Preventing familial breast and ovarian cancer: major research advances with little implication

Women's HEALTH

"It is now the time to focus on [next-generation sequencing]-based technology to complete genome sequencing instead of simple genotyping and to create sophisticated methods to understand how gene expression is regulated by functional molecular networks…"

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Primary prevention of hereditary breast–ovarian cancer syndrome, which accounts for 5–10% of all breast cancer diagnosis, represents a prime paradigm of excellence of personalized medicine [1,2]. However, genetic testing can reveal that *BRCA* mutation carriers account for less than 25% of the familial risk. There has been little progress in explaining the missing heritability of the remaining 75% of women with family history who test negative for *BRCA* mutations. Neither recently identified common low-penetrance variants alone, nor their interactions with established environmental risk factors, are able to explain missing heritability. But even among *BRCA* mutation carriers, the decision by an expert scientific team for the optimal preventive strategy, choosing between prophylactic surgery and intensive surveillance, is very difficult and should be individualized for each woman. Here we discuss the latest advances in breast cancer genetics, their potential to impact prevention strategies and practices, and the future perspectives for a true personalized preventive medicine.

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Heritability and environment determine the complex landscape of tumorigenesis, but the magnitude of their risk contribution varies considerably among individuals. Genetic testing in women with a family history of breast or ovarian cancer, or both, for identifying causal heritable mutations in *BRCA1* or *BRCA2* genes has been a standard approach for decision-making regarding prevention or treatment of breast cancer and ovarian cancer. Although mutation carriers face a very high lifetime risk, personalized accurate and age-adjusted timely prediction still remains elusive, whereas even women with negative genetic testing, but strong family history, have an increased risk of developing breast and ovarian cancer. Multiple questions on an optimal preventive or therapeutic approach are raised by both positive and negative *BRCA* testing results. Here we discuss the latest advances and challenges in genomic and personalized medicine with hereditary breast ovarian cancer syndrome as a prime paradigm [1,2]. We also describe the challenges and problems for complex medical decisions balancing the risks and benefits of each medical choice for individual women with family history, based primarily on *BRCA* testing but also multiple other variables.

Rare *BRCA* mutations

The discovery of *BRCA* genes less than two decades ago has revolutionized our thoughts on how mutations in single genes can cause diseases such as cancer. The *BRCA* are tumor suppressor genes, and *BRCA1* and *BRCA2* have roles as regulators of DNA repair, transcription and the cell cycle in response to DNA damage. Evidence from both basic and clinical science has demonstrated that inherited mutations in *BRCA* genes lead to breast and ovarian cancer. But how and why these mutations affect cancer development, and by which molecular mechanisms normal breast or ovarian cells are transformed into cancer cells are not clearly understood [3].

Rare mutations in these genes confer high relative breast cancer risks to carriers of ten- to 20-fold, corresponding to a 30–60% risk by the age of 60 years, compared with 3% for the general population [4]. When we consider lifetime risks, the probability that a *BRCA* mutation carrier will develop cancer reaches up to 85%, as

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compared with a 12% risk in the general population. Genetic screening of high-risk families for identifying one of 1000 causal cancer mutations in *BRCA* genes has been well established and in some countries, such as the USA [1], has long been a standard approach to prevent breast and ovarian cancer.

> "If there are rare variants with large effects, it is not surprising that these rare mutations could not be captured by available association studies..."

Germline mutations in *BRCA* can explain approximately 16–20% of familial risk. Another approximately 5% of familial risk is attributable to very rare mutations in some genes such as *PTEN*, *CDH1*, *RAD51* and *CHEK2*. Collectively, less than 25% of the familial risk can currently be explained [5]. However, how can the 75% of familial risk that is termed as 'missing heritability' be explained?

Missing heritability

Previous work has suggested the polygenic model to help understand the 75% of breast cancer familial risk [6]. According to this model, the missing heritability could be explained by the accumulation of low to moderate genetic risk variants other than *BRCA1/2* genes, namely *BRCA3* or *BRCA4* high-penetrance genes. Indeed, more than 15 years after the discovery of *BRCA1/2* genes, the 'classical' linkage studies in high-risk families have identified no other high-penetrance genes. The completion of the HapMap 3 project with a database of common and rare variants [7] and high-throughput screening technology has allowed a new generation of association studies to provide improved understanding of the genetics of familial cancer.

Genome-wide association studies

Over the past 4 years, genome-wide association studies (GWAS) began to scour human genetic samples for the signals of individual variations. Typically, such studies assess hundreds of thousands of genetic variants in thousands of individuals sorted by traits: a certain height, obesity or various disorders [8]. The simplest and most common type of genetic variant, in which one DNA letter is changed to another, are single nucleotide polymorphisms (SNPs). The present generation of GWAS has used SNP microarrays containing 50,000 to 1 million SNPs to screen populations for assessing significant differences. The disappointing result of this first-generation GWAS is the assessment of small size effects of these newly discovered variants, despite the statistically significant differences observed [8]. Indeed, generally, associations between SNPs and traits tend to be of modest effect size, with a median odds ratio per copy of the risk allele of 1.33 [8]. This is confirmed in a more recent study attempting to link ten common low-penetrance variants identified by recent GWAS with a breast cancer prediction model. Little clinical implication could be found by integrating the SNPs into predictive models [9].

Explanations for missing heritability include rare variants, which are not captured by current GWAS; structural variants, such as copy number variants, which are poorly captured by current studies; other forms of genomic variation such as genomic rearrangements; or interactions between genes or between genes and environmental factors [10].

Next generation of GWAS

Most GWAS have used genotyping platforms with less than 1 million SNPs, without consideration of copy number variants or genomic rearrangements. These studies were designed to detect SNPs at a frequency of over 5% in the population. If there are rare variants with large effects, it is not surprising that these rare mutations could not be captured by available association studies [8].

To overcome these challenges, vendors such as Illumina and Affymetrix, based on more recently released data with much larger numbers of genetic variants provided by the HapMap 3 project [7], will develop assays with 5 million SNPs in the next year [11]. By using these microchips in larger sample sizes, rarer mutations at a frequency of 0.5% could be detected. But will such rare mutations be proven to have large effects and thus yield identification of individuals at very high risk of developing cancer? Considering the complex biological processes involved in carcinogenesis, apart from genetic and epigenetic alterations, there is strong scepticism as to whether high-risk variants currently exist, other than of the already available identified *BRCA* genes.

Whole-genome & exome sequencing

The next-generation sequencing (NGS) technology-based ability to provide, for the first time, a complete landscape of the genetic rationale underlying cancer has revolutionized biomedical sciences. NGS technology, scanning both protein-coding genes (exons, the set of which is

also called the exome) and the whole genome, including the noncoding region, as well as information on genetic regulation, now provides a rational strategy for understanding the structural and functional basis of complex diseases including cancer [12–14]. Using this massive parallel sequencing technology and the latest bioinformatics developments for cost-effective quality control and data analysis, we will be able to reliably complete the mutations' catalogue for each cancer type separately [15]. Translating these important basic research achievements from model organisms into humans now provides the most rational approach to improve healthcare [16]. At present, however, in the prevention of breast cancer, what are the potential implications of this biomedical research revolution?

Current practical preventive approaches

In the real world of day-to-day clinical practice, family history and *BRCA* testing continue to be the standard of care in the prevention of familial breast and ovarian cancer. Yet these methods are still preliminary and few of the recent genomic advances can be incorporated into medical practice.

Positive BRCA *test*

Women with inherited *BRCA* mutations face a very high risk of developing breast or ovarian cancer. The optimal management of these mutation carriers has not yet been established. Preventive options include surgical prophylaxis and nonsurgical interventions. Evidence has demonstrated that risk-reducing surgery almost eliminates the risk of cancer development at a specific organ. Risk-reducing surgery, such as prophylactic bilateral mastectomy, has been proven to be a highly effective approach to prevent both breast cancer development and death from breast cancer. Prophylactic bilateral salpingo-oophorectomy has the advantage that it not only drastically reduces the risk of ovarian cancer and death from ovarian cancer but also reduces, by approximately 50%, the risks of breast cancer and death from this disease [17]. Therefore, laparoscopic salpingo-oophorectomy is thought to be considered as a more beneficial approach with better cosmetic results as compared with mastectomy, but both surgical procedures are associated with behavioral and psychosocial adverse effects. It is not surprising, therefore, that a substantial proportion of women with *BRCA* mutations select a medical intervention with the use of tamoxifen and/or intensive surveillance that includes mammographic screening, MRI, transvaginal ultrasonography and CA-125. However, it should be emphasized that there is an increased risk of late diagnosis at a young age and death from breast cancer or ovarian cancer despite prevention with tamoxifen and intensive surveillance [18].

Negative BRCA *test & low-penetrance common variants*

Family history of breast cancer is known to be one of the strongest risk factors for this disease. For example, meta-analysis of familial breast cancer studies gives lifetime risk ratios of 1.80 in families with one affected first-degree relative, 2.93 in families with two affected relatives, and 3.90 in families with three affected relatives [19]. Most of these women have no mutations in *BRCA* genes and, despite efforts, the genetic basis of this particular familial breast cancer remains missing [10]. The hope that GWAS-based identification of genetic variants could help to identify high-risk women has so far failed either by combining both risk SNPs and established risk factors or studying gene–environment interactions [9,20]. These two studies reconfirm the oversimplification in expecting to understand the high complexity of breast tumorigenesis by simple genotyping. It is now the time to focus on NGS-based technology to complete genome sequencing instead of simple genotyping and to create sophisticated methods to understand how gene expression is regulated by functional molecular networks [13,14]. Such knowledge is essential in translational medicine for improving health [16] as, for example, in tumorigenesis-based development of genetic tests as biomarkers for personalized breast cancer risk prediction.

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In practice, no standard approach exists to manage women with family history and a negative *BRCA* test. Women with a significant family history of breast cancer (i.e., two or more breast cancers under the age of 50 years, or three or more breast cancers at any age), but who test negative for *BRCA* mutations, have approximately a fourfold increased risk of breast cancer.

A recent study demonstrated that this increased risk translates to a 20–40% lifetime risk of developing breast cancer [21], and suggests caution for these women, who may be candidates for tamoxifen chemoprevention and/or intensified breast screening with MRI. Risk-reducing surgery can be considered as an aggressive preventive approach for these moderate-risk women.

Conclusion

Women with a significant family history of breast cancer, ovarian cancer or both should be referred to a specialized cancer center. Risk-reducing surgery in *BRCA* mutation carriers reduces both risk of cancer development and mortality from the disease. Given behavioral and psychosocial adverse effects of prophylactic surgery, intensive surveillance and tamoxifen chemoprevention can also be discussed, but this approach is associated with increased risks of late diagnosis and cancer death. Caution is suggested for women with family history who test negative for *BRCA* mutation. They face a 20–40% lifetime risk of breast cancer development and should be incorporated into intensive surveillance programs. There is high hope that NGS technology-based systematic studies and international consortiums will be able to reveal how genetic variants deregulate gene expression and functional molecular networks leading to cancer.

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