Breast cancer is the most common malignancy in women; it affects about one in eight women. Familial breast cancer typically presents earlier than sporadic breast cancer, and is more often bilateral than in sporadic cases. Ovarian cancer is more common in familial breast cancer. A large number of studies have confirmed an increased breast cancer risk in patients with a significant family history of breast cancer. The breast cancer genotype has an autosomal dominant pattern of transmission. This article considers familial breast cancer and various aspects of breast cancer management in primary care, including the genetics of familial breast cancer, and guidelines on referral to secondary care.

The GP curriculum and familial breast cancer

Clinical module 3.02: Genetics in primary care requires GPs to:

- Demonstrate an awareness that preventative measures or targeted treatments exist for some genetic conditions (for example: mastectomy and/or oophorectomy for BRCA1/2 mutation carriers)
- Demonstrate an awareness that a genetic diagnosis in an individual may have implications for the management of other family members who may ask for a consultation

Clinical module 3.06: Women’s health states that GPs should:

- Use screening strategies relevant to women (e.g. cervical, breast, other cancers, postnatal depression), advise patients on their advantages/disadvantages, intervene urgently with suspected malignancy and have a low threshold for the referral of breast lumps

Familial breast cancer (FBC) is typically identified when an unusually large number of family members are affected by breast or ovarian cancer. A definition suggested for FBC is the occurrence of two or more affected first-degree relatives, including the index patient (Anderson, 1971). Highly penetrant mutations in genes such as BRCA1, BRCA2, and TP53 can produce these familial clusters of breast cancer. BRCA1 and BRCA2 mutations account for up to 10% of all breast cancers (Campeau, Foulkes, & Tischkowitz, 2008). FBC is also associated with early onset presentation. The incidence of breast cancer under the age of 30 years in FBC is 6.9% compared with 1.8% in the general population (Lynch et al., 1976).

The cost of cancer care in the NHS is £5 billion annually (DH, 2015). Despite improving cancer survival, our survival rates from breast cancer are not as good as other countries in Europe (Ferlay et al., 2014). Increased public awareness of breast cancer and FBC, is improving compliance with the breast cancer screening programme and early referral to specialist centres is essential for breast cancer survival rates to improve in the UK.

Breast cancer

Breast cancer can be familial or sporadic, and both forms involve alterations to genetic material. However, FBC can be attributed to a constitutive mutation in a precise gene, which increases the chances of an individual developing cancer. Since the initial discovery of the first high-risk breast cancer gene in 1990, specific genes such as BRCA1/2 have been recognised as high-risk genes, producing a 45–60% lifetime risk of developing breast cancer.
in women (Table 1). It is important to note that in a family with a known BRCA mutation and a family history of breast or ovarian cancer, not all of those in the family affected will have inherited the mutation. The majority of breast cancer cases are sporadic with no hereditary influence.

### Genetics of FBC

In the early-1990s, clusters of breast cancer and ovarian cancer within certain families were recorded, suggesting a genetic predisposition. Linkage studies isolated a particular gene on chromosome 17, which is now known as BRCA1. BRCA1, BRAC2 and TP53 are all tumour suppressor genes, which aid in repairing DNA damage and trigger cell death in mutated cells. For example, BRCA1 enables DNA repair through the process of homologous recombination and the identification of double-stand breaks in DNA. Mutations in these genes thus result in an increased susceptibility to neoplastic transformation. In FBC, mutations in BRCA1/2 have an autosomal dominant pattern of inheritance (Fig. 1). In cases of FBC, it is possible for a sporadic mutation to occur with a risk of cancer from a complete loss of tumour suppressor function, rather than from the effects of a BRCA1/2 mutation.

The risk of developing breast cancer is significant compared with the baseline population risk of 12% (one in eight); up to 65% of women with BRCA1 and 45% with BRCA2 are susceptible to developing breast cancer by the age of 70 years (Antoniou et al., 2003). Other risk factors outlined below, may have an additive effect on these predicted risks, so these figures should be considered carefully. A BRCA1/2 germline mutation also carries an increased susceptibility to ovarian cancer. A BRCA1 mutation pre-disposes women to a 36 to 46% risk of ovarian cancer, and individuals with a BRCA2 mutation have a 10 to 27% risk of ovarian cancer, compared with the baseline risk of 1.4% (Smith, 2012).

Mutations in BRCA1 and BRAC2 genes seem to appear more frequently in particular ethnic groups, most notably in Ashkenazi Jews. Specific foundation mutations such as BRCA1 185delAG, BRCA1 5382insC, and BRCA2 6174delT are more prevalent in this population (Dillenburg et al., 2012).

There are genes other than BRCA1/2 that confer an increased risk of developing breast cancer. These include PTEN, TP53, PALB and STK11, which lead to oncogenesis through various mechanisms, and are associated with specific cancer predisposing syndromes (Campeau et al., 2008). These syndromes are rare and not limited to an association with breast cancer. Extensive genome-wide association studies are identifying new gene susceptibility loci and patterns in the pathophysiology of each type of FBC, which may allow treatment to be tailored more effectively.

### Risk factors for breast cancer

There are risk factors for breast cancer other than the high-risk gene mutations responsible for FBC. These risk factors can further increase the risk of breast cancer for patients with a high-risk gene mutation and need to be considered when managing patients with FBC. Risk factors include increasing age, early menarche, late menopause and late pregnancy. These factors all increase oestrogen exposure, which has been indicated to be a major determinant of breast cancer risk through hormone-related pathways (Travis & Key, 2003).

Modifiable hormonal risk factors include the use of the oral contraceptive (OC) pill and hormone replacement therapy (HRT), which increase the risk of breast cancer by 10% and 23%, respectively. In studies of breast cancer in HRT there is an effect on the incidence of breast cancer in current users of HRT (Anothaisintawee et al., 2013). Breastfeeding has a protective effect,

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**Table 1. Important lifetime risks associated with BRCA1/2 mutations.**

|            | General population risk (%) | BRCA1 (%) | BRCA2 (%) |
|------------|-----------------------------|-----------|-----------|
| **Female** |                             |           |           |
| Breast cancer (in unaffected women up to the age of 80) | 12         | 60–90     | 45–85     |
| Ovarian cancer (lifetime risk)          | 1.5         | 40–60     | 10–30     |
| **Male**   |                             |           |           |
| Male breast cancer (lifetime risk)      | 0.1         | 0.1–1     | 5–10      |
| Prostate cancer (lifetime risk)         | 12          | 10        | 20–25     |

Adapted with permission from Royal Marsden NHS Foundation Trust Patient information. Data from NHS Lothian.
reducing the risk of breast cancer by up to 11%, with the effect increasing to 28% if breastfeeding is continued for 12 months or longer (Anothaisintawee et al., 2013). Lifestyle changes, such as lower dietary intake of fat, reduced alcohol consumption, a reduction in smoking and increased physical activity, are also beneficial in reducing overall risk and should be targeted in the prevention of breast cancer (McKenzie et al., 2015).

**Initial assessment in primary care**

GPs have an important role in ensuring effective risk assessment of patients with FBC. This assessment includes taking a comprehensive family history to inform referral to a specialist genetics service. Genetic tests are available to identify BRCA1/2 mutations in individuals, but are only considered when there is a significant personal history or family history suggestive of a mutation. Further recommendations in primary care assessment are outlined in Box 1. An example of a common presentation is given in Box 2, with an appropriate assessment plan.

**What does a positive test result mean?**

It is important to consider the implications of a positive test for the patient and their relatives. The inheritance of mutations follows an autosomal dominant pattern, with offspring and siblings having a 50% risk of inheriting the mutation. GPs can have an important role in supporting families and recommending referral of at-risk family members to specialist genetic services.

Family planning may be discussed with individuals who are BRCA1/2 carriers. Concerns about the transmission of gene mutations to offspring can be discussed and

*Figure 1. Autosomal dominant pattern of inheritance. Credit: U.S. National Library of Medicine.*
Important factors to note in a family history to aid in assessment for FBC.

Box 1. Recommendations in primary care assessment for FBC.

**Recommendations in primary care assessment for FBC**
- A first and second-degree family history should be taken for appropriate risk stratification when an individual presents with no previous history of breast cancer or with breast symptoms
- In women older than 35 years taking the OC pill, take a relevant family history
- In women with long-term HRT use take a relevant family history
- A second-degree family history (involving relatives on both maternal and paternal sides) must be recorded before risks and options are explained to the individual
- Important factors to note in a family history to aid in referral decisions include:
  - Age of diagnosis of cancer in relatives
  - Tumour location
  - Bilaterality of cancer (or other multiple cancers)
  - Jewish ancestry

**Referral guidelines**
- Referral to a specialist genetics service should take place when high-risk mutations in genes such as BRCA1/2 or TP53 have been identified
- Referral to a specialist genetic service for patients without a personal history of breast cancer but with:
  - One first-degree female relative with breast cancer diagnosed under age 40 years
  - One first-degree male relative with breast cancer diagnosed at any age
  - One first-degree relative with bilateral breast cancer under the age of 50 years
  - Two first-degree relatives diagnosed with breast cancer at any age
  - One first-degree and one second-degree relative with breast cancer at any age
  - Jewish ancestry
  - Sarcoma in a relative younger than 45 years
  - Glioma or childhood adrenal cortical carcinomas
  - Complicated patterns of multiple cancers at a young age
  - Very strong paternal history (four relatives diagnosed at younger than 60 years of age on father’s side of family)

*First-degree relatives include: Mother, father, daughter, son, sister, brother. Second-degree relatives include: Grandparent, grandchild, aunt, uncle, niece, nephew, half-sister and half-brother.

**Box 2 Clinical example.**

A 32-year-old lady presents to her GP concerned and anxious. Her sister has recently been diagnosed with breast cancer at the age of 40 years. Her aunt had bilateral breast cancer and was diagnosed in her late-30s. She is unaware of her BRCA status. This patient has an increased risk of breast cancer. The role of the GP is to:
- Establish rapport, assess and allay patient’s concerns where appropriate
- Take a comprehensive family history including first-degree and second-degree, maternal and paternal relatives to allow appropriate individual risk stratification
- Ask about breast and other cancers, including ages at diagnosis, cases of bilateral breast cancer, multiple tumours, and Jewish ancestry as these can all give a strong indication for referral to specialist genetic services
- After a detailed history referral can be discussed, particularly in such high-risk patients and in patients where a BRCA1/2 gene has been identified. Referral to specialist genetic services is recommended
- Provide and discuss information on the risk of breast cancer in the general population and the risk based on family history
- Provide and discuss information on risk reduction, including lifestyle advice, use of contraceptives and HRT, breastfeeding and family planning
- Provide breast awareness information
- Encourage regular attendance for screening
- Encourage follow-up consultations to discuss any relevant change in family history or new breast symptoms

Options explained. Options include use of donor gametes and pre-implantation genetic diagnosis (PGD). PGD offers couples the opportunity to select only healthy embryos for implantation. The option of termination of a pregnancy when there is a risk of transmission of BRCA1/2 mutations presents difficult ethical questions and requires appropriate counselling and specialist referral.

**Management**

Carriers of a BRCA1/2 mutation are at high risk of breast cancer. According to the National Institute for Health and Care Excellence (NICE) a BRCA1/2 mutation carries a lifetime risk of breast cancer from age 20 years of 30% (NICE, 2013). When an individual is a known carrier of a harmful BRCA1/2 mutation, the two main risk-reducing options include enhanced screening and prophylactic surgery.
Enhanced screening is recommended for individuals who test positive for BRCA1/2. Enhanced screening involves more regular clinical breast examinations and annual mammograms from as young as 25 years (Burke et al., 1997). This enables cancer to be detected early and the potential for better survival. Magnetic resonance imaging (MRI) scans can provide a high sensitivity level for detecting breast cancer (a high probability of a positive result in patients with breast cancer), but can miss some cases identified by mammography, increasing false-negative results if used without mammography (Obdeijn, 2010). In women with a high risk of breast cancer, both mammography and MRI screening is recommended. A detailed summary of screening recommendations is given in Box 3.

More patients at high risk of breast cancer are choosing to have prophylactic surgery as a preventative measure. Individuals with a high risk (30% or greater) of developing breast cancer, including those with BRCA1/2 mutations, are being offered prophylactic surgery. Bilateral mastectomies can reduce the risk of breast cancer by at least 90% in high-risk patients (Hartmann et al., 1999; Rebbeck et al., 2004). However, there is a small residual risk of cancer developing if not all of the susceptible tissue is removed. Patients should be counselled on the physical and psychological consequences of this operation, which has the potential to have an impact on sexual wellbeing and body image (Razdan, Patal, Jewell, & McCarthy, 2016). Breast reconstruction and minimizing pre-operative distress can be helpful for patients undergoing surgery.

In addition to mastectomy, bilateral prophylactic salpingo-oophorectomy can reduce the risk of breast cancer by 50%. Oophorectomy in premenopausal women reduces oestrogen levels and the potential for oestrogen to promote tumour growth in breast cancer. A bilateral prophylactic salpingo-oophorectomy can also reduce mortality from ovarian cancer by almost 80% (Domchek et al., 2010). It is also important to discuss the harmful consequences of early menopause and loss of fertility with patients. The consequent exacerbation of menopausal symptoms and other long-term effects include reduced bone density and a reduced libido.

Chemoprevention is also an option for women with the harmful BRCA1/2 gene mutation. Chemoprevention involves the use of drugs to limit the development of breast cancer, and currently two such drugs, raloxifene and tamoxifen, are recommended by NICE (NICE, 2013). Other similar drugs are being developed and assessed.

These drugs are selective oestrogen receptor modulators that have different effects in different tissues, based on different degrees of oestrogen sensitivity in different tissues. The STAR trial (Study of Tamoxifen and Raloxifene) found that over the first 47 months of treatment, both medications were similarly effective in...

Box 3 Surveillance measures for high-risk individuals.

**Surveillance measures for high-risk individuals**

- Annual mammography screening for women aged 40–60 years who are known carriers of the BRCA1/2 mutation
- Annual mammography screening for women aged 40–59 years at high risk of breast cancer, but with a 30% or lower chance of being a BRCA carrier
- Annual mammography screening for women aged 40–59 years who have not had testing for the mutation but have a greater than 30% chance of being a BRCA carrier
- Surveillance as part of the population screening programme for women aged 60 years and over with a high risk of breast cancer, but a 30% or smaller chance of being a BRCA carrier
- Surveillance as part of the population screening programme for women aged 60 years and older who have not had genetic testing, but have a larger than 30% chance of being a BRCA1/2 carrier
- Surveillance as part of the population screening programme for women aged 70 years and over who are known carriers of a BRCA1/2 mutation
- Annual MRI surveillance for women aged 30–49 years who have not had genetic testing, but have a larger than 30% chance of being a BRCA1/2 carrier
- Annual MRI surveillance for women aged 30–49 years who are known carriers of a BRCA1/2 mutation

**Surveillance measures for high-risk individuals to consider in following cases**

- Annual mammography screening for women aged 30–39 years at high risk of breast cancer, but with a 30% or smaller chance of being a BRCA carrier
- Annual mammography screening for women aged 30–39 years who have not had genetic testing, but have a larger than 30% chance of being a BRCA carrier
- Annual mammography screening for women aged 30–39 years who are known carriers of the BRCA1/2 mutation.

National Institute for Health and Care Excellence (2013) Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Available from: www.nice.org.uk/guidance/cg164. NICE guidance is prepared for the National Health Service in England, and is subject to regular review and may be updated or withdrawn. NICE has not checked the use of its content in this article to confirm that it accurately reflects the NICE publication from which it is taken.
reducing the risk of breast cancer in post-menopausal women (Vogel et al., 2010). Over a 7-year period tamoxifen was more effective at reducing breast cancer risk (Vogel et al., 2010).

Tamoxifen can be taken by both pre- and post-menopausal women, but raloxifene should only be prescribed to post-menopausal women. Treatment with both raloxifene and tamoxifen is for up to 5 years in women who are at high risk of breast cancer. Contraindications, however, include a previous history of endometrial cancer or thromboembolic disease. The absolute risks and benefits of chemoprevention for individuals at high risk of breast cancer need to be discussed in the context of an overall management strategy, usually within a specialist genetic clinic.

**Conclusions**

FBC caused by BRCA1/2 mutation can account for up to 10% of breast cancer cases and is a diagnosis gaining public awareness. A detailed family history of breast and other cancers is essential in the assessment of risk and referral of patients to specialist genetic services. GPs play an important role in referring patients at high risk of developing breast cancer, and supporting patients through the diagnostic and screening process. Risk-reducing options are available to individuals with a positive test result, such as prophylactic surgery and chemoprevention. Enhanced screening and regular self-examination are important in patients at high risk of breast cancer.

**Key points**

- FBC is the occurrence of breast cancer in one or more first-degree relatives
- FBC can be attributed to the effects of highly penetrant gene mutations, for example, in BRCA1/2
- Carriers of the BRCA1/2 gene are at increased risk of breast cancer, and efforts should be made to detect and refer cases early to improve survival rates
- There can be additional hormonal and lifestyle risk factors for breast cancer in the presence of BRCA1/2 gene mutations that need to be addressed
- Primary risk assessment includes a comprehensive and detailed family history, to establish whether referral to a specialist genetics service is warranted
- Risk-reducing options include enhanced surveillance and prophylactic surgery
- Chemoprevention with raloxifene or tamoxifen taken for 5 years may be appropriate in some at risk patients

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