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NEWS AND COMMENTARY

Breast cancer susceptibility genes analysed into three groups

Genomics and breast cancer: the different levels of inherited susceptibility

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Our understanding of inherited breast cancer susceptibility has changed dramatically over the last 5 years, with the discovery of many genes in which mutations influence the risk of developing breast cancer.

These fall into three main groups: genes in which mutations confer a high risk of developing cancer, but where such mutations are rare; uncommon mutations in genes conferring a moderate increase in risk (odds ratios of approximately 2–4), and common polymorphic variants which each confer only slight risk alterations (odds ratios rarely above 1.2 for variants conferring increased risk). The discovery of these genes and loci was predicated on linkage analysis (for high-risk genes), screening for mutations in candidate genes selected because they were involved in functional pathways related to BRCA1 and BRCA2 function (moderate risk), and genome-wide association studies (low penetrance polymorphisms).

However, with this increased knowledge comes the difficulty of knowing how this information may best be utilized in clinical practice. The review by Ripperger *et al*[1] in this edition of the Journal examines the current knowledge of newly identified moderate and low risk susceptibility genes, classifying the genes involved in inherited breast cancer susceptibility into the categories described above. The tables and diagrams are helpful in indicating the relative frequency and penetrance for breast cancer of genetic variants in these different categories, and give some indication of the proportion of the disease burden associated with mutations in each gene.

The discovery of lower penetrance genes[2] indicates that inherited breast cancer susceptibility is due to a number of genetic factors, and it may well be that the familial clusters of breast cancer not due to mutations in *BRCA1* and *BRCA2*, originally attributed to *BRCA3*, are in fact due to a combination of the effects of lower penetrance gene mutations and environmental factors.

Healthcare providers will have the dilemma of deciding whether it will be cost-effective to introduce population screening of variants of these low penetrance genes and what level of risk would justify medical intervention. Inheritance of one low penetrance risk-conferring polymorphic allele may only confer a very minor increase in risk of developing cancer, but individuals who have inherited several high-risk polymorphic variants may be at significantly increased risk. It has recently been argued, for instance,[3] that individuals who have, say, six 'high'-risk alleles, may have a sufficiently increased risk to justify initiating mammographic surveillance 10 years before the generally recommended age for women in the general population, and women with six low risk alleles could start screening at a later age.

Highly penetrant genes

Mutations in the rare high penetrance breast cancer predisposing genes *BRCA1* and *BRCA2* account for 16–25% of the inherited component of breast cancer. Mutations in *TP53*, which cause the Li–Fraumeni syndrome, *STK11* causing Peutz–Jeghers syndrome, and *PTEN* causing Cowden syndrome are uncommon causes, as are mutations in *CDH1*, although these mutations may be highly penetrant for breast cancer. These syndromes have all been well characterized. Probands and their relatives are identified and offered genetic counselling, and genetic testing may be available to them, allowing appropriate screening and prophylactic measures to be put in place.[4]

The intermediate penetrance breast cancer susceptibility genes

After the identification of the highly penetrant genes, research mainly based on candidate gene testing led to the discovery of genes in which inherited mutations conferred an intermediate increase in risk of breast cancer. The discovery that mutations in *ATM*, *CHEK2*, *BRIP1*, *BARD1*, and *PALB2*[1,2] can cause an increased odds ratio for breast cancer of 2–4 is of particular interest because these genes are all involved in the same DNA repair pathways, but it is curious that they do not confer the high risk of breast and ovarian cancer seen in women who carry mutations in *BRCA1* and *BRCA2*. Also of great interest is that biallelic mutations in *BRCA2*, *BRIP1*, and *PALB2* cause Fanconi anaemia subtypes FANC D, J, and N respectively, further indicating overlap in the functions of these genes. Another gene which interacts with *BRCA1* and is involved in DNA repair is *RAD50*, and a founder Finnish truncating mutation has been reported to confer an increased risk of breast cancer (odds ratio: OR = 4.3), but the contribution of *RAD50* mutations to breast cancer susceptibility overall is still debatable. The implications of such mutations are discussed in the review, making the point that, with some exceptions, these mutations are rare[5] in the population and screening for such mutations would not be cost-effective unless there was a founder mutation conferring a significantly

increased risk. Such testing could lead to unnecessary anxiety for those who carry these mutations, as the current literature does not usually suggest a particular strategy with regard to surveillance and prophylactic management strategies for them. However, testing for founder mutations may present a scenario where such testing could be cost-effective.

Other syndromes discussed in this review which may be associated with a moderately increased breast cancer risk include neurofibromatosis type 1 and Nijmegen breakage syndrome mutation carriers, and the slight increase in risk associated with Lynch syndrome is referred to, although the relative increase in breast cancer risk in Lynch syndrome is debated and generally considered to be low, but may vary with the different genes involved.

The common low-penetrance breast cancer susceptibility alleles

The rapid increase in case–control studies[6] utilising single nucleotide polymorphisms has led to an abundance of literature on this subject and has been well summarized by this review. The authors demonstrate clearly that some of these studies currently provide contradictory evidence of the importance of the role of such polymorphisms. However, there is good evidence now that there are up to eight polymorphisms, which are reproducibly found to influence breast cancer risk, particularly the *FGFR2* gene. Carriers of two low risk rs2981582 alleles at the *FGFR2* locus (frequency 38% of the population) have a relative risk of breast cancer of 0.83 compared with the general population, carriers of one high-risk and one low-risk allele (47%) have a relative risk of 1.05, and carriers of two high-risk alleles (14%) have a relative risk of 1.26. The overall importance of these polymorphisms remains high, because their effect appears to be multiplicative, such that an individual possessing several polymorphisms conferring increased risk may have a significantly increased risk of breast cancer.[3,7]

Many of these polymorphic loci are of unknown function, and the polymorphic site may be outside any functional gene locus. The associated risks with each polymorphism are low, and the five most significant loci described by Easton *et al*[8] account for only 3.6% of the excess familial breast cancer risk in the European population. Interestingly, the polymorphisms at 10q26 and 5q11, and homozygosity for a variant in *RAD51* also affect risk in women who carry mutations in *BRCA2*, but not in *BRCA1* mutation carriers (thought likely to be related to the predominance of oestrogen negative tumours in *BRCA1* mutation carriers). However, mutations in *CHEK2* appear not to have such an effect, presumably because this gene acts in the same functional pathway as the *BRCA1/2* genes, and as these functions are already disrupted in BRCA1/2 mutation carriers, further disruption of this pathway may not have any appreciable additional effect.

The role in the overall causation of breast cancer of variants of uncertain pathogenicity in BRCA1, BRCA2 in the causation of breast cancer susceptibility is uncertain.[7] Clearly, there may be many more low penetrance susceptibility polymorphisms,[9] which may differ in frequency in different populations.

Commercial companies have rapidly seized upon literature describing low penetrance polymorphisms in breast cancer and have adapted them for use in commercially provided susceptibility testing. The keen media interest in this kind of testing has demonstrated the potential appetite of the general public for personalized genetic testing. What is less clear is whether the implications of genetic screening are fully understood, in terms of risk, the effects of lifestyle modification, and service provision. They are based on the best available state of knowledge of these low risk polymorphisms, which, however, is evolving. This has already lead to a situation where individuals undergo this type of screening, and may then present to their general practitioners and genetic clinics, concerned because they possess a susceptibility polymorphism which increases their cancer risk only marginally.

The current difficulty in determining the ideal breast cancer susceptibility test is based on constantly evolving genetic knowledge. Lifestyle factors, such as smoking, age at menarche and menopause, childbearing, breast feeding, and use of hormonal contraception and HRT are still very important influences on the development of breast cancer and should not be underestimated. The identification of these highly variable polymorphisms is a paradigm shift in our understanding of the pieces of the susceptibility jigsaw, but at the current state of knowledge, how they all fit together and what implications they have for counselling is still uncertain until we fully understand how all the elements of susceptibility, both genetic and environmental, interact ■

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