EDITORIAL

Breast and Ovarian Cancer: The Power of Genome-Wide Association Studies

Breast cancer (BC) is the most common malignant tumor among women with approximately one million new cases per year worldwide. One of the main risk factors for breast cancer is family history, suggesting that genetic factors are important determinants of disease risk. Familial germline mutations are considered responsible for 5% of all breast cancer cases. The two most important BC susceptibility genes, *BRCA1* e *BRCA2*, were identified by linkage analysis and positional cloning in the 1990s. *BRCA1* and *BRCA2* mutations are uncommon, but confer high risk of breast and ovarian cancer and smaller risk for other tumors [1, 2]. It is estimated that *BRCA1* and *BRCA2* are involved in less than 25% of the familial risk of breast cancer, whereas mutations in other high-susceptibility genes (such as *TP53*, *PTEN*, *STK11*) or in moderate-susceptibility genes (such as *ATM*, *PALB2*, *CHEK2*, *BRIP1*) account only for about 5% of familial breast cancer. Several studies, performed on familial cases not associated with *BRCA1* and *BRCA2* germline mutations, have revealed the heterogeneous nature of the non-*BRCA1/2* tumors [3]. Thus, most of the familial risk of BC can plausibly implicate a multiple combination of several low-penetrance susceptibility alleles, each conferring a small effect on BC risk. This model defined polygenic allows to evaluate not only the risk associated with different allelic variants but also their combined effects and the interactions with lifestyle and other factors. Several studies suggested that no one gene is responsible for a significant portion of BC susceptibility, strengthening the hypothesis of the polygenic model. Thus, despite the efforts made during the last years, the majority of familial cases is unexplained and other BC susceptibility genes still remain to be identified. The identification of new genes could have a significant impact in risk prediction [4].

Two main strategies have been used to identify several susceptibility genes: genetic linkage analyses in multiple cases of the familial non-*BRCA1/2* tumors and Genome-Wide Association Studies (GWAS). While linkage studies, performed even in many families, have limited power to detect such genes, instead case-control association studies have provided the opportunity to better identify most common variants (allele frequencies $\geq$ 5 %) associated with cancer [5].

Genome Wide Association Studies represent a new powerful approach to identify low-penetrance alleles whose combined effects may be used for cancer risk prediction. The power of GWAS is to examine all or most of the genes in the genome of different individuals in order to evaluate the association of genetic variants at different loci on different chromosomes (LD) in large series of cases versus controls, analyzing a panel of hundred thousand SNPs (single nucleotide polymorphisms) simultaneously, to identify new alleles of susceptibility to cancer [6, 7]. In the past years, novel risk alleles for BC were identified by four recent GWA studies: Breast Cancer Association Consortium, Cancer Genetic Markers of Susceptibility, DeCode Islanda, Memorial Sloan-Kettering Cancer Center. Comparing the results obtained from four major studies of GWA, it has been highlighted a correlation of allele frequency of some SNPs located on the genes: *FGFR2*, *TNRC9*, *MAP3K1*, *LSP1* and *H19*. The combined analysis of these GWA studies allowed to identify the main allelic variants showing a stronger statistical evidence of association with increased familial risk: rs2981582 lies in intron 2 of *FGFR2*, rs12443621 and rs8051542 within *TNRC9*, rs889312 lies in a region that contain *MAP3K1* gene, rs3817198 lies in intron 10 of lymphocyte-specific protein 1 (*LSP1*) and rs2107425 within the *H19* gene. New susceptibility allelic variants associated with BC risk were recently discovered through large replication studies in combination with the original GWAS data [8].

Family history represents the strongest risk factor for ovarian cancer (OC) with disease predisposing mutations identified in 15% of the tumors. Also, *BRCA1* and *BRCA2* germline mutations confer a high risk of OC for non-*BRCA1/2* tumors. In population-based studies, *BRCA1* and *BRCA2* mutations are present in 5-15% of all OC cases [9]. In recent years, the research and identification of low-penetrance susceptibility loci played a key role in the etiology of OC. To date, a few low-penetrance genes that confer increased susceptibility to ovarian cancer have been isolated. In this perspective, numerous genetic association studies were performed to identify common ovarian cancer susceptibility variants. Allelic variants with the strongest evidence for an association with OC include SNPs on chromosomes 8q24, 9p22.2, 19p13, and 2q31, and the rs2854344 in the *RB1* gene. The main involved pathways are DNA repair, cell cycle, sex steroid hormone and oncogenic pathway [10].

However, several drawbacks of GWASs were observed, including their high cost and a poor capacity of replication. Moreover, there is a common scepticism toward these new approaches because it is not known the mechanism by which the novel allelic variants cause the susceptibility. In conclusion, the recently discovered data could open up new streets for basic research. In future, a new generation of large-scale association studies, in combination with replication analyses and multiple scans could be able to identify many more loci [8].

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