Introduction to epidemiology of breast and ovarian cancers

Over the last several decades, our understanding of the molecular epidemiology of breast and ovarian cancers has taken great leaps. Multiple reproductive, demographic and life-style factors influencing a woman’s risk of developing breast or ovarian cancer were identified [1, 2]. The characterization of shared risk factors, such as hormonal and dietary exposures or demographic traits, shed more light on the role of possible biological events determining the susceptibility to both diseases. Because a family history of breast or ovarian cancer is the strongest risk factor for developing the disease, the elucidation of inherited genetics has been the major focus in these efforts. Two decades ago, the discoveries of the BRCA1 and BRCA2 genes and the establishment of their association with familial breast and ovarian cancers propelled the dramatic shift in the understanding of the role that genetic factors play in the etiology of common cancers [3]. Much of the excitement following these discoveries has been specifically concentrated on clinical utility of BRCA1/2 in improved preventive algorithms. Clinical testing for BRCA1/2 germline mutations combined with specific prophylactic clinical interventions (mastectomy, oophorectomy) has resulted in unprecedented risk reduction in high-risk individuals in the population. In ovarian cancer, for example, prophylactic bilateral salpingo-oophorectomy in patients with BRCA1/2 mutations almost completely removes cancer risk. These significant improvements suggest that the clinical management of breast and ovarian cancer patients strongly benefits from the availability of meaningful genetic markers, allowing for more personalized assessment of individual risk.

The mutations in BRCA1/2, however, associate only with a tiny fraction of breast and ovarian cancers, and hence only a small subset of individuals currently benefit from the BRCA1/2-targeted prophylactic measures. While hereditary breast and ovarian cancers represent ~10%–20% of the disease fraction in the population, only ~10% of hereditary cases are due to mutations in BRCA1/2. This suggests that there are other, yet unknown genetic-risk factors to be identified. Also, while the mutations in BRCA1/2 present the strongest risk, their age-specific penetrance is incomplete; carriers of BRCA1/2 have an ~80% lifetime risk of developing breast cancer, while the lifetime risk for ovarian cancer associated with BRCA1/2 mutations is only ~50%. This indicates that there may be other genetic loci or environmental exposures that modify the penetrance of BRCA1 and BRCA2 mutations. Addressing these outstanding questions has been the central focus of molecular epidemiology of breast and ovarian cancers in the past few years.

Due to recent advances of genomic technologies, the genome-wide association studies (GWASs) have identified numerous common genetic variants conferring a risk of both breast and ovarian cancers in a sporadic population, some of them associated with risk effects in both diseases [4, 5]. Interestingly, many of the GWAS loci show specific association patterns in BRCA1 (SNPs at 19p13) and BRCA2 (FGFR2, ZNF365) carriers, suggesting that common genetic variants also modify BRCA1/2 penetrance [6]. Similar to BRCA1 and BRCA2 mutations, the GWAS loci contribute to the clinical heterogeneity of breast and ovarian cancers. For example, FGFR2 is associated with estrogen-positive breast tumors, while common variants at 19p13 have been found to associate with triple-negative breast tumors. In ovarian cancer, the 9p22 locus shows the strongest effect in serous epithelial ovarian carcinoma, while the common variants at 2q31 were associated with both serous and mucinous subtypes. However, while many of these alleles have been systematically validated in large meta-analyses, the risk effects associated with GWAS loci are small, which makes the current clinical applicability of these variants questionable. The proposed polygenic model assuming the combined effects of multiple-associated common variants from these scans explains an additional ~10% of variance attributed to genetic factors in both diseases [5, 7]. The combined attributable risk, however, associates only with a tiny fraction of population; hence the clinical implications of the GWAS polygenic model in preventive algorithms will likely be limited. It is clear that while common genetic variants identified in GWASs have added some important information into the complex picture of genetic susceptibility to breast and ovarian cancers, individually they do not suffice as clinical markers with risk-predicting utility.

In recent years, the methods of whole-genome/whole-exome sequencing offered an unprecedented opportunity to assess the missing genetic risk of breast and ovarian cancers, by identification of variants or mutations at low-population frequencies (rare variants). While the technology is still prohibitively costly to be used on a population scale, a focus on cases with a strong family history that are negative for BRCA1 and BRCA2 is a feasible alternative for the discovery of a missing high-risk genetic component. The systematic candidate re-sequencing of larger subsets of familial breast and ovarian cancer cases negative for BRCA1 and BRCA2 mutations has already revealed the presence of other moderate-to-high risk loci (relative risks of two to five) in familial settings. These
include mismatch DNA repair genes (e.g. Lynch syndrome [8, 9] or rare mutations in RAD51C, PALB2 or ATM [10–13]. It is certain that the ongoing efforts of high-resolution next-generation sequencing in familial kindreds will identify many more such moderate-to-high penetrant rare variants/mutations, which would serve as genetic markers with better translational potential for improved preventive models. Given the high sensitivity of next-generation sequencing technologies, it is reasonable to expect that, once completed, such high-resolution approaches will likely capture most of the significant fractions of considerable genetic heterogeneity present in both diseases.

Our capacity for more complex investigation of molecular events underlying breast and ovarian tumorigenesis grows with the new technological approaches that are constantly advancing. The incorporation of information from multiple advanced genomic platforms has been a leading force of breast and ovarian cancer molecular epidemiology and genetics in recent years. The biological investigations of BRCA1 and BRCA2, for example, have opened new avenues in the molecular characterization of breast/ovarian tumors resulting in novel treatment opportunities, as evidenced, e.g. in successes for PARP inhibitors in BRCA1/2-mutated patients, or efficient treatment alternatives in patients overexpressing the HER2 receptor [14, 15]. Thus, it is apparent that the systematic molecular profiling of breast and ovarian cancers can discover novel biomarkers that can be efficiently utilized in prognostic or treatment applications. The growing amount of information generated by the multi-institutional Cancer Genome Atlas is rapidly changing the current knowledge of molecular processes underlying breast and ovarian tumorigenesis. The novel molecular subtypes with specific therapeutic potential identified by large integrative analysis of genetic and epigenetic profiles in breast tumors [16, 17] or the discovery of novel molecular pathways altered in the ovarian cancer genome are only a few examples from these ongoing efforts. In years to come, the integration of somatic profiles with germline information on common and rare variants identified with next-generation sequencing and information on environmental and life-style risk factors will likely lead to a significant improvement in the value of preventive and prognostic assessment of breast and ovarian cancers. In addition, the discovery of novel markers in these future integrative studies will likely point to novel molecular pathways with the capacity to be efficiently targeted by improved therapies.

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disclosure
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