Genetics of breast cancer: management strategies and risk-reducing surgery

ABSTRACT

The last two decades have witnessed major advances in genetic sequencing which have led to more accurate identification of women at risk of developing breast cancer and calculating the associated cancer risk. This review discusses the current genetic mutations conferring risk of developing breast cancer and the management pathway for these women with identifiable mutations as well as those with a strong family history for breast cancer.

Management of these individuals is complex and should involve a multidisciplinary team with interest and expertise in breast cancer genetics. There are several treatment options ranging from surveillance to risk-reducing surgery. Risk reduction surgery has been popularised by celebrities who are carriers of breast cancer genes, and raised public awareness of breast cancer genetics and associated risk.

Breast cancer is the most common cancer in the UK and the most common female cancer worldwide; 1 in 7 women are diagnosed with breast cancer in their lifetime (Cancer Research, 2018). Inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms and in breast cancer their contribution is only 27% compared to environmental factors (Lichtenstein et al, 2000). Before breast cancer genes were identified, details of family history of breast cancer had been an important aspect of history taking to identify individuals with an increased risk of breast cancer.

Breast cancer risk varies significantly according to the extent of family history. *Table 1* summarizes the different categories of family history. The lifetime excess risk of breast cancer is observed in patients with a positive family history of breast cancer and varies depending upon the number of relatives affected. For example, a woman with one affected first-degree relative will have an incidence of breast cancer of 5.5%, whereas for women with two affected first-degree relatives the risk is 13.3% compared to patients who do not have a family history of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2001).

There have been major advances in sequencing DNA (e.g. next generation sequencing) which allow detailed and in-depth analysis of genes which are potentially involved. This has enabled genetic testing to enter the public realm with increasingly affordable options for patients both online and via the health service. Patients are asking clinicians more questions regarding their options for genetic testing. This article provides an overview of the current evidence and latest clinical developments in hereditary breast cancer and risk-reducing surgery.

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Genetics of breast cancer

The majority of cases of breast cancer are sporadic, meaning it is not an inherited disease and develops as a result of somatic mutations which arise during an individual's lifetime (Stratton et al, 2009). There is also increased risk in some individuals with a family history of breast cancer syndromes associated with other forms of cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2001).

Up to 10% of breast cancers arise as a result of germline mutations. These are heritable mutations which are passed on from one generation to the next leading to increased risk. Germline breast cancer genes are divided by their level of penetrance or the gene expression; that is to say the likelihood of the carrier developing breast cancer can be classified into high, moderate and low penetrance (*Table 2*). Patients who

Table 1. Degree of relative

First degree	Parent, child, sibling
Second degree	Grandparent, grandchild, aunt, uncle, niece, nephew, half-sibling
Third degree	Great grandparent, great grandchild, first cousin

Table 2. Penetrance

Penetrance	Examples of germline mutation
High penetrance	BRCA1, BRCA2, TP53, PTEN, CDH1, STK11
Moderate penetrance	PALB2, ATM, CHEK2
Low penetrance	Single nucleotide polymorphisms (CYP1A1, CYP1A2)

carry high penetrance genes have a lifetime risk of developing breast cancer of >30% (National Institute for Health and Care Excellence, 2019). The commonly implicated genes are BRCA1 and BRCA2 (Miki et al, 1994). BRCA genes are involved in the repair of DNA breakage and the BRCA mutations (tumour suppressor genes) result in inefficient DNA repair which consequently leads to malignancy.

The frequency of mutated BRCA genes is estimated to be between 1 in 400 to 1 in 800 in the general population, but it is significantly higher among genetically isolated populations such as the Ashkenazi Jews who have an increased overall incidence of 1 in 40 (Ford et al, 1995). Patients with BRCA and other germline mutation carriers tend to develop breast cancer early on in life, often multiple members are affected and frequently these women can have bilateral breast cancers and an increased incidence of ovarian cancers. The reported breast cancer risk by the age of 70 years is as high as 60% in BRCA1 and 55% in BRCA2 carriers and the median age of development of breast cancer was 42 and 45 years respectively. The risk of ovarian cancer is estimated to be 59% in BRCA1 and 16.5% in BRCA2 carriers by the age of 70 years (Mavaddat et al, 2013).

Other less common high penetrance genes that carry risk for breast cancer are TP53, PTEN, CDH1 and STK11, many of which carry a risk for other solid cancers in the carrier group. TP53 is a tumour suppressor gene and the mutation results in Li-Fraumeni syndrome characterized by development of sarcomas, brain and other solid tumours besides early onset of breast cancer. The mean age of development of breast cancer in patients with a TP53 mutation is 32 years (Bougeard et al, 2015). PTEN mutation results in multiple benign and malignant tumours, particularly thyroid, breast, renal and colorectal cancers. The frequency is estimated to be 1 in 250 000, the mean age of development of breast cancer is 42 years and up to 50% are bilateral breast cancers (Nieuwenhuis et al, 2014). Germline mutation of STK11 results in Peutz–Jeghers syndrome and is implicated in hamartamatous gastrointestinal polyps, gastrointestinal malignancies and breast cancer. The age of onset of breast cancer is estimated to be 44 years (van Lier et al, 2010). CDH1 germline mutation are associated with development of lobular cancers and 42% of patients with this mutation develop breast cancer by the age of 40 years (Hansford et al, 2015).

Moderate penetrance genes include mutations of PALB2, ataxia telangiectasia (ATM) and CHEK2 genes. PALB2 is associated with a 35% risk of developing breast cancer by the age of 70 years and its penetrance is modified by other environmental factors (Antoniou et al, 2014). ATM gene mutation carriers have a 33% risk of developing breast cancer by 80 years of age (Marabelli et al, 2016). Low penetrance genes, such as polymorphisms in oestrogen metabolite biosynthesis, occur relatively infrequently and their mechanism of action is less well understood (Shimada et al, 2009).

Family history clinics

Family history clinics are set up in specialized breast units that usually have either an integrated genetic unit or links to a genetic referral unit and local screening unit. Patients who are referred to family history clinics are assessed and screened initially using a questionnaire. Various prediction models to determine the risk of carrying mutated germline genes have been developed based on different studies. Some of the prediction models, for example Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), involve a detailed family history of bilateral cancer, ovarian cancer and male breast cancer. It provides an estimate of the risk of breast cancer development in women with a family history of breast and ovarian cancer (Lee et al, 2016). These are complex computer models and may not be useful for assessing patients in a primary health-care setting, but are often used in specialised genetic units. For primary care clinicians, scoring systems are available to use which predict the probability of a genetic mutation conferring risk. The Manchester scoring system is one such tool which uses clinical information to predict the probability of carrying the BRCA gene – this has been validated in various studies (Evans et al, 2004). The genetic team at Guy's has also developed Cancer Genetics, an easy to use free assessment application for mobile phones and tablet devices, to assist clinicians in classifying patients into different categories and advising on referral to a genetic centre (https://apps.apple.com/gb/app/cancer-genetics/id999802455).

The referred population is categorised into low risk (population risk 17%), moderate risk (17–30%) and high risk (>30%) of developing breast cancer in their lifetime from the age of 20 years (*Table 3*). The low risk (<17%) group have the same risk as the general population and no further screening or test is required. When patients have a moderate risk of developing breast cancer (17–30%), they have a higher risk than the population risk but lower than the risk of a woman carrying a known genetic mutation that causes breast cancer. It is recommended that these women have yearly screening mammograms from the age of 40 years until the screening age where they will have 3-yearly mammograms as per the general population

Table 3. Recommendation on surveillance and risk-reducing surgery for women with no personal history of breast cancer

Lifetime risk of developing breast cancer	Surveillance	Offer risk-reducing surgery
Low risk (<17%)	Comply with population breast screening programme – no additional screening or tests required	No
Moderate risk (17–30%)	40–49 years old – yearly screening mammograms	No
	49–59 years old – consider yearly mammograms	
	60+ years old - mammograms as part of the population screening programme	

> Once patients are found to be carrying a high-risk gene, they are referred to breast surgeons to discuss breast cancer risk reduction options.

screening programme (between the ages of 49–59 years yearly mammograms can be considered). These women are referred to the local screening unit which has the facility to provide mammographic screening. This group of patients should not be offered risk reduction mastectomy according to the National Institute of Clinical Excellence (2019) guidance. High-risk patients (>30% lifetime risk) should be referred to a specialist genetic clinic.

Who to refer to a family history clinic?

All symptomatic patients should be referred to a symptomatic breast clinic for triple assessment, which includes detailed history and examination, appropriate imaging and biopsy if required, irrespective of their family history. The National Institute for Health and Care Excellence (2019) has published guidelines with recommendations as to who should be referred and the type of surveillance in moderate and higher risk groups. However, individuals without a positive family history and average lifetime risk need only to be advised on breast awareness and encouraged to comply with breast screening in due course.

Who to refer to a specialist genetic clinic and who to offer genetic testing?

There are clear National Institute for Health and Care Excellence (2019) guidelines with recommendations as to who should be referred to a specialist genetic clinic. This includes those patients that have a 10% or greater chance of being a carrier of a germline mutation, a greater than 8% risk of developing breast cancer in the next 10 years or a greater than 30% lifetime risk of developing breast cancer (National Institute for Health and Care Excellence, 2019).

Genetic testing for those who have a probability of greater than 10% of being a carrier of a germline mutation (National Institute for Health and Care Excellence, 2019) enables a detailed discussion with patients about various strategies to either reduce the risk of developing breast cancer or dying from the disease. Counselling these individuals before gene testing is essential, so that there is a clear understanding of the implications of the results, both positive or negative. Single gene testing is replaced by next generation sequencing which has the advantage of being able to detect smaller sequence changes and larger deletions and rearrangements (Behjati and Tarpey, 2013). Next generation sequencing can be used for a targeted panel approach or whole genome sequence or whole exon sequencing (Xue et al, 2015). While these technologies help to test a large panel of genes and detect previously unrecognized gene associations, they also detect variation of uncertain significance. Detecting variation of uncertain significance can pose challenges in interpretation to clinicians and distress to patients as these patients' genetic risk of developing breast cancer is uncertain. It is inadvisable for patients to undertake genetic testing outside of this supportive multidisciplinary team approach. Patients should be discouraged from having genetic testing via online platforms without the appropriate counselling and guidance from clinical geneticists.

Hereditary cancer clinics

In the UK, once patients are found to be carrying a high-risk gene, they are referred to breast surgeons to discuss breast cancer risk reduction options. However, there are no established multidisciplinary clinics to deal with these complicated cases in most parts of the UK. At Guy's and St Thomas' NHS Trust a dedicated hereditary breast and ovarian cancer clinic has been developed with an integrated multidisciplinary service with experience in management of these patients since 2006.

The multidisciplinary team consists of clinical geneticists, psychologists, specialist nurses, gynaecologists and oncoplastic breast and plastic surgeons as well as a research coordinator. Patients who have been diagnosed as carriers of one of the high-risk cancer genes or who have a cancer risk more than 30% are invited to attend the clinic to discuss management of their risk. Patients have the opportunity to consult all the specialists, all the options are discussed on the same day and they are given written information to take away.

Treatment options

There are numerous options available to these women which include lifestyle modifications, surveillance, chemoprevention and surgery.

Lifestyle modification

Lifestyle factors can contribute to the development of breast cancer and modification of such factors can help in cancer prevention strategies. Therefore, modifiable risk factors shoulder be discussed with all high-risk patients (*Table 4*). High body mass index in postmenopausal women is associated with an increased risk of breast cancer, but for premenopausal women it is suggested that high body mass index could decrease breast cancer risk (Xia et al, 2014). Exercise decreases the risk of breast cancer in both pre- and postmenopausal women; a meta-analysis found an overall risk reduction of 13% in women with the

Table 4. Modifiable risk factors

Oral contraceptive pill and hormone replacement therapy
Alcohol consumption
Breastfeeding
Weight and physical activity
Smoking

highest rates of physical activity (Wu et al, 2013). The risk of breast cancer also increases with increased alcohol intake, one large study has reported an increase risk of up to 7% with each alcoholic drink per day (Hamajima et al, 2002).

Women should be encouraged to breastfeed when possible, as a landmark study of approximately 50 000 breast cancer cases found that the relative risk for breast cancer in parous women is reduced by 4.3% for every 12 months a woman breastfeeds and is reduced by 7% for each birth independently (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). Smoking has been linked to breast cancer, and general smoking cessation advice should be given. The risk of developing breast cancer is 7–13% higher in current smokers and 6–9% higher in former smokers compared with never-smokers, but there is the possibility of confounding factors in these studies (Gaudet et al, 2013, 2017; Macacu et al, 2015).

Other modifiable risk factors include the exogenous intake of hormone replacement therapy and the oral contraceptive pill. The risk is higher in oestrogen-only hormone replacement therapy preparations compared to combined oestrogen and progesterone (Rossouw et al, 2002; Beral and the Million Women Study Collaborators, 2003; Anderson et al, 2012). The association of the oral contraceptive pill with breast cancer risk is inconsistent but there is evidence that suggests that the risk of breast cancer is increased in women who currently or have recently used the oral contraceptive pill compared to women who have never used hormonal contraceptives. It is thought that the risk of breast cancer increases with longer duration of use, but the absolute increase risk is small (one extra case of breast cancer for every 7960 women using hormonal contraception for 1 year) (Mørch et al, 2017).

Surveillance

Ultrasound should not be offered to any patients in moderate or high risk groups as a screening tool as it is operator dependant and can potentially miss microcalcifications. Ultrasound would only be considered if magnetic resonance imaging is not suitable or to corroborate findings on mammography or magnetic resonance imaging (National Institute for Health and Care Excellence, 2019). The type of surveillance for those high-risk patients is dependent on a number of factors, including if the patient is a BRCA carrier or has a greater than 30% probability of being a BRCA carrier, if the patient has a known TP53 mutation or has a greater than 30% probability of being a TP53 carrier.

Annual magnetic resonance imaging scans should be offered to all patients aged 30–49 years who are untested but have a greater than 30% probability of being a BRCA carrier, or any known BRCA carrier. Annual surveillance vis magnetic resonance imaging should start at the age of 20 years for known carriers of the TP53 mutation. This age can be extended if the breast is dense until the age of 69 years.

Annual mammography is offered to high-risk patients aged 40–59 years and BRCA-positive patients aged 40–69 years. Annual mammography can be considered in patients aged 30–39 years based on individual risk. Mammographic surveillance should not be offered to a patient who has tested positive for TP53 or who has more than a 30% chance of having a TP53 mutation because of the radiation risk and the possibility of radiation-induced neoplasms in this patient group (Heymann et al, 2010; National Institute for Health and Care Excellence, 2019).

> “The greatest benefit of chemoprevention is in high-risk patients as assessed by family history and genetic testing.”

Chemoprevention

The greatest benefit of chemoprevention is in high-risk patients as assessed by family history and genetic testing (Cuzick et al, 2015). For moderate risk patients, this can be considered but the benefit is less and in BRCA patients it is uncertain, especially in patients with the BRCA1 mutation as they are at high risk of developing oestrogen-negative cancers (Musolino et al, 2007). Various risk reduction trials show the beneficial effect of selective oestrogen receptor modulators such as tamoxifen and raloxifene in reducing the risk of oestrogen-positive cancers by 40% when taken for 5 years by blocking the effect of oestrogen (Fisher et al, 2005). A study with a median follow-up period of 16 years demonstrated that tamoxifen offers a very long period of protection after treatment cessation, and thus substantially improves the benefit-to-harm ratio of the drug for prevention of breast cancer (Cuzick et al, 2015).

Current National Institute for Health and Care Excellence (2019) guidelines recommend offering tamoxifen for 5 years to premenopausal women at high risk of breast cancer, unless contraindicated. In high risk postmenopausal women, it is recommended to offer anastrozole for 5 years unless they have severe osteoporosis. These chemoprevention drugs are generally well tolerated but common side effects include vaginal dryness, hot flushes, nausea and leg cramps. Infrequent side effects include venous thromboembolism and endometrial cancer and these should be discussed when tamoxifen is considered for chemoprevention (Cuzick et al, 2013).

Risk reduction surgery

Patients who opt against taking selective oestrogen receptor modulators or who want to go ahead with risk-reducing surgery should also be counselled by the multidisciplinary team and an individualised treatment plan developed. The term risk-reducing is preferred to prophylactic as the former correctly implies that not all cancers are preventable. It has been shown that mastectomy reduces the breast cancer risk by at least 90% (Domchek et al, 2010). Although there is no unequivocal evidence that it leads to a reduced mortality, reduction of risk is considered as a surrogate for reduction in mortality (Carbine et al, 2018). Nipple preservation does not compromise the risk reduction.

KEY POINTS

- The risk of breast cancer increases if a patient has affected first-degree relatives, but most women with one affected first-degree relative never develop breast cancer.
- Genetic mutations are identified in only 3–10% of the population.
- Referral to a family history clinic can be done based on National Institute for Health and Care Excellence guidelines or local protocols.
- Eligible patients are offered genetic tests for mutations in BRCA and other lesser known genes. Women who have a moderate risk of developing breast cancer can be offered early screening from the age of 40 years after risk assessment in a family history clinic.
- Women who have susceptibility genetic mutations or those who have higher than 30% risk of developing breast can be offered risk reduction strategies including risk reduction mastectomy and immediate breast reconstruction.
- A multidisciplinary team of professionals should be involved in offering risk reduction strategies and detailed counselling of patients to aid decision making.

Risk reduction surgery involves major surgery. Patients therefore should be given time to assimilate information and further appointments should be arranged with the relevant surgeon and specialist care nurse if the patient decides to go ahead with risk reduction surgery. Patients should be seen more than once to discuss in detail the procedure, the aesthetic results and its complications, and photographs should be shown so that patient is aware of what to expect in the postoperative scenario.

In patients with a personal history of unilateral breast cancer, the decision regarding removal of the healthy contralateral breast is more complex. There is no evidence that there is a survival advantage of contralateral risk-reducing mastectomy as the patient's prognosis is determined by the diagnosed index cancer. However, there is benefit in reducing the risk of new cancer in the contralateral breast. Carriers have a four times higher risk of contralateral breast cancer than sporadic cases (Fayanju et al, 2014; Carbine et al, 2018).

Women with no personal history of breast cancer should have a mammogram and magnetic resonance imaging to rule out any occult malignancy before undergoing risk reduction surgery and should be counselled regarding the detection of incidental cancers in risk reduction specimens. This is reported to range from 0.1–7.7% (Tadler et al, 2014). Surgery involves either skin-sparing or nipple-sparing mastectomy with or without immediate reconstruction of the breasts. It is very unusual for women opting for risk-reducing mastectomy to decline having immediate reconstruction although delayed reconstruction should be discussed as an option.

There are generally two reconstruction options; prosthetic (implant) or autologous breast reconstruction. Careful and detailed discussion regarding surgical complications, recovery, expectations and further surgery are fundamental to an informed consent process. Furthermore, health-care professionals should adopt an advisory role rather than enticing patients to undertake surgery, which can have a significant impact on a patient's psychological wellbeing and quality of life. Autologous reconstruction involves using a patient's own tissue to reconstruct the breasts. There are various donor sites for this tissue flap including the abdominal wall (transverse abdominal myocutaneous flaps or deep inferior epigastric perforator flaps; Saint-Cyr et al, 2007), the legs and gluteal region (superior gluteal artery perforator flaps and transverse myocutaneous gracilis flaps), and the back (latissimus dorsi flaps).

Skin-sparing and nipple-sparing mastectomy can be performed through a variety of incisions and should be individualised to each patient. With recent developments in technology prosthetic implant-based reconstructions with the use of mesh or acellular dermal matrix are more frequently used. There is a variety of prosthetic reconstruction techniques which differ between surgeons' preference and experience. All breast reconstruction options should be offered to patients and patients referred to a specialist centre if these are not available locally.

Conclusions

Sporadic breast cancer accounts for the majority of cases of breast cancer. The risk could be higher where patients report a positive family history of the disease or related malignancies. Breast cancer secondary to genetic mutations is rare and accounts for 3–10% of all breast cancers. Referral to a family history clinic can help in assessing individual patient risk, and National Institute for Health and Care Excellence guidelines and locally developed protocols can help to select patients eligible for referral to such clinics. Risk reduction mastectomy and immediate breast reconstruction is an option for patients with high family risk or BRCA mutation. Ideally this service should be offered in a specialized unit with a multidisciplinary team comprising surgeons, geneticists, psychologists and breast care nurses. **BJHM**

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