The role of molecular genetic testing in modern breast health management

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Abstract

Defects in the BRCA tumor suppressor genes contribute significantly to the development of breast cancer in South Africa. Additive genetic effects and lifestyle risk factors underlie variable expression patterns in affected families, while also increasing breast cancer risk in the general population. Modifiable environmental factors could determine whether individuals with genetic risk factors develop cancer or fail to respond to treatment. Consequently, there is an increasing demand for genetic testing not only in patients with familial breast cancer, but also in healthy women and patients with sporadic cancer. Today, genetic testing in breast health extends from single-gene diagnostic tests to multi-gene treatment-based tests. For women in whom established breast cancer risk reduction approaches such as surgery and pharmaceuticals are not acceptable or inappropriate, treatment is based on molecular-genetic targets for individualised medical, nutrition and lifestyle intervention. Genetic testing as part of a holistic approach to breast health management translates into individual needs-based risk reduction interventions. ***(SA Fam Pract 2005;47(9): 38-40)***

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Introduction

Breast cancer is the most common cause of cancer mortality in women worldwide and its incidence continue to increase.[1] Cancer initiation is triggered by genetic alterations while interaction with environmental factors and the ability of cells to repair DNA damage determine cancer development.[2] A better understanding of the molecular basis of malignancy allows the development of rational surveillance, prevention and treatment strategies.

High-penetrance mutations in the BRCA1 and BRCA2 genes confer a lifetime risk of between 40-85% for breast cancer development in females and approximately 10% in males. These genes contribute significantly to the 5-10% of breast cancers that are inherited in families, while sporadic breast cancer is ascribed mostly to interaction between environmental risk factors and multiple low-penetrance mutations (Figure 1). Gene expression or the penetrance of individual mutations is significantly influenced by non-genetic factors. This implies that breast cancer can be prevented by early intervention if treatment is targeted at the combination of contributing genetic

Figure 1: Proportion of breast cancer caused by high-penetrance mutations (familial breast cancer) or environmental factors that could trigger low-penetrance mutations into cancer development (sporadic breast cancer).

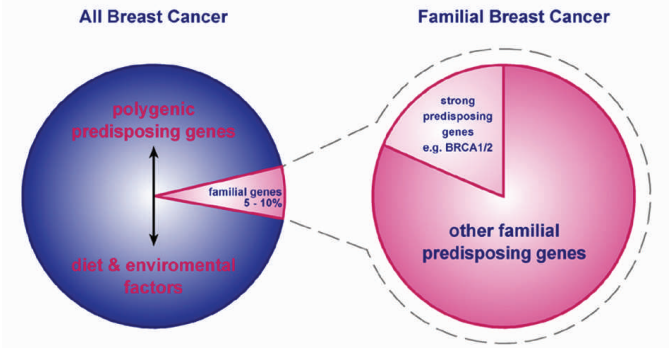
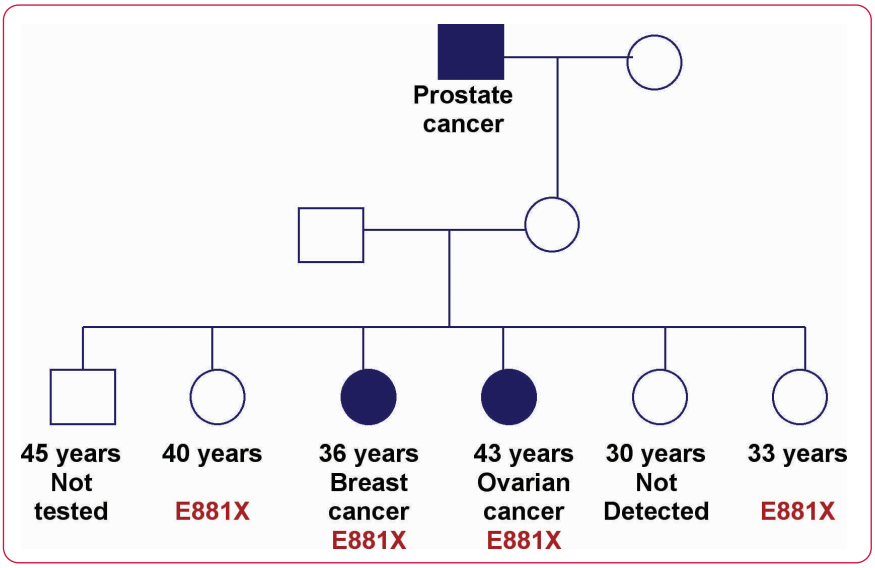


Figure 2. Variable disease expression in a South African family with familial breast cancer. Four siblings inherited the BRCA1 mutation E881X while their 70-year old mother, an obligate mutation carrier, has not (yet) developed breast or ovarian cancer.



and lifestyle risk factors identified.

Genetic counselling and testing

Counselling should be offered to all patients who undergo genetic testing and informed consent obtained. Genetic counselling facilities are available in different regions in South Africa and further support is provided through a multi-disciplinary health professional network (www.genecare.co.za).

Affected families need to understand the potential benefits as well as the limitations of genetic test options for breast cancer, ranging from diagnostic to predictive tests that are linked to particular risk reduction interventions. In our experience, genetic testing allows people to derive personal meaning and empowerment from the information communicated to them during counselling sessions. Different types of breast cancer genetic tests are available, including:

- Single-gene screening for mutation detection in BRCA affected families
- Multigene-gene screening for risk reduction intervention in familial or sporadic breast cancer
- Prognostication, treatment response and toxicity prediction in established breast cancer

Familial breast cancer: BRCA gene screen

BRCA mutations identified in South Africa[3-5] account for cancer development in less than 20% of affected South African families with a strong family history of breast cancer. Due to the clinical limitations of screening for only a small number of known mutations in a routine DNA test, exon-by-exon DNA sequencing of the entire BRCA1 and BRCA2 genes is the ultimate method for the detection of deleterious mutations in these genes. Our approach therefore is to first test for relatively common mutations in the BRCA1 and BRCA2 genes, followed by full gene screening of the remaining coding regions in mutation negative cases, by using a new method that saves both time and cost.

Ideally, an affected family member should be tested first to identify whether a BRCA mutation is present. The indication for testing rests on certain selection criteria including early-onset breast/ovarian cancer in two or more first-degree relatives. If a BRCA mutation is found, mutation screening is used to identify family members at high risk of cancer development. Siblings of BRCA carriers have a 50% chance of also having inherited the same mutation and consequently have a high risk of developing breast, ovarian and other cancers. Variable clinical expression of the founder-type BRCA1 mutation E881X is illustrated in Figure 2. Both the mother and father in the second generation of this family are clinically unaffected, despite the fact that four of their children (two diagnosed with breast cancer) inherited the BRCA1 mutation. These and similar findings in many other families studied by us are in accordance with the report of King et al.,[6] who demonstrated that modifiable lifestyle factors such as lack of obesity and high physical activity are protective in patients with BRCA mutations.

Sporadic breast cancer: Multigene risk reduction test

The majority of breast cancer cases (90-95%) are sporadic with only a modest or absent family history of breast or ovarian cancer. Sporadic cancer is considered to be a polygenic or multifactorial disorder involving many genes that interact with nutrition and lifestyle factors.[7] In addition, oestrogen exposure is one of the most important risk factors since its metabolites can attack DNA and cause double-strand breaks. For this reason, functional polymorphisms of genes involved in oestrogen metabolism have been selected for inclusion in a multigene breast cancer risk reduction assay, based on previously-described selection criteria.[8] Detection of low-penetrance mutations include analysis of the catechol O-methyl transferase (COMT) gene involved in catechol oestrogen (CE) detoxification by conjugation reactions involving methylation, manganese superoxide dismutase (MnSOD) involved in protection against reactive oxidative species-mediated oxidation during the conversion of CE-semiquinone (CE-SQ) to CE-quinone (CE-Q), and glutathione S-transferase (GST) M1 and T1 genes involved in CE-Q metabolism. None of these genetic

polymorphisms would significantly increase breast cancer risk on their own, but in the presence of prolonged oestrogen exposure or other relevant dietary and lifestyle risk factors, the risk for breast cancer is significantly increased.[9-11] Normal folate status appears to be of particular importance in this context, because an increasing number of COMT low-activity alleles is significantly associated with increased breast cancer risk in women with below median levels of folate.[12] Notably, the risk of a secondary therapy-induced malignancy appears to be increased in patients with combined GSTM1 and GSTT1 deletions.[13]

All breast cancer: Gene-based risk reduction intervention

Identification of low- and high-penetrance mutations associated with increased risk of breast cancer allows for implementation of individualised risk management strategies, ranging from nutrition and lifestyle intervention to medical treatment. In the case of BRCA mutation carriers, prophylactic surgery would reduce the risk to that of the general population (from ~80% to 10%). Predictive genetic testing could furthermore improve response rates to therapy and avoid inappropriate treatment, as in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. Defects in the DPYD gene may lead to severe neurotoxicity that may be lethal in patients treated with 5-flourouracil (5FU). Therefore it is recommended that mutation detection be carried out routinely prior to initiation of therapy.[14]

Prognostic genetic testing is used to identify patients with a poor prognosis and the need for intensive therapy. For example, HER2/neu gene amplification in breast cancer, available at our laboratory by using a real-time polymerase chain reaction (PCR)-based test (rapid assay) and/or fluorescence *in-situ* hybridisation (FISH), is associated with early recurrence and poor survival. HER2/neu over-expression is observed in 25-30% of breast tumours and is associated with resistance to tamoxifen and methotrexate containing chemotherapy regimens; conversely, herceptin (trastuzumab) treatment reduces the recurrence rate in these patients by about 50%. Although response rates can be improved in a subset of patients by HER2neu testing, a predictive marker for chemotherapy is still lacking to reduce the large number of breast cancer patients who receive inappropriate treatment. Most exciting therefore is the introduction of a 70-gene prognostic assay, which improves discrimination between good and poor prognoses by several orders of magnitude versus conventional prognostic factors such as lymph node involvement, size and grade of the tumour.[15] A local validation process to be completed in 2005 will ensure that South African women also benefit from the application of advanced microarray technology, which allows simultaneous analysis of multiple breast cancer-related genes on a single chip.

Conclusions

By assigning patients to different risk categories based on genetic test results integrated with medical history and lifestyle risk factors, effective and individualised intervention becomes possible. Identification of low-penetrance mutations in the presence of relevant lifestyle risk factors is an indication for regular surveillance and provides information on how to manage risk at the gene-diet (nutrigenetics) or gene-drug (pharmacogenetics) level. On the other hand, detection of high-penetrance mutations indicates risk reduction interventions such as bilateral mastectomy, bilateral oöphorectomy or chemoprevention. Prognostic genetic testing can furthermore be used to match the aggressiveness of the therapy to the aggressiveness of the cancer. Ultimately, comprehensive cancer genetic testing offered as part of routine clinical practice, will translate into breast cancer prevention at the population level.

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