Screening for breast / ovarian cancer risk genes other than BRCA1/2 is clinically valuable

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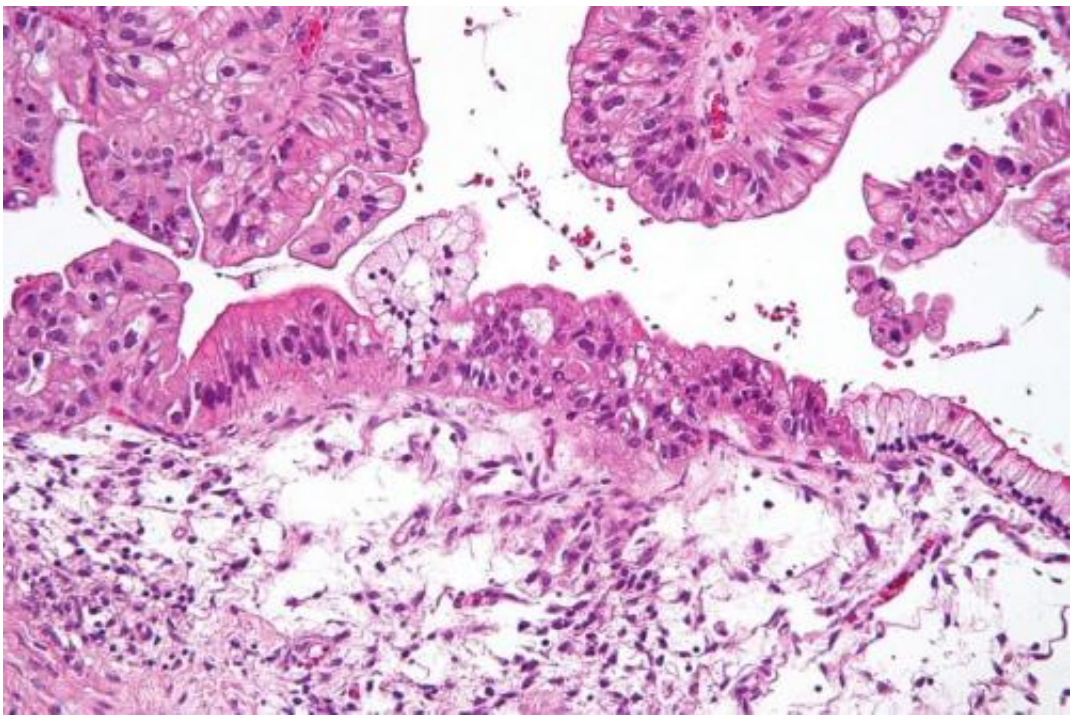

Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. H&E stain. The micrograph shows: Simple mucinous epithelium (right) and mucinous epithelium that pseudo-stratifies (left - diagnostic of a LMP tumour). Epithelium in a frond-like architecture is seen at the top of image. Credit: Nephron /Wikipedia. CC BY-SA 3.0

A study by researchers at three academic medical centers has shown that

screening women with a suspected risk of hereditary breast or ovarian cancer for risk-associated genes other than BRCA1 and 2 provides information that can change clinical recommendations for patients and their family members. The report from a team led by a Massachusetts General Hospital (MGH) Cancer Center investigator is being published in the August issue of *JAMA Oncology*.

"The traditional approach has been to test most women with suspected hereditary risk for breast and/or ovarian cancer for BRCA1/2 alone," explains senior author Leif Ellisen, MD, PhD, program director for Breast Medical Oncology at the MGH Cancer Center. "The concern about broader testing has been that the results really wouldn't change what we told women about their risk and management - either because the risk associated with the other genes are not as high as for BRCA1/2 or because the clinical practice guidelines associated with other genes are less specific. Our study shows that, even under current practice guidelines, finding mutations in these other genes is likely to change the clinical management recommendations both for patients and for family members who also carry the associated mutations."

The study examined whether use of currently available multigene panels to test for mutations in breast or ovarian cancer risk genes other than BRCA1/2 would change recommendations for women carrying those mutations. Investigators enrolled 1,069 patients who had been referred for genetic counseling for breast or ovarian cancer risk at MGH, Stanford University School of Medicine or Beth Israel Deaconess Medical Center and who did not carry BRCA1/2 mutations. For most participants, testing utilized one of two commercially available multigene panels - one a 25-gene panel, the other a 29-gene panel - screening genes associated with increased risk for breast and/or ovarian cancer and sometimes for other tumors.

Of all the screened patients, 63 were found to carry risk-associated

mutations, most of which were consistent with their personal and family cancer histories. The 3.8 percent prevalence of these mutations among 1,046 patients tested with the two multigene panels - compared with 9 percent usually reported for BRCA1/2 mutations - is similar to what has been seen in previous studies. In almost one-third of these patients (20 of 63), the identified mutations were considered high-risk - including mutations associated with Lynch syndrome, which increases risk of colorectal, ovarian and other cancers. In each case, established guidelines for patients with those mutations would call for additional screenings and possibly preventive surgery that would not have been recommended on the basis of personal/family history alone.

Among those found to carry mutations conferring a low or moderate increase in cancer risk, current guidelines would have called for enhanced screening or preventive surgery for 10 patients with breast cancer risk genes and additional screening for 3 patients with mutations associated with pancreas cancer risk. Overall, 52 percent of patients in whom a mutation was identified would be recommended for additional screening or preventive measures above and beyond what would be called for by personal and family history. In addition, the presence of the identified mutations would lead to recommendations that close female relatives of 72 percent of the patients also be screened for the mutations, which if present would change their recommended clinical management as well.

"These results suggest that multi-gene testing can provide important additional information to guide recommendations for screening and prevention of future cancers," Ellisen explains. "For example, results that point to a higher risk of breast cancer than would be predicted by history alone might call for breast MRI in addition to mammograms. The Lynch syndrome mutations signify a need for increased colorectal cancer screening and in some cases preventive hysterectomy or ovariectomy. But it's important to note that multigene genetic testing is not appropriate

for everyone and is most useful where personal and family histories suggest hereditary cancer, which is not the case for most patients with breast or ovarian cancer."

A professor of Medicine at Harvard Medical School, Ellisen adds that the next step will be to examine whether recommendations based on multigene testing lead to better prevention, early detection and improved patient survival, a project that will take many years. "These future studies will help us refine and modify gene-based management recommendations over time. We've been testing for BRCA1/2 for more than 15 years, and outcome studies and guideline modifications are still ongoing. Genetic testing and its interpretation are getting more complex, so now more than ever, it makes sense for patients to seek out trained genetic counselors and practitioners to help them decide whether to be tested and how to interpret the test results."

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