest genome-wide association study in any cancer to date. Researchers found 41 new DNA sequences associated with breast cancer. Incorporating the DNA sequences into risk models is expected to significantly improve the ability to predict which women are at greater risk of developing breast cancer.

The researchers, including Dr. Couch and authors from Cambridge University's Centre for Cancer Genetic Epidemiology, integrated information from more than 30,000 breast cancer patients and more than 30,000 healthy controls.

The Mayo studies are part of the Collaborative Oncological Gene-environment Study (COGS), an international research collaboration involving investigators from Europe, Asia, Australia and North America, which identified 49 new DNA sequences associated with an increased risk for breast cancer, ovarian cancer and prostate cancer. "This was an unprecedented study of genetic and lifestyle factors that involved the genotyping of more than 250,000 individuals by 117 research institutes around the world," says Dr. Couch. "The studies were so large that the results are really trustworthy."

Mayo Clinic Cancer Center co-authors on the three papers include Julie Cunningham, Ph.D.; Janet Olson, Ph.D.; Susan Slager, Ph.D.; and Celine Vachon, Ph.D.

Funding for COGS came from multiple sources, with the largest contributors being the European Union Seventh Framework and Cancer Research UK. Support for Dr. Couch's research came from the National Institutes of Health grant R01CA128978, a Specialized Program of Research Excellence (SPORE) in breast cancer (P50 CA115201) and the Breast Cancer Research Foundation.

About Mayo Clinic Cancer Center

As a leading institution funded by the National Cancer Institute, Mayo Clinic Cancer Center conducts basic, clinical and population science research, translating discoveries into improved methods for prevention, diagnosis, prognosis and therapy. For information on cancer clinical trials, call 507-538-7623.

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