Chapter 23

Reducing the risk of breast cancer

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Introduction to reducing the risk of breast cancer

Breast cancer is the most common cancer in women, with an annual incidence of more than 49 000 cases in the UK; exceeding the incidence of lung cancer in men and women combined (CRUK, 2011). It is second only to lung cancer as the major cause of cancer-related death in the world (CRUK, 2012). The direct cause(s) of the disease remains elusive. The discovery of the *BRCA1* and *BRCA2* mutations (Miki, 1994; Wooster, 1995) provided some understanding as to the pathogenesis of breast cancer, while posing more questions and presenting major challenges in the management of women who are carriers. It is estimated that 7% of breast cancer patients in the general population have an inherited basis for the disease (Claus, 1996).

The first part of this chapter will describe the principles of reducing the risk of breast cancer for women without a cancer diagnosis, the surgical risk-reducing measures available and the risks, benefits and limitations of these measures. The second part of the chapter will examine the options for breast reconstruction following risk-reducing mastectomy (RRM), highlighting the different techniques available and the issues surrounding these options.

The learning objectives for Chapter 23 are:

- to be able to describe the available measures for reducing the risk of breast cancer;
- to be able to discuss the risks, benefits and limitations of these measures.

Options for reducing the risk of breast cancer

Women at high risk of breast cancer due to a *BRCA1/2* gene mutation or based on verified family history have extremely difficult decisions to make, and therefore an understanding of the magnitude of risk is fundamental to informed decision-making. Health professionals have the responsibility and the challenge of conveying the relevant statistics in simple and clear language. Furthermore, women at high risk of breast cancer but with no previous history of the disease face complex decisions within limited choices in order to reduce their risk. There are few options available, and these have variable efficacy in reducing the risk of developing or dying from breast cancer: the options include risk reducing mastectomy (RRM), chemoprevention with agents such as tamoxifen, pre-menopausal bilateral oophorectomy and/or breast surveillance (see Chapter18).

Chemoprevention

It has been observed that there is a modest decline in the incidence of breast cancer following early menopause and reduction in endogenous oestrogen. The risk of breast cancer is reduced by 50% in *BRCA1/2* mutation carriers following pre-menopausal bilateral oophorectomy (Rebbeck, 2002) and normal BRCA1 protein reduces epithelial proliferation in response to exposure to oestrogen. Several studies have shown a significant reduction in the risk of breast cancer in women with a family history or high risk of breast cancer following tamoxifen administration (King, 2001; Cuzick, 2002;). These particular studies showed a significant risk reduction in *BRCA2* carriers but not in those with a *BRCA1* mutation (although the total number of *BRCA1/2* carriers was small), suggesting that tamoxifen and other anti-oestrogen agents are only effective in reducing oestrogen receptor positive cancer. However, studies involving pre-menopausal bilateral oophorectomy showed significant reduction in the incidence of breast cancer in both *BRCA1* and *BRCA2* carriers. Furthermore, in a large study (Gronwald, 2006), the benefit of tamoxifen was seen equally in *BRCA1* and *BRCA2* carriers. The biological basis for the discrepancy between different studies is not yet clear. However, there is sufficient evidence to support the administration of tamoxifen for 5 years to reduce the risk of breast cancer in *BRCA1/2* carriers and in women at moderate and high risk following thorough discussion of the benefits, limitations and side effects (NICE, 2013).

Risk-reducing mastectomy

Surveillance relies on early detection, not prevention, of breast cancer, although it may reduce the risk of dying from the disease. However, it is estimated that as many as 25% of high-risk women who undergo regular surveillance will die of distant metastases despite a relatively early diagnosis (Klijn, 1997). Mastectomy has been established as the most effective means of reducing breast cancer risk. Several large studies have consistently shown that the reduction in breast cancer risk following bilateral mastectomy is as high as 90% (Hartmann, 2001; Meijers-Heijboer, 2001; Rebbeck, 2004). This risk reduction is shown to be even higher in women who have also undergone pre-menopausal oophorectomy (Rebbeck, 2002). Mastectomy may also be associated with a modest increase of number of life years gained (Schrag, 1997). As a result, an increasing number of carriers opt for bilateral RRM in preference to other measures. Mastectomy is considered to be mutilating surgery and it is not surprising that for some women it is not an option they can contemplate. Guidelines recommend that the option of RRM is discussed with women at high risk based on verified family history following genetic risk assessment (NICE, 2013). Women who choose not have RRM should not be solicited by health professionals to undergo surgery; two factors have been shown to contribute to poor outcome and recovery, namely inadequate and inferior-quality information and the clinician influencing the woman's decision (Josephson, 2000).

Women who embark on RRM have several important issues to address and should be given ample time to grasp, digest and reflect on the information and implications of the

surgery and the opportunity to consult their surgeon as often as necessary. It is fundamental to the woman's welfare to have appropriate and adequate counselling in order to evaluate anxiety and stress levels and explore coping strategies. It is good practice for women to be referred to an onco-psychologist before undergoing surgery (Price, 2007), but at the very least all women considering RRM should be offered pre-operative counselling about the psychosocial and sexual consequences of surgery and have access to support groups or contact with other women who have undergone RRM (NICE, 2013).

RRM should be carried out by a specialist, skilled, accredited oncoplastic surgeon, and any woman considering this surgery should be referred for a genetic assessment prior to the surgery (NICE, 2013). It is important to convey to women contemplating this surgery that even a well-performed mastectomy does not eradicate all breast tissue, hence the term 'risk reducing' rather than prophylactic mastectomy. It is equally important to explain the potential post-operative complications and physical consequences, with particular reference to the risk of scarring and loss of sensation of the mastectomy flaps.

Surgical options for reducing breast cancer risk

Various mastectomy techniques are available, and all are oncologically safe and effective. However, there are some aesthetic aspects that must be taken in consideration and discussed with patients. Total mastectomy is associated with significant skin loss and therefore leads to inferior cosmetic results. This technique is rarely used now in risk-reducing surgery. The skin-sparing mastectomy (SSM) technique, which allows maximum preservation of breast skin, provides better cosmetic results than standard mastectomy. SSM is probably the most commonly used technique in RRM (Slavin, 1998). However, SSM does have the disadvantage of sacrificing the nipple. Nipple preservation (nipple-sparing or subcutaneous mastectomy, SCM) provides a superior aesthetic result to SSM with minimal compromise in risk reduction (Hartmann, 1999). Two studies (Hartmann, 1999; Rebbeck, 2004) found that all the post-mastectomy breast cancers that occurred in the study cohorts developed following SCM. Risk appears to be related to residual parenchymal tissue due to limited access rather than just due to preservation of the nipple areola complex. This observation highlights a very important issue; although mastectomy is carried out as a risk-reduction procedure and in the absence of breast cancer, it should not be compromised in exchange for aesthetics. Adequate access and careful dissection are fundamental oncological principles. This potential drawback of SCM should be clearly shared with women embarking on mastectomy with nipple preservation, together with the fact that preserved nipples are functionless and devoid of sensation.

One study found invasive breast cancer in 0.1–7.7% of the breasts removed for risk reduction (Heemskerk-Gerritsen, 2007). It is good practice therefore to carry out a thorough physical examination and breast imaging with bilateral mammography and magnetic resonance imaging to identify asymptomatic or occult breast cancer prior to surgery. Post-operative histological examination of the breast tissue should be carried out according to agreed protocols and by specialist pathologists, and the possibility of breast cancer being

diagnosed histologically following surgery should be discussed with women pre-operatively (McIntosh et al., 2004).

The risks, benefits and limitations of surgical risk reduction

The decision to undergo mastectomy with all the evidence of successful risk reduction is far from straightforward. *BRCA1/2* mutation carriers of any age live every day with the fear of being told that they have breast cancer and young women under the age of 30 are no exception. Predictive genetic testing is offered to women as young as 18 years of age. Young women sometimes request mastectomy, despite understanding that their risk levels do not rise significantly until their late 20s. There are no guidelines to ascertain the acceptable minimum age for RRM. For young women there are compounding factors such as career, marriage, starting a family and breast-feeding. These issues add significant weight to the complexity of the decision-making, coupled with persistent anxiety.

Several studies have reported adverse effects of RRM on body image and sexual relationships (Mulvihill, 1982; Frost, 2000). In a small study, 13/15 (87%) women reported that the cosmetic results were better than expected, but 8/15 (53%) reported that they felt the reconstruction was not part of their bodies (Josephson, 2000). In another study, 7/45 (16%) women required psychiatric help following RRM (Hopwood, 2000). Frost (2000) reported high levels of satisfaction in women who did not have reconstruction. However, despite the fact that mastectomy is irreversible, studies have overwhelmingly found that women who have undergone RRM report satisfaction with the decision, having no regrets and lower levels of anxiety and fear about developing breast cancer (Stefanek, 1995; Borgen, 1998; Hatcher, 2001).

Breast reconstruction

The aim of breast reconstruction is the maintenance of quality of life following mastectomy. There have been a number of advances in breast reconstruction over the past few years, leading to safer and more reliable surgery. With an increase in the available options, the advantages and disadvantages of each technique can be combined with individual patient characteristics to achieve the best results (Table 23.1). In patients undergoing RRM, reconstruction is always performed at the same time.

In broad terms, current options can be divided into use of prosthetic material or autologous (patient derived) tissue. Prosthetic options include single-stage implant reconstruction or a staged tissue expander followed by implant reconstruction. Autologous reconstructions involve harvesting tissue from one area of the body and transferring it to the mastectomy site. The flap of tissue may retain its original blood supply (pedicled flap) or be joined to a new blood supply at the recipient site (free flap) requiring microvascular anastomoses. Pedicled flaps include the latissimus dorsi (LD) and transverse rectus abdominis myocutaneous (TRAM) flaps. Free flaps include the deep inferior epigastric perforator (DIEP), superior gluteal artery perforator (SGAP), transverse myocutaneous gracilis (TMG) and its modification the profunda artery perforator (PAP) flap (Fig. 23.1).

Table 23.1 Advantages and disadvantages of different breast reconstruction techniques

Procedure	Advantage	Disadvantage	Comment
Two stage with expander/implant	Quick, simple, no donor site	Two operations, symmetry	High rate of capsular contracture
One stage with ADM	Quick, simple, no donor site	High rate of seroma and infection	Lower rate of capsular contracture
Latissimus dorsi flap	No microsurgery	Shoulder dysfunction, need for implant	Scar, seroma
Pedicled TRAM	No microsurgery	Abdominal hernia	
DIEP flap	Good tissue match, no implant	Microsurgical expertise needed	Failure rate of 2%
SGAP flap	For slim patient	Complex flap raising	Indentation of buttock
TMG/PAP flap	Easy flap harvest	Pain, seroma	Good for very slim patients with small breasts

ADM, acellular dermal matrix; TRAM, transverse rectus abdominis myocutaneous; DIEP, deep inferior epigastric perforator; SGAP, superior gluteal artery perforator; TMG, transverse myocutaneous gracilis; PAP, profunda artery perforator.

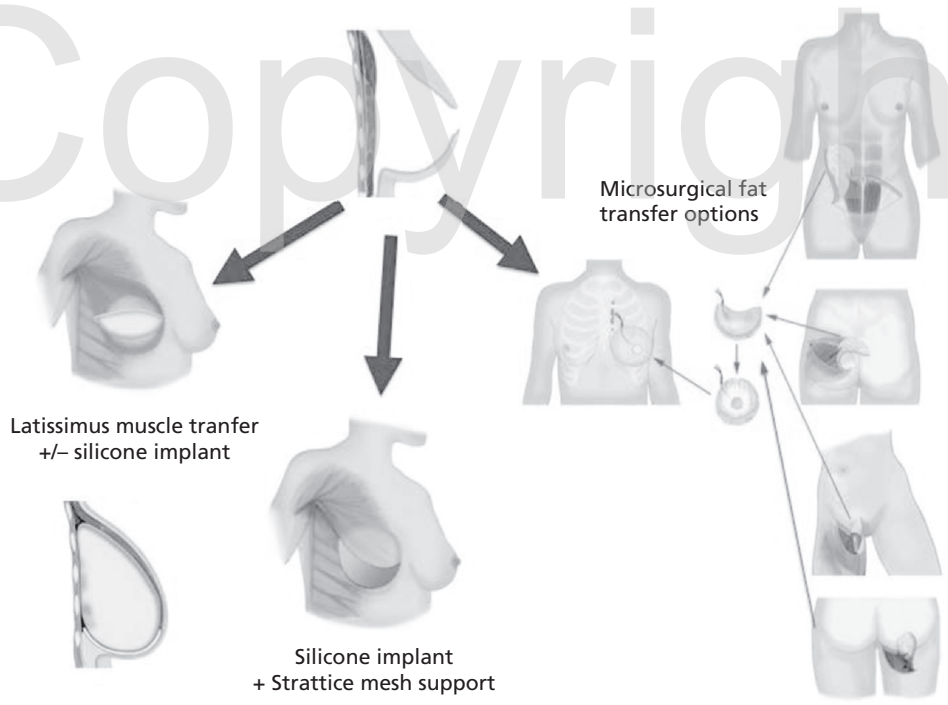

Figure 23.1 Breast reconstruction options. This figure shows all the different options for immediate breast reconstruction that are currently available (2014).
Image courtesy of Jian Fahardi

Prosthetic reconstruction

Implants

The advent of silicone breast implants in the late 1960s allowed the option of post-mastectomy implant-based reconstruction. The implant is inserted under the pectoralis major muscle as a single-stage operation. Implant reconstruction is a simple, short operation with no flap-associated morbidity.

Tissue expander/implant reconstruction

In a SSM the initial tissue expander is placed under the chest muscle to gain full coverage of the implant later. The expander can be subsequently inflated within an out-patient clinic setting to the desired volume. A second-stage operation is then performed to exchange the expander for a matched implant. An advantage of the expander technique is the ability to adjust the final volume. This technique involves two operations with the associated complications for implant placement. A major disadvantage to any implant-based reconstruction technique is the increased risk of fibrosis. Fibrosis and contracture around the implant compromise the aesthetic outcome of the reconstruction and may necessitate further revision surgery.

Acellular dermal matrix

Most recently, acellular dermal matrix (ADM) has been used as an adjuvant product in prosthetic reconstructions. ADM is a sterile, acellular surgical mesh. It consists of dermis (human, porcine or foetal bovine) which is stripped from its cellular components to make it biochemically inert. ADM acts in a number of ways to enhance implant reconstruction. It acts as a scaffold for the ingrowth of cells needed to regenerate and heal the surgical wound locally and can provide additional soft tissue cover for prosthetic devices. The additional tissue cover is hypothesised to reduce implant-related complications such as rippling and contour deformity, but one of the main advantages is the possibility of a one-stage breast reconstruction with an implant without the introduction of an expander. Furthermore, the use of ADM has reduced capsular contracture rates to 2–3% in non-irradiated breast reconstruction (Spear, 2012).

Autologous reconstruction

Autologous reconstructions are based on the concept that a patient's own tissue is most likely to mimic breast tissue lost during mastectomy. Abdominal tissue is most commonly utilised, as the texture and consistency of the subcutaneous tissue matches well to breast tissue, but tissue may be harvested from other sites. In addition, the harvested skin will age with the patient and create natural ptosis and a good aesthetic outcome.

Free flaps can have post-operative vascular complications if the donor or recipient vessels are compromised.

Latissimus dorsi (LD) flap

The flap is raised from the large muscle of the back and is tunnelled through the axilla to the pectoral region. The flap remains attached to its vascular pedicle, the thoracodorsal

pedicle, which is robust and therefore guarantees low flap necrosis and failure rates. LD flaps can also be used to cover implants if more breast volume is desired.

Deep inferior epigastric perforator (DIEP) flap

The DIEP flap has gained increasing popularity amongst plastic surgeons as the abdominal perforator flap of choice for immediate breast reconstructions. It is a modification of the free TRAM flap. The TRAM flap can be either harvested as a pedicled flap using the superior epigastric vessels or a free abdominal flap using inferior epigastric vessels (Hartampf, 1982). The flap is based on the rectus abdominis muscle and its overlying skin and subcutaneous tissue. Harvesting the flap results in an iatrogenic weakness in the abdominal wall which is repaired using a synthetic mesh. Despite mesh repair, patients are at risk of developing abdominal wall herniation at this site (Serletti, 2006). Since the introduction of the DIEP flap, the TRAM flap is less often used.

The DIEP flap is based upon the perforating vessels of the abdominal tissue and therefore avoids the need to dissect fascia and muscle (Granzow et al., 2006), thus reducing the risk of abdominal wall herniation and bulging. Raising the DIEP flap involves careful microdissection of the perforating branches to provide a suitable pedicle for anastomosis in the chest. In light of this, operating times for a bilateral reconstruction are often in excess of 8 hours and heavily rely on the skill of the surgeon. The flap requires a sufficient amount of abdominal tissue and is therefore not suitable for those patients with a low body mass index (BMI). Similarly, patients with very high BMI, diabetes or those who are heavy smokers are known to have increased post-operative complications (Seidenstuecker et al., 2011). The abdominal flap harvest is similar to an abdominoplasty procedure and offers patients the simultaneous advantage of a tummy tuck, which remains an attractive option for post-menopausal women.

Transverse myocutaneous gracilis (TMG) flap and profunda perforator artery (PAP) flap

The TMG flap is derived from the inner thigh, and as such is a useful option for reconstruction in thinner, small to moderately breasted patients. As a free flap it relies on the proximal pedicle of the gracilis muscle and consists of the whole muscle and an elliptical transverse cutaneous paddle. The flap is relatively quick to raise due to the fairly constant anatomy. Thigh lift is an addition benefit from the procedure. The PAP flap is a further development of the TMG flap in which an adipocutaneous free flap is based on a perforator from the adductor magnus (Allen, 2012).

Superior gluteal artery perforator (SGAP) flap

This flap is based on the superior gluteal artery perforating vessels which supply the overlying subcutaneous tissue and skin in the gluteal region. Perforators are identified and dissected through the gluteus muscle, and as such, a limited pedicle length can be achieved. Dissection is often time-consuming and challenging. The gluteal muscle is preserved and therefore donor site morbidity is low with minimal post-operative pain. The nature of the

donor tissue is firm and hence it provides good texture and projection to reconstructed breasts (Werdin et al., 2010).

Nipple reconstruction

A range of surgical techniques are available for nipple reconstruction. All aim to use a small section of skin to re-create a nipple using a single pedicled local flap. The results are variable with little evidence to recommend one technique over another (Farhadi et al., 2006).

Summary

BRCA1/2 mutation carriers who know they have a very high risk of breast cancer are faced with difficult and complex decisions. There are various risk-reduction options, ranging from surveillance and chemoprevention to mastectomy. The latter is the most difficult choice of all but it confers maximum risk reduction. The complexity of the decision requires multidisciplinary team management and the full support of all involved. Mastectomy has been shown to significantly reduce anxiety, but there are other complex psychological issues associated with altered body image. There are a variety of modalities available for breast reconstruction, making it possible to offer implant-based as well as autologous options. It is important to offer every woman a comprehensive consultation in which all options are discussed. The greater availability and choice of mastectomy technique and advances in reconstructive surgery have assisted with minimising post-surgical psychological morbidity and restoring normality to the lives of these women.

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