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Two studies find new genetic links to ovarian cancer risk

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An international consortium of scientists has discovered new genetic variants in five regions of the genome that affect the risk of ovarian cancer in the general population, according to two separate studies published today, online in *Nature Genetics*.

The consortium, including scientists from the U.S., Europe, Canada and Australia, based the new work on their earlier research comparing 10,283 women with ovarian cancer to 13,185 women without the disease. That effort had found a stretch of DNA on chromosome 9 containing single DNA letter variations (SNPs) associated with ovarian cancer risk.

The researchers have now found additional stretches of DNA on chromosomes 2, 3, 8, 17 and 19 after grouping patients according to the type of ovarian cancer they had developed. Four out of five of the new DNA variations were more common in women who had developed the most common and aggressive form of disease, known as serous ovarian cancer.

Andrew Berchuck, MD, professor of gynecologic oncology at Duke University Medical Center and head of the steering committee of the international Ovarian Cancer Association Consortium (OCAC), says the associations of these genetic variants with ovarian cancer were discovered using genome-wide association studies (GWAS).

"Since the critical validation of these findings was performed by a large

consortium of investigators from around the world, we see this research as a triumph of science without borders for the benefit of women everywhere."

Ovarian cancer is the fifth most common cancer among women in developed countries, and often detected in later stages when the chances of cure are small. As a result, the disease claims more lives in the U.S. than all other gynecological cancers combined. Every year, about 13,000 women in the U.S. and 130,000 worldwide die from the disease.

"These latest findings raise the possibility that in the future, women in the general population who are at the greatest risk of developing ovarian cancer because they carry these newly discovered DNA variants can be identified and given closer surveillance to look for early signs of ovarian cancer when it is most treatable," says Berchuck. "It also suggests that preventive approaches could be targeted towards these women."

Ellen Goode*, PhD, a genetic epidemiologist at the Mayo Clinic College of Medicine and the lead author of one of the studies, says "additional research will be required to learn more about the specific genes and DNA changes in these DNA stretches that could be causing ovarian cancer," but she says the newly implicated regions of the genome also contain some familiar suspects.

"Common genetic 'typos' at 8q24 have already been shown to render some people vulnerable to prostate, colorectal, breast and bladder cancers, so it's not too surprising that there may be something there related to ovarian cancer," Goode said. "What is surprising is that we found that three of the most common SNPs for ovarian cancer lie quite a distance away from this bunch of troublemakers - in an apparent gene desert - which suggests they may be causing functional problems by a very different mechanism."

A second study** in the same issue of Nature Genetics found a region of DNA on chromosome 19 that also affects ovarian cancer risk. And a third study in the same issue found that variation in this same region of chromosome 19 also increases the risk of breast cancer in women who already carry a faulty copy the BRCA1 gene*** on chromosome 17.

Researchers have known for some time that heritable mutations in the BRCA1 and BRCA2 genes can dramatically increase a woman's chances of developing breast and ovarian cancer, but these mutations only account for a small percent of ovarian cancers. Because DNA variations such as those described in these new studies are much more common in the general population than BRCA1 and BRCA2, researchers conclude that they probably cause a much greater proportion of all ovarian cancers, even though the overall cancer risks associated with these SNPs are smaller.

Simon Gayther, PhD, Professor of Preventive Medicine at the University of Southern California and senior author of the second ovarian cancer study, said: "Our study shows that the same genetic region plays a role in both breast and ovarian cancer, suggesting that the same faulty pathway can cause both diseases, just like BRCA1 and BRCA2 do. This is important because it suggests that women who carry certain versions of this stretch of DNA could benefit from closer monitoring for both breast and ovarian cancers."

Paul Pharoah, PhD, of Cancer Research UK Center for Genetic Epidemiology at Cambridge University and a senior author on both studies, says, "I think that the most important message women can take away from this work is that we are making progress in understanding ovarian cancer."

"We are slowly but clearly leading toward a time when we will be able to draw an individualized profile of a woman's risk of ovarian cancer and

respond with appropriate prevention and treatment options."

The findings may represent the tip of the iceberg, according to Georgia Chenevix-Trench, PhD, from the Queensland Institute of Medical Research in Australia, who led development of a consortium dedicated to studying the outcomes associated with BRCA1 and BRCA2 mutations. She said future research may yield additional genetic regions that alter a woman's risk of ovarian and other cancers.

More information: Citations (all of them are available today here: www.nature.com/ng/journal/vaop/ncurrent/index.html):

* Ellen Goode et al., Identification of four novel ovarian cancer susceptibility loci identified in a genome-wide association study, *Nature Genetics* (2010).
** Kelly Bolton et al., A genome-wide association study of survival in ovarian cancer identifies a locus at chromosome 19 that is associated with susceptibility to ovarian cancer, *Nature Genetics* (2010).
*** Antonis Antoniou et al., A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population, *Nature Genetics* (2010).

Provided by Duke University Medical Center