

Management of inherited breast cancer: implications for carriers and clinical trials

James Mackay* (MA, MD, FRCP, FRCPE) and Ailsa Taylor (BSc Hons).

Institute of Human Genetics and Health,
University College London,
Wolfson House,
4 Stephenson Way,
London, NW1 2HE,
United Kingdom.

Tel: 0207 380 6931

Fax: 0207 679 5052

* Corresponding Author

E-mail: j.mackay@ucl.ac.uk

E-mail: ailsa.taylor@clinisys.co.uk

Estimation of Breast Cancer Risk

In the UK, the National Institute for Health and Clinical Excellence (NICE) is 'the independent organisation responsible for providing guidance to the National Health Service on the promotion of good health and the prevention and treatment of ill health.'¹ The recommendations are based on available evidence and aim to be both explicit and transparent. In May 2004, NICE issued guidelines for healthcare professionals providing care to women who present with concerns about the risk of developing breast cancer because of a family history.² These guidelines have been designed to help clinicians triage unaffected women into high, moderate or near population risk categories for developing breast cancer.

Familial Breast Cancer

Over the past few years there has been rapid progress in understanding the genetic basis of familial breast cancer. At least seven genes are now known to cause susceptibility to breast cancer.³ In the context of high-risk families the genes BRCA1 and BRCA2 are by far the most significant^{4,5,6}. Studies have estimated that germ-line mutations in BRCA1 and BRCA2 between them account for approximately 16% of all families with multiple cases of breast and/or ovarian cancer⁷. In a study of 237 high risk families, the majority (81%) of the breast-ovarian cancer families were due to BRCA1, with most others (14%) due to BRCA2. Most families with multiple cases of male and female breast cancer were due to BRCA2 (76%).

In these families, BRCA1 mutations confer a high lifetime risk of breast cancer (over 70% by age 70) as well as a high risk of ovarian cancer (40-60% by age 70) and a smaller but significant risk of prostate and colon cancer. In these families, BRCA2 mutations appear to cause a similarly high risk of breast cancer together with a smaller risk of ovarian cancer (around 25% by age 70). BRCA2 mutation carriers also suffer significantly increased risks of pancreatic and prostate cancer, and ocular melanoma. BRCA2 mutations (and, to a lesser extent, BRCA1 mutations) cause an increased risk of breast cancer in men^{8,9}.

Testing BRCA Genes; The Current Situation in the UK

The NICE guideline for familial breast cancer recommends that only women in the high risk category should be offered genetic testing, meaning that direct BRCA gene testing is only offered to a small proportion of women in the UK. Both genes have a long coding sequence, of around 17,000 bases, and an altered gene can be caused by subtle changes anywhere along the sequence of both genes. BRCA1 and BRCA2 testing is therefore a complex process which is broken down into a two stage procedure.

In the first stage a blood sample is taken, with informed consent, from a patient who is affected with either breast or ovarian cancer. The DNA is extracted from white blood cells, and then the sequence is examined in the laboratory. There is at least a 50% chance of first degree relatives of a person who has a mutation, having the normal copy of the BRCA gene. Since the identification of BRCA1 in 1994¹⁰ and BRCA 2 in 1995¹¹, over 1600 distinct disease-causing mutations in these

genes have been found in patients with breast or ovarian cancer. Once a mutation has been identified in a family, it is then possible to go on to the second stage and offer other unaffected family members a test, to determine whether they have inherited the mutation.

In London about 3,000 families have been offered a 60% Stage 1 test by the NHS. During their pre-test counselling session/s, these patients were told that the results would take 6-12 months and that current practice was to examine 60% of the total gene sequence for mutations. Consent was taken for future, more complete testing if resources became available. They were also told that complete 100% sequencing of BRCA1/2 genes was available for a fee of around £1,800 from the company Myriad Genetics Inc., based in Salt Lake City, Utah. In January 2006, Myriad established a partnership with a company in the UK named Lab21 for the provision of BRCA1/2 testing in the UK and Ireland¹². This test takes around three weeks. If results are required urgently, the results can be done more rapidly (in 10-12 days) at an extra cost.

NICE has issued guidance on the management of familial breast cancer, recommending that BRCA1/2 testing should aim for as close to 100% sensitivity as possible...and that the whole gene(s) should be searched."¹³ The recent government White Paper, states that by 2006, "genetic test results should be available within three days where the result is needed urgently (e.g. for prenatal diagnosis), within two weeks where the potential genetic mutation is already known (e.g. because another family member has already been tested) or within eight weeks for unknown mutations in a large gene"¹⁴. The government has invested £18 million between 2003 and 2006 in improving genetic services.

A recent UK wide survey of BRCA gene testing by CancerBACUP, demonstrated a wide variation in the services offered by Regional Genetics Services¹⁵. The results showed that that, while many laboratories had purchased new equipment for testing 100% of BRCA genes, only half of those who responded to the survey were currently offering this service. In addition, the results showed that there are variations in the way different genetics centres communicate information about the limitations of the BRCA test offered to patients. Psychological studies have indicated that a patient's risk perception may be influenced, not only by test results, but also by their state of psychological distress.¹⁶ This means that it may be easy for the patient to misinterpret an uninformative test result, if the limitations of the test they underwent are not effectively communicated.

In accordance with government targets, the London and South East England Clinical Genetics Network Advisory Group has recommended that patients who have previously received an uninformative laboratory report for a 60% BRCA1/2 test should be re-contacted, to ask for their further consent, before a complete test is carried out. However, patients in the North East Thames region have already given consent for further testing at the time of their initial test and will not be required to give another blood sample since their original sample has been stored at the laboratory. A questionnaire study was carried out to find out what level of understanding patients from the North East Thames region have of their own risk status, following the receipt of an uninformative result for a partial BRCA1/2 test and genetic counselling session(s). The results of this study will inform the decisions taken about informing patients when re-testing of stored samples commences. This information may also be used to inform the decision of other Regional Genetics Centres facing the same situation. Results will be submitted for publication shortly.

Large Scale Pharmacogenetic Studies

Few clinical trials on pharmacogenetics have been attempted to date. The BRCA Trial is the first study of chemotherapy based on inherited genetic make-up in the world. The trial is funded by Cancer Research UK and Breakthrough Breast Cancer and recruitment began in the UK in September 2005. The trial aims to test two clinical hypotheses: Firstly, are tumors in BRCA carriers more sensitive to platinum than other drugs? Secondly, is the normal tissue in BRCA carriers more sensitive to platinum than other drugs?

The BRCA2 gene encodes a protein involved in the repair of DNA strand breaks. There are two pathways by which double stranded DNA can be repaired. In the absence of BRCA2 the second, more error prone pathway is used. In an affected BRCA2 carrier no BRCA2 protein is translated in the cancerous cells, meaning that the more error prone pathway for DNA repair is used. It is

therefore hypothesised that the double stranded DNA breaks caused by platinum cause BRCA2 carriers to be more sensitive to platinum in chemotherapy.

In order to test this hypothesis, a randomised study in known BRCA carriers with breast cancer at relapse of a platinum versus a taxane is now in progress (see fig.1). Given that the frequency of BRCA mutations in the British population is only about 10% of all breast cancers, strong international support will be essential in order to recruit enough volunteers to achieve statistically significant results for this study.¹⁷

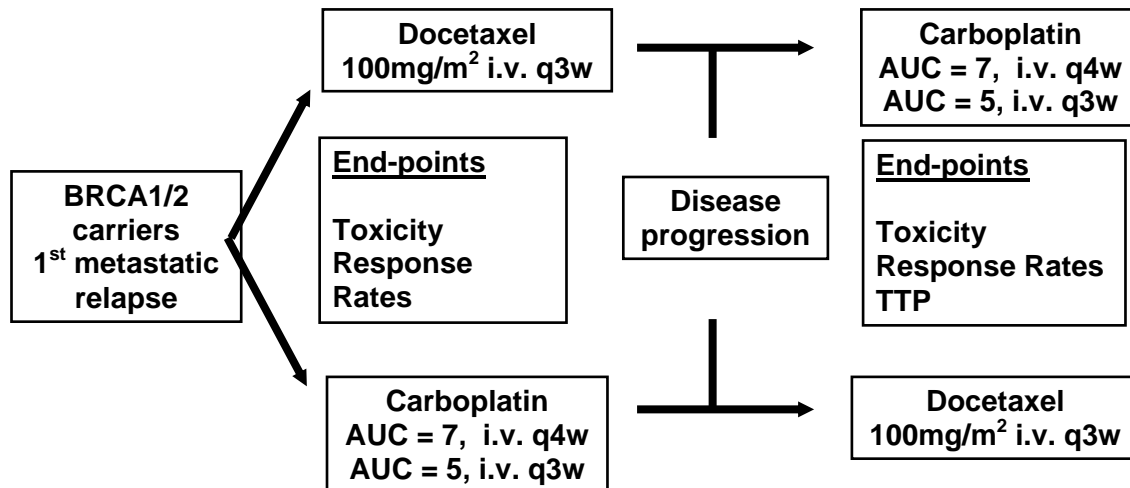


Fig.1: BRCA Trial Design

Exploring the Research Potential of Electronic Healthcare Records

CliniSys Solutions Ltd is a leading European supplier of integrated healthcare IT solutions and the market leader for electronic chemotherapy prescription in the UK¹⁸. They supply a sophisticated chemotherapy prescription database, known as ChemoCare, which provides electronic prescribing, pharmacy management and a chemotherapy scheduling system for inpatients and outpatients. ChemoCare aims to improve the collection of routine clinical data, thus offering enhanced patient safety and security above the alternative manual process.

The ChemoCare database holds a very accurate record of drug dose, prescription and delivery for over 2.4 million prescriptions. Over 150 chemotherapy protocols are recorded on the database, including detailed information on common and rare side effects for all laboratory tests performed since chemotherapy was started. A new organisation, called the Doctors Organisation for Clinical Studies (DOCS), aims to use the Chemocare database to facilitate clinical research in the field of pharmacogenetics.

In the first phase, the ChemoCare database will be used to identify two distinct cohorts of patients who have either mild or severe side effects following a particular drug regime. With informed consent, a blood sample will be taken from patients in each of the two cohorts. DNA will be extracted from these blood samples and the genetic variation examined to identify which metabolising enzymes are likely to be associated with the observed side effects.

In the second phase, DOCS hopes to employ a similar approach to identify genetic markers of tumour biology, by examining the genetic variation in samples of tumour tissue taken at different stages of disease and comparing it to the side effect profile. The results from these pharmacogenetic studies will be used to predict those who are most likely to develop severe side effects following a particular chemotherapy regime. The development of pharmacogenetic tests for chemotherapy drugs is a major step in working towards individualised cancer care.

Creating a Centre for Excellence in Genetics Research

The recent Department of Health White paper entitled 'Best Research for Best Health: a new NHS research strategy' promises to "exploit the potential of the NHS to improve national health and

increase national wealth by creating a world-class environment for research focused on the needs of patients.”¹⁹ With its exceptional ethnic and genetic diversity, and multitude of academic research institutions, the city of London provides a unique world-class environment for clinical research. By providing genetic services for clinical trial activity within a commercial framework, a new organisation called the London Genetics Centre Ltd aims to facilitate greater interaction between the NHS, academia and the bio/pharmaceutical industry in the UK.

Start up funding of £2 million has come from the Department of Trade and Industry²⁰ and the London Development Agency²¹. Seven centres of academic excellence in clinical research have collaborated to launch this novel initiative; comprising of Imperial College London, King’s College London, St. George’s Hospital Medical School, Queen Mary’s University, the London School of Hygiene and Tropical Medicine, the Institute of Cancer Research and University College London. It is proposed that initial activities will be in the field of oncology before rapidly moving into other disease areas, such as cardiovascular disease, mental health, endocrine and autoimmune disease. Ultimately, it is the mission of the London Genetics Centre to make London the European centre for genetic medicine.

Conclusions

The importance of inherited genetic variation in causing cancer has been understood for years. Recently it has become clear that inherited genetic variation may also be responsible for different clinical outcomes seen in cancer treatment. Inherited genetic variation may affect both toxicity profile and treatment efficacy. Prospective randomised trials looking at these issues are starting. Chemotherapy prescription databases may well be useful indicators of clinical outcome, allowing large scale pharmaco-genetic studies to be performed. The London Genetics Centre aims to put London at the centre of genetic medicine in Europe. Close collaboration with European partners will be essential if this aim is to be realised.

References

- ¹ 'National Institute for Health and Clinical Excellence website.' Available at www.nice.org.uk, accessed February 2006.
- ² 'Clinical Guidelines for the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care.' NICE, guideline ref. CG014, May 2004. Available at www.nice.org.uk/pdf/CG014Fullguideline.pdf, accessed February 2006.
- ³ Evans DGR, Lalloo F. 'Risk assessment and management of high risk familial breast cancer.' *J Med Genet*, 2002; 39:865–871.
- ⁴ Hall JM, Lee MK, Morrow J et al. 'Linkage analysis of early onset familial breast cancer to chromosome 17q21.' *Science*, 1990; 250:1684-9.
- ⁵ Miki Y, Swensen J, Shattuck-Eidens D, et al. 'A strong candidate for the 17q-linked breast and ovarian cancer susceptibility gene BRCA1.' *Science*, 1994; 266:66-71.
- ⁶ Wooster R, Bignell G, Swift S et al. 'Identification of the breast cancer susceptibility gene BRCA2.' *Nature*, 1995; 378:789-792.
- ⁷ Irving M, Elmslie F, Berg J. 'Genetics of breast cancer'. , 2002; 56(9):677-82.
- ⁸ Easton DF, Steele L, Fields P, et al. 'Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12-13.' *Am J Hum Genet*, 1997; 61:120-128.
- ⁹ Ford D, Easton DF, Stratton M, et al. 'Genetic Heterogeneity and Penetrance Analysis of the BRCA1 and BRCA2 Genes in Breast Cancer Families.' *Am. J. Hum. Genet.* 1998; 62:676–689.
- ¹⁰ Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994; 266, 66–71.
- ¹¹ Wooster R, Bignell G, Lancaster J, et al, 'Identification of the breast cancer susceptibility gene BRCA2.' *Nature*, 1995; 378(6559):789-92.
- ¹² Lab21, www.lab-21.com, accessed Jan-2006.
- ¹³ National Institute for Clinical Excellence in Health. 'Clinical Guidelines for the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care.' May-2004.
- ¹⁴ Department of Health. White Paper 'Our Inheritance, Our Future: Realising the potential of genetics in the NHS', June 2003.
- ¹⁵ CancerBACUP Survey 'Breast cancer genetic testing - wide variety in UK services, CancerBACUP survey shows.' (2005) available at: www.cancerbacup.org.uk/News/Press/Pressreleasesstatements/2005/91989565
- ¹⁶ Croyle RT, Lerman C. 'Risk communication in genetic testing for cancer susceptibility.' *J Natl Cancer Inst Monogr.* (1999);25:59-66.
- ¹⁷ UCL Cancer Trials Centre, 'BRCA Trial Protocol'. 2005. Available on request, website at: www.ucl.ac.uk/cancertrials/index.htm
- ¹⁸ Clinisys Solutions website. Accessed 2006. Available at www.smsol.com/oncology/index.htm
- ¹⁹ Department of Health, 'Best Research for Best Health: A new NHS research strategy', Sep-2005, available online at: www.dh.gov.uk, gateway reference 5923, accessed 2006.
- ²⁰ Department of Trade and Industry Homepage. , Accessed 2006. Available at www.dti.gov.uk
- ²¹ London Development Industry Homepage. Accessed 2006. Available at www.lida.gov.uk