BRCA testing for familial breast cancer

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Summary

Mutations in the BRCA1 and BRCA2 genes are associated with hereditary breast and ovarian cancer. Genetic testing is available in specialised laboratories, but is expensive and presents a significant technical and interpretative challenge. Identification of a causative mutation carries lifelong health and psychosocial implications for the woman and her relatives. It also influences surveillance and treatment options. Testing should therefore only be considered with professional genetic counselling by specialists in familial cancer clinics.

Key words: genetic testing, mutations, ovarian cancer.

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Introduction

Breast cancer is the most common form of cancer among women in Australia. A woman has approximately a 1 in 10 chance of developing breast cancer at some point in her life. Most of these breast cancers are sporadic, reflecting the inevitable accumulation of errors in a person's DNA with age. However, 5–10% of affected women have a strong underlying and heritable predisposition to develop breast cancer.

Mutations in many different genes can cause a predisposition to develop breast cancer. For most women with familial breast cancer, the causative mutation is unknown and cannot be identified. However, the mutations most commonly identified in women with familial breast cancer are breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2). Together these mutations are found in approximately 20% of cases (that is, 1–2% of all breast cancers). Mutations in other genes, for example, TP53, CDH1, PTEN and STK11, are associated with rare genetic syndromes which can also predispose to breast cancer.

BRCA1 and BRCA2 genes

The BRCA1 gene is found on chromosome 17 and the BRCA2 gene is found on chromosome 13. They are tumour suppressor genes. The proteins encoded by these genes are part of a multi-protein complex which repairs damaged DNA. The complex normally repairs double-strand breaks in the DNA by homologous recombination. A cell which has lost BRCA1 or BRCA2 activity is unable to repair this damage and can rapidly accumulate mutations which eventually lead to cancer.[1]

A heritable mutation in either gene greatly increases the chance that a cell will become malignant. These mutations are inherited as autosomal dominants and there is a 50% chance that a child will inherit the abnormal gene from a carrier parent. The child will also inherit a normal copy of the gene from the other parent which will function, but the cell lacks a backup should this normal copy fail. With the inevitable accumulation of genetic errors with age, the normal copy may eventually become mutated (sometimes called the 'second hit') and the cell is left with no functioning BRCA gene. The resulting rapid accumulation of uncorrected errors in the cell's DNA usually leads to cancer.

For reasons that are not clear, the loss of BRCA1 or BRCA2 function increases the risk of some but not all cancers. Female carriers of a mutation in BRCA1 or BRCA2 are at high risk of developing breast cancer and ovarian cancer, while male carriers are at increased risk of breast and prostate cancer. In addition there is also a slightly increased risk of a wide range of other cancers, but the predominant cancer risk by far is that of breast and ovarian cancer.[1]

It is possible for someone to carry both a BRCA1 and BRCA2 mutation (double heterozygote) but this is very rare, accounting for less than 1% of all BRCA mutation carriers. For reasons that are not clear, double heterozygotes do not have a higher risk of cancer nor more severe disease compared to single mutation carriers.

Indications for BRCA testing

A family history of breast or ovarian cancer is the basis for making a clinical diagnosis of familial breast or ovarian cancer in a specific patient. The family history can also provide an indication of the risk of breast or ovarian cancer in an unaffected woman. Simple guidelines for assessing and interpreting a family history of breast and ovarian cancer are available from the National Breast and Ovarian Cancer Centre (www.nbocc.org.au).[2]

The clinical diagnosis of familial breast or ovarian cancer is not necessarily an appropriate indication for genetic testing for

mutations in the BRCA1 and BRCA2 genes, as the majority of women with familial breast cancer do not have an identifiable mutation in a known gene. Mutation analysis of the BRCA1 and BRCA2 genes is complex and expensive and is not justified in many women with familial breast or ovarian cancer. The current cost to the Australian healthcare system is $2–3000 per patient screened. There are a number of algorithms to estimate the likelihood of finding a BRCA1/BRCA2 mutation in a patient, but the positive predictive value of these algorithms is generally poor. The general consensus among familial cancer specialists in Australia is that a woman should be offered genetic testing for the BRCA1 and BRCA2 mutations if the estimated probability of finding a mutation is greater than 10%. The mutation search usually starts with testing the blood from an affected individual. Once a mutation has been identified, genetic testing of unaffected relatives (often called presymptomatic testing) may provide useful information regarding the risk of cancer and allow carriers to undertake specific cancer prevention and detection strategies before the development of disease.

Genetic testing of an unaffected person for a BRCA1 or BRCA2 mutation is generally not recommended unless a mutation has already been identified in a family member. If a mutation has not already been identified in a relative, it is impossible to interpret a normal result in an unaffected person. The normal result could mean that the person tested has not inherited the family's (unidentified) BRCA mutation, or that the person tested has inherited the family's non-BRCA mutation.

Genetic testing for a BRCA1 or BRCA2 mutation raises challenges in identifying which women should be tested, interpreting a complex test result, and managing the medical and psychological consequences of the result for both the patient and her relatives. For these reasons, the guidelines of the National Health and Medical Research Council recommend, and Australian laboratory standards require, that the testing is limited to specialists in familial cancer clinics. There are clinics across Australia and their services can be accessed by referral from medical practitioners.[3]

Mutation detection methodology

Analysis of the BRCA1 and BRCA2 genes is not simply 'two tests'. The BRCA1 and BRCA2 genes together consist of approximately 20 000 nucleotides. Analysis of each nucleotide in this length of DNA sequence presents a significant technical and interpretative challenge. There are approximately 10 laboratories in Australia which provide this service. DNA is extracted from a patient's blood sample and each exon of each gene is amplified by the polymerase chain reaction. Bidirectional sequencing is then performed on the products of the polymerase chain reaction. Any variation from the normal reference sequence must be assessed to determine if it is a benign variant, pathogenic mutation, or a variant of unknown clinical significance.

Direct sequencing does not detect large deletions or duplications which might involve many consecutive exons. Some laboratories can quantify the copy number of each exon relative to normal controls.

Interpretation of results

A normal person can have thousands of variations in their genetic code. In analysing the 20 000 nucleotides of the BRCA1 and BRCA2 genes, the laboratory will find many genetic variants. Some of these will be common variants that are well documented as being benign. The laboratory may also identify a variant which inactivates the gene and is documented as being pathogenic, that is, places a woman at high genetic risk of developing breast or ovarian cancer. There are international databases which catalogue variants and assist the laboratory in determining the significance of a particular variant. The laboratory may also identify one or more rare variants which are of unknown clinical significance.

The identification of a pathogenic variant carries significant implications for both the woman tested and members of her family. For this reason, the interpretation of a variant requires a high degree of scientific skill and accountability.

The failure to identify a pathogenic variant does not exclude the diagnosis of familial cancer. This is because the majority of women with familial breast or ovarian cancer do not have an identifiable mutation in the BRCA1 or BRCA2 genes.

The identification of a variant of unknown clinical significance is troubling for both the clinician and patient. However, such variants should not be the basis for clinical decision-making because, as more information is accumulated worldwide, many of them will turn out to be rare benign variants.

Once a pathogenic variant has been identified, other at-risk adult family members (male or female) can have a presymptomatic genetic test to determine their cancer risk. In this situation, the interpretation is much simpler. The relative has either inherited the pathogenic variant or not. This type of testing carries significant medical, psychological, ethical and social consequences. National clinical and laboratory standards require that such testing be accompanied by expert genetic counselling. For men, the principal reason for knowing their carrier status is to clarify the risk of their daughters inheriting the mutation.

Management

The main benefit of finding the familial BRCA mutation is the prevention or early detection of cancer in at-risk relatives. The care of someone carrying a BRCA1 or BRCA2 mutation must be individualised because the issues and options vary with the gene involved and the gender and age of the person.[4] Options include breast cancer surveillance, risk-reducing surgery and chemoprevention with drugs such as tamoxifen. Management involves the general practitioner and potentially multiple

specialists and genetic counsellors. At this time, BRCA mutation status usually makes little difference to the treatment of the cancer for the affected individual, but this may change with the availability of new drugs.

Genetic counselling

Genetic testing differs from most routine laboratory tests in that the detection of a mutation carries lifelong implications for the patient as well as relatives. The testing for BRCA1/BRCA2 mutations must always be accompanied by appropriate genetic counselling. This counselling should commence before any genetic testing and should be provided by a practitioner with professional genetic counselling training and experience.

Conclusion

BRCA1 and BRCA2 mutations are an important cause of familial breast and ovarian cancer. Genetic testing should take place in the context of appropriate pre-test and post-test genetic counselling, as provided by familial cancer clinics. The identification of pathogenic mutations has important implications for the clinical management of the patient and family members. However, a normal test result must be interpreted with caution. On one hand, the absence of an identified mutation in an affected woman does not exclude the clinical diagnosis of familial breast cancer. It is likely that the woman has a mutation in a different yet-to-be-identified gene. On the other hand, once a mutation has been identified in the family, a normal test result means that the person has not inherited the family's predisposition to develop cancer and does not require special cancer surveillance.

References

1. Petrucelli N, Daly MB, Feldman GL. BRCA1 and BRCA2 hereditary breast and ovarian cancer. GeneReviews. 1998, updated 2011 Jan. www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=brca1 [cited 2011 Mar 9]
2. National Breast and Ovarian Cancer Centre. Information for women about family history of breast cancer and ovarian cancer. 2011. www.nbocc.org.au/view-document-details/fhic-information-for-women-about-family-history-of-breast-cancer-and-ovarian-cancer [cited 2011 Mar 9]
3. Centre for Genetics Education, NSW Health. Family cancer services. www.genetics.com.au/services/canclin.asp [cited 2011 Mar 9]
4. Suthers GK. Cancer risks for Australian women with a BRCA1 or a BRCA2 mutation. ANZ J Surg 2007;77:314-9.

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Book review

Therapeutic Guidelines: Antibiotic Version 14 (2010)

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This book has become the most essential desktop clinical tool of this well regarded series. It aims to guide antimicrobial use within both hospital and community settings. It is reassuring with the release of this new edition to know that you are consulting the updated version when you are seeking prescribing advice.

The accessibility of the information is strengthened by the ongoing presentation of concise, evidence-based prescribing advice in a systematic format. This makes the information easily usable within consultations.

Beyond providing immediate advice in unfamiliar prescribing situations, this book usefully discusses some common clinical problems, rewarding a read outside the consultation room. This includes expanded guidance on the management of patients who report penicillin hypersensitivity, and the treatment and prophylaxis of influenza. New recommendations for gentamicin as empirical therapy are another major change in this version.

The book also provides useful summaries of the latest management guidelines of important and diverse conditions, such as when to recommend symptomatic treatment of otitis media rather than antibiotic treatment, and the procedures requiring antibiotics for the prevention of endocarditis.

A change in structure in this edition has led to the removal of some sections which overlapped with other Therapeutic Guidelines editions. Some readers may be disappointed to find that some common gastroenterological, dermatological or respiratory conditions requiring antimicrobial management are no longer included in this book, with the reader being directed to other books in the series.

I recommend this book to busy clinicians, which is just about all of us! It is an essential guide to prescribing antimicrobials, although the electronic version, as part of the complete set, may be necessary to get a more complete coverage of the clinical scenarios the reader will face.