

## Case Discussion: Familial Breast Cancer

### Epidemiology

Breast cancer is the most common form of cancer affecting women with a lifetime risk of 9-11% predominantly occurring post-menopause. NICE guidelines have been introduced that identify risk of breast cancer according to family history. See Box 1 for risk factors and Box 2 for factors suggestive of inherited disease.

### Genetics

- Mutations in the breast cancer 1 (BRCA1, chromosome 17q) and breast cancer 2 (BRCA2, chromosome 13q) genes cause 2-3% of breast cancer.
- Approximately 10% of women with onset of breast cancer under the age of 40 years have a BRCA1 or 2 gene mutation.
- Inheritance is autosomal dominant.

#### Cancer risks with BRCA1:

- Up to 70 years of age, breast cancer 65%, ovarian cancer 39%.

#### Cancer risks with BRCA2:

- Up to 70 years of age, breast cancer 45%, ovarian cancer 11%. BRCA2 gene carriers are also particularly at risk of pancreatic, prostate and male breast cancers and malignant melanoma

### Case Scenario (see with Fig 1)

A twenty-five year old female (III:2) is referred to the genetic clinic regarding her family history of cancer. She wishes to know whether a genetic test is possible to determine her risks of developing cancer. Her mother (II:4) developed bilateral breast cancer at 47 and 49 years of age. Her maternal grandmother died from ovarian cancer in her 60's. Her maternal uncle (II:1) died of prostate cancer, having developed the disease when he was 58 years old. Her maternal cousin (III:1) was diagnosed with breast cancer when she was 38 years old. The consultant (III:2), has one identical (monozygotic) twin sister who has decided she does not wish to have a genetic test. See Figure 1.

#### Clinical and Genetic Counselling Issues

- It is important to confirm the diagnoses of affected relatives, where possible, via cancer registries, hospital records and death certificates.
- This is a high-risk breast cancer family with autosomal dominant inheritance, III:2 has a 50% risk of having inherited a familial gene mutation.
- Individual III:2 is requesting a predictive genetic test, which is only possible if the familial gene mutation has previously been identified by DNA testing in an affected relative
- Counselling for predictive genetic testing should include implications to relatives, available screening tests, therapeutic interventions, insurance and psychosocial issues.
- Counselling for predictive genetic counselling often occurs over 2 or more appointments in a clinical genetics clinic.

#### Ethical Issues

- Confidentiality is a major issue particularly when different members of the same family seek genetic advice
- Consent from living affected relatives must be obtained prior to accessing any of their medical records

- Consent from the affected relative identified to have a gene mutation (or if deceased, their next of kin) should be obtained prior to use of their genetic information for DNA testing in relatives
- If III:2 has a genetic test, then effectively her monozygotic twin sister, III:3 is also being tested. In this scenario, the twin sister has decided she does not want a test, therefore it would be extremely important to counsel both sisters regarding the implications of any genetic result in the other
- Written consent to proceed with a predictive genetic test should be obtained from the individual
- There needs to be a discussion about the risks of the non tested twin hearing of her twin sisters result.
- Predictive testing for genetic diseases is usually only offered to adults unless the disease in question has implications in childhood

### Screening

- Monthly self-breast examination
- According to NICE guidelines, women at increased risk of breast cancer should be offered annual mammography from 40-49 years of age and thereafter once every 3 years.
- Breast MRI screening is also available for those women at very high risk of breast cancer at a young age or known gene mutation carriers, starting at age 30 for BRCA1/2 and age 20 for Li-Fraumeni (TP53) mutations.
- Screening for ovarian cancer in women at increased risk is currently being assessed in a research study, UKFOCCS, which includes pelvic trans-vaginal USS and CA-125 measurements.

### Therapeutic Intervention

Options include:

- Prophylactic bilateral mastectomy
- Prophylactic bilateral salpingo-oophorectomy

Nb. A residual risk of malignancy remains despite these interventions

### References

National Institute of Clinical Excellence (NICE). Clinical guidelines for the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care breast cancer. NICE, 2004 and NICE CG41 Familial breast cancer. Updated July 2006. Available at [www.nice.org.uk](http://www.nice.org.uk)

#### BOX 1

##### Risk factors for breast cancer:

- Early menarche & late menopause
- Nulliparity and lack of breastfeeding
- Oral Contraceptive Pill & Hormone Replacement Therapy
- Obesity
- Alcohol
- Family history of breast/ ovarian cancer
- Family history of other cancer syndromes eg Peutz-Jeghers syndrome, Li-Fraumeni syndrome, Cowden syndrome, Heterozygous carriers for ataxia telangiectasia.

#### BOX 2

##### Factors suggesting inherited breast cancer:

- Autosomal dominant inheritance pattern

- Young age of onset
- Multiple primary tumours in an individual
- Breast, ovarian and prostate cancer occurring on same side of family
- Breast cancer in a male relative
- Oestrogen receptor (ER) negative breast tumour
- Ethnic origin: Ashkenazi Jewish, Icelandic

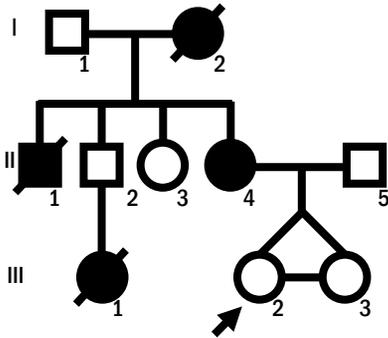


Figure 1. Pedigree. Squares denote male family members, circles female family members, symbols with a slash deceased family members, black solid symbols indicate individuals with cancer, arrowed individual the proband, intergenerational numbers are in Roman numerals to the side of the pedigree, individual identifiers are in Arabic numerals underneath the symbol

?Photos  
Graph of cancer risk with age for BRCA1/2  
Mammogram/MRI