Genetic risk score associated with breast cancer risk; predictive of type of disease

27 July 2010

Women with higher risk scores that consisted of having certain genetic variants most strongly linked to breast cancer had an associated higher risk of breast cancer, with these scores also highly predictive of estrogen receptor-positive disease, according to a study in the July 28 issue of *JAMA*.

"Findings from genome-wide association studies (GWAS), together with analyses of specific candidate polymorphisms [gene variations], have identified a number of variants that are definitely or probably associated with breast cancer risk. There is also increasing evidence that some genetic factors have different effects on different subtypes of breast cancer," the authors write.

Gillian K. Reeves, Ph.D., of the Cancer Epidemiology Unit, University of Oxford, U.K., and colleagues conducted a study to analyze breast cancer risk, overall and by tumor subtype, in relation to 14 individual single-nucleotide polymorphisms (SNPs;) and a polygenic (relating to an inheritable character that is controlled by several genes at once) risk score. The study included 10,306 women with breast cancer (average age at diagnosis, 58 years) and 10,393 women without breast cancer, who in 2005-2008 provided blood samples for genotyping. The researchers estimated the per-allele odds ratio (OR) for individual SNPs and the cumulative incidence of breast cancer to age 70 years in relation to a polygenic risk score based on the 4, 7, or 10 SNPs most strongly associated with risk.

The researchers found that the odds ratios for breast cancer were greatest for the SNPs FGFR2-rs2981582 and TNRC9-rs3803662 and, for these 2 SNPs, were significantly greater for estrogen receptor (ER)-positive than for ER-negative disease, both in the data of this study and in meta-analyses of other published data. The next strongest association was for 2q-rs13387042, for which the per-allele OR was significantly greater for bilateral than unilateral disease and for lobular than ductal tumors.

"When the effects of the 7 SNPs most strongly associated with overall breast cancer risk in these data were combined using a polygenic risk score, the cumulative risk of breast cancer to age 70 years among women in the top fifth was twice that in the bottom fifth (8.8 percent vs. 4.4 percent). Both the relative and, particularly, the absolute difference was much greater for ER-positive disease (7.4 percent vs. 3.4 percent) than for ER-negative disease (1.4 percent vs. 1.0 percent)," the authors write.

"In this large study including 10,306 women with breast cancer and 10,393 without the disease, we confirm that some of the more important common genetic variants for breast cancer have different effects on different tumor types."

"Certain established risk factors for breast cancer have similar, or even greater, effects on breast cancer incidence than the differences seen here between women in the highest vs. the lowest fifth of polygenic risk score. Indeed, our estimate of the cumulative incidence of breast cancer to age 70 years in women in the top fifth for polygenic risk score (8.8 percent) is similar to that for women in developed countries with one first-degree relative with breast cancer (9.1 percent), and considerably less than that for women with 2 affected first-degree relatives (15.4 percent). Furthermore, no interactions have been found between the effects of the genes investigated here and the other risk factors for breast cancer. Hence, as others have suggested, subdividing women on the basis of their polygenic risk is, at this stage, not a useful tool for population-based breast cancer screening programs but may be useful for understanding disease mechanisms," the researchers conclude.

More information: JAMA. 2010;304[4]:426-434.

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