Study identifies genetic mutations associated with cancer risk for hereditary cancer syndrome

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(Medical Xpress) -- Among various genetic mutations for individuals with Lynch syndrome, a hereditary cancer syndrome that carries a high risk of colon cancer and an above-normal risk of other cancers, researchers have identified mutations associated with a lower cancer risk and mutations associated with an increased risk for ovarian and endometrial cancer, according to a study in the June 8 issue of *JAMA*, a theme issue on cancer.

The Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer syndrome, accounts for 3 percent to 5 percent of all colorectal cancers. "Providing accurate estimates of cancer risks is a major challenge in the clinical management of Lynch syndrome," according to background information in the article. "Having more accurate knowledge of the age-dependent cancer risks associated with mismatch repair [MMR; a system within the cell for correcting errors in DNA] gene mutations would help in improving preventive strategies."

Valerie Bonadona, M.D., Ph.D., of the Centre National de la Recherche Scientifique, Villeurbanne, France, and colleagues conducted a study to estimate the specific cancer risks associated with mutations in the genes MLH1, MSH2, and MSH6 by analyzing a large sample of families with Lynch syndrome. The study included 537 families with segregating mutated genes (248 with MLH1; 256 with MSH2; and 33 with MSH6). The families were enrolled between January 2006 and December 2009

from 40 French cancer genetics clinics.

The researchers found significant differences in estimated cumulative cancer risk between the 3 mutated genes. "For colorectal cancer, the estimated cumulative risks by age 70 years were 41 percent for MLH1 mutation carriers, 48 percent for MSH2, and 12 percent for MSH6. The estimated cumulative risks in carriers did not begin to increase until age 30 years, irrespective of gene mutation. For endometrial cancer, the estimated cumulative risks by age 70 years were 54 percent for MLH1, 21 percent for MSH2, and 16 percent for MSH6. By age 40 years, the estimated cumulative risk did not exceed 2 percent, irrespective of gene mutation. For ovarian cancer, the estimated cumulative risks by age 70 years were 20 percent for MLHl, 24 percent for MSH2, and 1 percent for MSH6. By age 40 years, the estimated cumulative risk did not exceed 1 percent, irrespective of gene mutation."

"These results contribute new complementary data to the discussion of preventive gynecological care. Clinical guidelines state that prophylactic gynecological surgery should be considered in women with Lynch syndrome," the authors write. "Our findings should help in identifying more precisely the target population for surgery and address the issue of optimum age."

For other Lynch syndrome-associated cancers, the estimated cumulative risks by age 70 years did not exceed 3 percent overall and were consistently lower among families with the MSH6 mutations than in those carrying the other gene mutations.

"This analysis of a nationwide series of 537 families with Lynch syndrome provides age- and gene-specific risk estimates for each tumor of the spectrum. The results should help clarify the phenotypic differences between MSH6, MLH1, or MSH2 mutation carriers and highlight the clinical significance of the risk of gynecological (and

especially ovarian) cancers," the researchers conclude.

More information: *JAMA*. 2011;305[22]2304-2310

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