
1 An Overview of the Breast and Breast Cancer

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INTRODUCTION

Breast Cancer is the most common cancer in women in the UK, with a lifetime risk of 1 in 9 (Cancer Research UK, 2009). Approximately 44 000 women are diagnosed annually in the UK. It is therefore very likely that most nurses will find that they will care for women with breast cancer at some point in their career or will have a personal connection with someone who has breast cancer.

Worldwide, breast cancer has a high media and political profile. October is breast cancer awareness month, which is hard to escape anyone's attention. Magazines, broadsheets and tabloids alike will have articles about breast cancer, people come to work dressed in pink for 'Wear it Pink' day, and the shops are adorned with pink ribbons and pink products. With women forming a large proportion of the voting public, breast cancer and breast cancer screening is high on the political agenda.

Women are increasingly well informed about breast cancer and its treatments. Therefore, to nurse these women with care and understanding, it is vital to have a good theoretical and practical working knowledge regarding the breast, breast cancer and treatments.

This chapter will look at the anatomy and physiology of the normal breast, the incidence and aetiology of breast cancer, the risk factors of developing breast cancer, the diagnostic pathway, certain characteristics of breast cancer and the staging of breast cancer.

ANATOMY AND PHYSIOLOGY OF THE BREAST

Breast development

The breasts, also known as the mammary glands, exist in both males and females but are only usually enlarged in the woman. The breasts begin to develop in the foetus at around the seventh week of gestation and progress to the budding stage at the twelfth week. They are formed from the ectodermal mammary ridge that runs from the axilla to the groin, often referred to as the nipple line. Between weeks 13 and 20, the epithelial bud branches and canalises to form the 16–20 major ducts found in the adult breast.

Occasionally at birth, a baby may produce a small amount of milk. This is due to high levels of luteal and placental hormones crossing the placenta and entering the foetal

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circulation during the late stage of pregnancy thus stimulating the foetal breast. At birth, the foetal and maternal circulatory systems are separated, resulting in the rapid fall of sex steroids in the baby's blood, whereas the baby's pituitary gland continues to secrete prolactin. The baby's prolactin level then declines and the secretions dry up. This is classed as a normal physiological event. Accessory nipples may also be found along the ectodermal ridge, most commonly below the normal breast. These are harmless and only need to be removed if they cause distress to the individual.

Changes at puberty

The female breast starts to change at the time of puberty. The pituitary gland begins to produce the gonadotrophins, follicle stimulating hormone (FSH) and luteinising hormone (LH). As the levels of these hormones rise, the egg follicles within the ovary start to produce oestrogen, which is responsible for the first stages of breast development. At around the age of 10 years old, the mammary tissue behind the nipple enlarges, producing the characteristic swelling referred to as a breast bud that may often be asymmetrical. Oestrogen also induces the connective tissue and vascular growth that is required to support the ductal system. The connective tissue in turn stimulates fat deposition. Once the ovulation cycles begin, the increased output of progesterone balances the oestrogen output and results in the maturation of the glandular tissue (Hughes *et al.*, 2000).

Anatomy of the adult breast

Gross structure

The breasts are situated on either side of the sternum between the second and sixth rib, overlying the pectoralis major muscle. The shape of the breast is hemispherical with a tail of tissue extending into the axilla, known as the tail of Spence. They are stabilised by a suspensory ligament known as Cooper's ligament, named after Sir Astley Cooper. The size of the breast will vary with the stage of development and age and will also vary between individuals. It is common to have one breast slightly larger than the other.

Centrally on each breast lies the nipple–areola complex. The areola is the pigmented circular area, measuring approximately 2.5 cm in diameter. The colour varies from pale pink in fair-skinned women to dark brown in dark-skinned women and will darken during pregnancy. On the surface of the areola are a number of small protuberances known as Montgomery's tubercles, which are modified sebaceous glands whose purpose is to lubricate the nipple during lactation. The nipple lies in the centre of the areola and is approximately 6 mm in length. The surface of the nipple is perforated by the openings of the lactiferous ducts. The nipple–areola complex is rich in smooth muscle fibres, which are responsible for nipple erection.

Microscopic structure

The breast is composed of fibrous, glandular and fatty tissue and is covered by the skin.

Fibrous bands divide the glandular tissue into approximately 16–20 lobes. Clinical findings, however, find the number to be more in the region of 7–8 lobes (Hughes *et al.*, 2000). Within each lobe is the milk-producing system. The lobe contains up to 40 lobules that contain 10–100 alveoli (or acini) which are the milk-secreting cells. The alveoli are

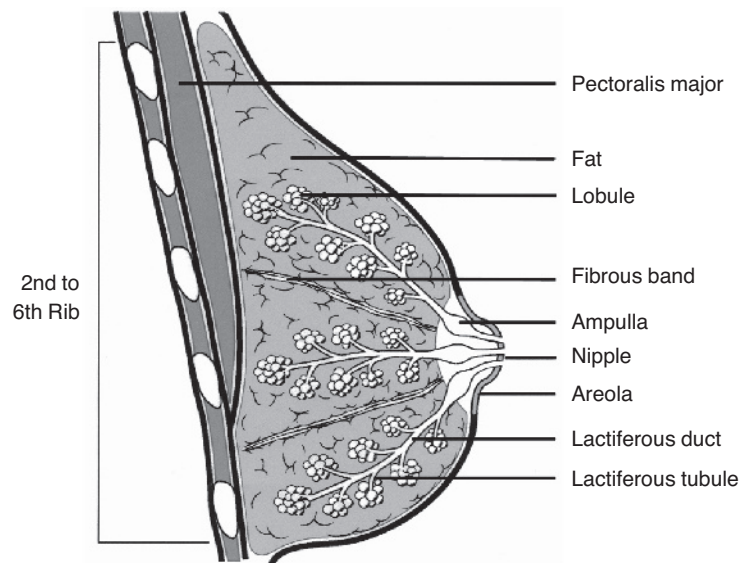


Fig. 1.1 Microscopic structure of the breast.

connected to lactiferous tubules, which in turn connect to the lactiferous duct, which is lined with epithelial cells. The lactiferous duct runs up towards the nipple and, when approaching the nipple, widens to form the ampulla, which acts as a reservoir for the milk to be stored. The lactiferous duct then continues on from the ampulla to open out onto the surface of the nipple (Fig. 1.1).

The glandular tissue of the breast is surrounded by fat. If weight is lost or gained, the breast will vary in size.

Blood supply

The blood supply is from the axillary artery and the internal mammary artery. The venous drainage is through the corresponding vessels into the internal mammary and axillary veins.

Nerve supply

The nerve supply to the breast is mainly from the somatic sensory nerves and the autonomic nerves accompanying the blood vessels. The most sensitive part of the breast is the nipple–areola complex, which is supplied by the somatic sensory nerves. The rest of the breast is supplied by the autonomic supply.

The somatic sensory supply is served via the supra-clavicular nerves (C3, C4) superiorly and laterally from the lateral branches of the thoracic intercostal nerve (3rd and 4th). The medial aspects of the breast receive supply from the anterior branches of the thoracic intercostal nerves, which penetrate the pectoralis major to reach the skin. The nerve supply to the upper outer quadrant of the breast is provided by the intercostobrachial nerve (C8, T1) (Hughes *et al.*, 2000).

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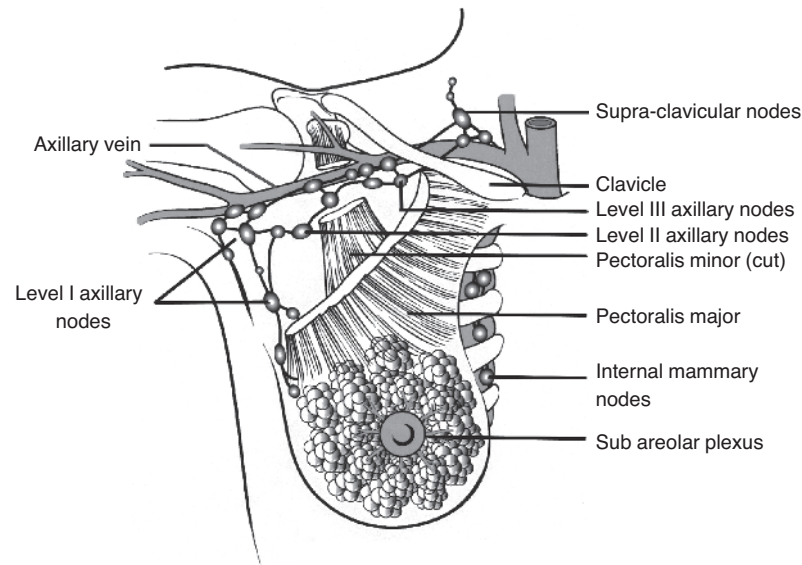


Fig. 1.2 Lymphatic drainage of the breast illustrating levels of axillary nodes.

Lymphatic system

The lymph fluid from the outer quadrants of each breast flows into the ipsilateral axillary lymph nodes along a chain which begins at the anterior axillary nodes and continues into the central and apical node groups. Lymph fluid from the medial quadrants drains towards the sternum via the inframammary nodes.

The major lymphatic drainage of the breast is to the axilla, and the axillary nodes are the first place a breast cancer will spread to. The axillary nodes are divided into three levels (Fig. 1.2).

- Level I – the nodes lie lateral to the lateral border of the pectoralis minor muscle.
- Level II – the nodes lie behind the pectoralis minor muscle.
- Level III – the nodes are located medial to the medial border of the pectoralis minor muscle.

Cyclical changes

During the menstrual cycle, the breasts undergo cyclical changes due to the changing levels of the hormone prolactin, which controls the secretion of the ovarian hormones, oestrogen and progesterone. These hormones cause the breast tissue and ducts to enlarge. The breast may change in size and consistency and become tender and nodular, usually 10–14 days prior to menstruation. These symptoms tend to resolve once menstruation occurs.

Changes during pregnancy

Changes in the breast are often the first symptoms of pregnancy. The woman may complain of fullness, tenderness and an increase in size. Veins become more prominent as the blood supply is increased and the areolar and nipple darken.

These changes are due to firstly oestrogen and progesterone and then to hormones produced by the placenta. Oestrogen stimulates the nipple–areolar complex, causing it to darken; progesterone causes proliferation of the alveoli in preparation for milk production. As the placenta enlarges, it secretes human placental lactogen, which works alongside oestrogen and progesterone to stimulate the hypothalamus to secrete prolactin-releasing hormone (PRH). This hormone stimulates the anterior pituitary gland to secrete more prolactin, and this is responsible for milk production. After 12 weeks, a clear watery fluid known as colostrum is secreted by the breasts and expressed from the nipple. Its main function is to clear the lactiferous ducts and tubules of dead epithelial cells to make way for the free flow of milk.

After birth and the expulsion of the placenta, an alteration in the levels of the hormones oestrogen and progesterone occurs, resulting in the release of prolactin from the anterior pituitary gland. Oestrogen suppresses the action of prolactin, so it is not until about 3 days that the milk ‘comes in’. In the meantime, the baby feeds off the colostrum, which is low in fat and contains vitamin A, protein and minerals.

Post-menopausal changes

When ovarian activity ceases at the menopause, causing the fall of oestrogen and progesterone, the glandular tissue in the breast starts to involute and atrophy, and is replaced by fat. The breasts tend to feel softer and become more pendulous. If hormone replacement therapy (HRT) is prescribed, the breasts may become fuller and can be tender.

INCIDENCE AND AETIOLOGY OF BREAST CANCER

Cancer is a common disease with a lifetime risk of more than one in three. Of all the cancers diagnosed in the UK, breast cancer is the most common female cancer, accounting for 31% of all new cases. Approximately 46 000 women are diagnosed in the UK annually. The estimated lifetime risk is now quoted to be one in nine (Cancer Research UK, 2009). Breast cancer in men is rare, with approximately 300 new cases annually (Cancer Research UK, 2009).

Although the incidence of breast cancer is seen to be rising, the mortality rate is fortunately on the decrease. In the UK in 2006, 12 319 women died from breast cancer compared to 15 625 in 1989. This reduction is thought to be due to earlier detection and improvement in treatment (Cancer Research UK, 2006). The 5-year relative survival rate for women with breast cancer is now estimated to be 82% (Office for National Statistics, 2005) compared to 50% for women diagnosed in 1971–1975.

Risk factors

The cause of breast cancer is not yet fully understood; however some risk factors have been identified. The risk factors can be divided into two: definite risks and potential risks.

Definite risks

Definite risks are the known risks that have been shown by research to increase the risk of developing breast cancer.

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Gender

Being female increases the risk of breast cancer. As stated earlier, males do get breast cancer but it is rare.

Age

As we get older, our chance of getting breast cancer increases. Breast cancer is rare in women under the age of 35 years; however, after that age, the incidence starts to rise. More than 80% of cases occur in women over 50 years of age (Cancer Research UK, 2005)

Strong family history

Having a strong family history of breast cancer increases the risk of developing breast cancer. Much research is being undertaken to identify faulty genes that are associated with the increased risk. Two such genes have been identified so far: *BRCA1* and *BRCA2*, and these will be discussed in depth in Chapter 3.

Not everyone who has a family history of breast cancer will be at a higher risk of developing breast cancer than the average population.

A family history may be described as significant in the following situations (NICE, 2006).

- One first-degree relative and one second-degree relative diagnosed with breast cancer before the average age of 50 years;
- Two first-degree relatives diagnosed before the average age of 50 years;
- Three or more first- or second-degree relatives diagnosed at any age;
- One first-degree male relative diagnosed with breast cancer at any age;
- One first-degree relative with bilateral breast cancer where the first primary was diagnosed before the age of 50 years;
- One first- or second-degree relative with ovarian cancer at any age and one first- or second-degree relative with breast cancer at any age (one should be a first-degree relative).

Those who fit the above criteria should be offered a referral to a Family History clinic, where they can have their risk assessed and have regular screening, where appropriate. Referral to a Regional Genetic Unit may be appropriate following assessment.

Exposure to hormones

The number of menstrual cycles a woman undergoes is a powerful determinant of breast cancer risk. A woman who has an early menarche and late menopause has an increased risk of developing breast cancer. It has been shown that women who undergo a bilateral oophorectomy under the age of 50 years have a 50% reduction in breast cancer for up to 9 years post-surgery (Fentiman, 2001). A woman who has had her first baby after the age of 35 years, or is nulliparous, also carries a higher risk of developing breast cancer.

These findings suggest that the unopposed circulating oestrogen increases the breast tissue's susceptibility to other risk factors for breast cancer (MacPherson *et al.*, 2000).

Benign breast disease

Several studies have looked at the correlation between breast cancer and benign breast disease (Fentiman, 2001). A consensus paper published by the American College of Pathologists (Winchester, 1985), based on the work of Dupont and Page (1985), uses three classifications: no risk, slight risk and moderate risk. Those in the slight-risk group (1.5–2 times) include: moderate or florid hyperplasia with no atypia, intraduct papillomas. Those in the moderate-risk group (5 times) include: atypical lobular or ductal hyperplasia. More recently, a group in the USA studied a large cohort of women with benign breast disease and made similar findings (Hartmann *et al.*, 2005). The relative risk associated with atypia was 4.24, compared with a relative risk of 1.88 with proliferative changes without atypia and 1.27 with non-proliferative lesions.

Ionising radiation

Exposure to ionising radiation is known to increase the risk of breast cancer, as was found in studies in the use of radiation to treat benign conditions such as ringworm and enlarged thymus (Modan *et al.*, 1989; Hildreth *et al.*, 1989; Preston *et al.*, 2002).

Women who have had radiotherapy to their chest for Hodgkin's lymphoma before their early thirties are at an increased risk of breast cancer and should be referred for early breast screening (Travis *et al.*, 2005).

It must be stressed that the amount of radiation delivered by a screening mammogram is very small, and the potential benefits obtained outweigh the small risk.

Oral Contraceptive pill

The Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC, 1996) carried out a meta-analysis of results of 54 studies which included 53 297 breast cancer cases and 100 239 controls. It found that those who had used oral contraceptives (both combined or progesterone only) has a small but statistically significant risk that disappeared 10 years after cessation. However, it is important to remember that these studies were using the older-style contraceptive pills, which tended to have a higher dose of oestrogen. It is not clear whether the modern, low-dose preparations of the combined pill are associated with the same breast cancer risk as the older higher-dose preparations. One population-base case-control study in the USA suggested that the new lower-dose pills may impart a lower risk of breast cancer than the older higher-dose preparations (Althius *et al.*, 2003).

It is important to remember that breast cancer is uncommon in young women (the age group more likely to use oral contraception) so this only leads to a few extra cases per year. The combined pill also reduces the risk of ovarian cancer (Hannaforde *et al.*, 2007).

Hormone Replacement Therapy

Several studies have looked at HRT and its affect on breast cancer risk. In 2003, the results of the Million Women Study were published which showed that if you took a combined HRT you had a relative risk of 2.00 compared to 1.30 if you took an oestrogen only preparation. This risk returns to the same level as in women who have never taken HRT, 5 years after stopping it. In real terms, this means that 10 years of use of a combined HRT will contribute to an extra 19 cases per 1000 users and to five extra cases per 1000 users if oestrogen-only HRT is taken (Million Women Study Collaborators, 2003).

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Obesity

Most studies have shown that obesity is a protective factor in pre-menopausal women but increases the risk in post-menopausal women (Van den Brandt *et al.*, 2000). This is because in post-menopausal women the major source of oestrogen comes from peripheral aromatisation of adrenal androgens in fat. Therefore obesity increases the risk of breast cancer (Ziegler *et al.*, 1996, Sellers *et al.*, 1992, Van den Brandt, 2000).

Alcohol intake

In a pooled analysis of cohort studies looking at the effect of alcohol consumption on the risk of breast cancer, Smith-Warner *et al.* (1998) found that it is associated with an increased risk. The type of alcohol consumed did not strongly influence risk estimates.

Potential risks

Potential risks are those that have not been proven but have led scientists to research further.

Diet

As yet there is no scientific evidence to link breast cancer with diet (McPherson *et al.*, 2000). The intake of fat in the diet has been studied showing no significant risk. Hunter *et al.* (1996) pooled the results from eight major cohort studies and showed no effect of fat intake on the risk of breast cancer. It showed that women whose intake of fat comprised of less than 20% of their calorie intake did not have any reduction in risk. Therefore, if western women reduce their fat intake, it is unlikely to lead to any significant reduction in breast cancer risk reduction.

There has been no conclusive evidence to suggest that a diet high in fruit and vegetables reduced the risk of breast cancer (Smith-Warner *et al.*, 2001).

Height

There has been inconsistency regarding the research findings regarding the influence of height on breast cancer risk. In studies where height was self-recorded there was no increased risk identified but in studies where the participants were formerly measured there was found to be a positive association between increased height and breast cancer risk (Fentiman, 2001). There is no strong evidence to suggest why height has a part to play in breast cancer risk. It is hypothesised that childhood diet, affluence and physical activity during puberty may have an influence (Van den Brandt *et al.*, 2000).

The diagnostic pathway

There are two main diagnostic pathways: screening and symptomatic. Breast screening is extensively covered in Chapter 4 so this chapter will focus on the symptomatic diagnostic pathway.

Patients should be referred to a specialist breast unit by their General Practitioner (GP). In 2005, the National Institute for Health and Clinical Excellence (NICE, 2005) produced guidelines for referral for suspected breast cancer. By December 2009, all breast referrals should be seen within 2 weeks of referral (Department of Health, 2007).

Specialist breast units offer triple assessment which involves clinical examination, radiological assessment and pathological assessment. Many specialist units offer a 'one-stop' service, where the patients get the results on the same day. This is especially advantageous for those who have benign disease. It can however be difficult for a patient who is diagnosed with breast cancer, who has not been prepared for the news. It is therefore important that the GP informs the patient of the process and warns them of any suspicions. With the increasing use of core biopsy, in the diagnosis of breast cancer, a 'two-stop' service is also common.

Methods of assessment

History taking

Before examining the patient, a detailed history should be taken. It is useful in helping make the diagnosis and identifying risk factors.

The details obtained should include the following:

- Patient's age;
- Past medical history;
- Family history of breast and ovarian cancer;
- Age at menarche/age at menopause;
- Date of the last menstrual period (LMP);
- Use of the combined oral contraceptive pill and hormone replacement therapy;
- Number of pregnancies;
- Age at first pregnancy;
- Whether the patient breast-fed her babies;
- Nature of the presenting symptom and its duration.

Clinical examination

It is important to ensure the environment is as pleasant as possible. A gown should be provided, curtains surrounding the examination couch drawn and the door closed to ensure privacy. A chaperone may be present, depending on individual hospital policy.

The clinical examination is divided into two parts:

- 1 Palpation;
- 2 Inspection.

Palpation

The patient is first examined lying supine on the couch with the arms above the head. This flattens out the breast tissue making it easier to examine. The clinician, having washed and warmed their hands, should use the flats of the fingers to palpate the whole of the breast using a steady medium pressure. Any abnormality found is then examined with the fingertips to assess for mobility and fixation. It is important to examine both breasts for comparison and ideally the 'normal' breast should be examined first. The breasts should also be examined in the sitting position.

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The axillary nodes should also be palpated either in the supine position or sitting up. The arm should be supported to ensure the muscle is relaxed. It is easy to miss nodes in a fatty axilla and it has been found that correlation between clinical examination and pathology is poor (Dixon and Sainsbury, 1998). The use of ultrasound is increasingly used in staging the axilla.

When the patient is sitting the supraclavicular nodes should be palpated and the examiner should sweep their hands down the chest wall feeling for any enlarged inframammary nodes.

The Royal College of Nursing (2002) and The Department of Health (1998) have recommended that nurses do not undertake the practice of breast palpation. It does however acknowledge that a small number of nurses with specialist training and who work within a specialist breast unit can practice breast examination.

Inspection

The patient should be in a sitting position. There are three different positions to inspect the breast:

- 1** Hands relaxed by the side;
- 2** Hands in the air;
- 3** Hands on the hips pushing in, contracting the pectoralis major muscle.

The signs to look for are:

- Size and contour of the breasts – is one breast larger than the other, has it always been? Is there any change in shape?
- Skin changes such as dimpling, increased vascularity and skin lesions.
- Nipple changes such as eczematous changes, discharge, crusting and a recent inversion.

Investigations

Following examination and inspection the clinician may organise further investigations. The following investigations are commonplace:

Mammography

A mammogram is a low-dose X-ray of the breast tissue. The dose of radiation is less than 1 Gy. Mammograms are generally not performed on women under 35 as the breast tissue in young women is relatively radio dense. Mammography is discussed in more depth in Chapter 4.

Ultrasound

Ultrasound is a painless procedure that uses high-frequency sound waves. It is a useful in women under 35, as an aid to mammography, measuring lesions and differentiating between a cystic or solid mass.

Magnetic Resonance Imaging

Breast magnetic resonance imaging (MRI) is increasing used in breast assessment although it not routinely used. It is used as an addition to mammograms and ultrasound in complex cases. MRI of the breast is the best technique for imaging implants and the post-surgical breast where local recurrence needs to be excluded. It is also beneficial in assessing the extent of lobular carcinoma in the breast or for multifocal disease. Breast MRI is now recommended for screening high-risk family history patients and those with known gene mutations (NICE, 2006).

To image the breast, the patient has to lie prone and an intravenous contrast is required.

Fine-needle aspiration cytology

Fine-needle aspiration cytology (FNAC) can be performed freehand by the clinician in the outpatient department or under ultrasound guidance. Usually a 10-ml syringe with a 21G or 23G needle is used. The skin is cleaned and the needle is inserted into the lump. Suction is applied whilst several passes are made into the lump in different directions. The material obtained is spread thinly on a slide and is left to air dry. The slides are then reported by the cytologist (Button *et al.*, 2004). The results are graded using a numerical system: C1 = inadequate, C2 = benign, C3 = indeterminate probably benign, C4 = indeterminate, probably malignant and C5 = malignant.

Core Biopsy

If the FNAC results are not conclusive, or histology is required, a core biopsy can be taken. Increasingly the use of core biopsy is replacing FNAC.

Core biopsies can be taken free hand or under image guidance. Local anaesthetic is injected into the breast, a small incision is made with a scalpel and a trocar/biopsy needle is inserted until the tip touches the lump. The biopsy gun is fired which takes a small core of tissue. Several passes are taken to gain a representative sample. The cores are then sent to histology. Pressure should be applied to prevent bruising. Caution should be taken with patients on warfarin, as they should have their INR taken first.

Core biopsies are graded the same way as cytology results but with a preceding 'B', e.g. B1, B2.

Staging investigations

If breast cancer is diagnosed staging investigations may be undertaken to assess for metastatic disease. Depending on need and individual hospital policy, blood tests (full blood count, urea and electrolytes, liver function and bone profile), a chest X-ray, a bone scan, abdominal ultrasound, computed tomography (CT) or MRI can be requested.

Psychological support

Being given a diagnosis of breast cancer is a very difficult time for women. For women who are diagnosed via the screening programme it can come as a complete shock as they were asymptomatic, whilst women who present with a symptom may have undoubtedly questioned in their minds whether they have cancer. It is therefore important that the Breast

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Care Nurses are available to give support and advice throughout the diagnostic pathway. Psychological support will be dealt with in more depth in Chapter 15.

Staging breast cancer

The pathologist is responsible for reporting the histological findings. The results should be discussed at a multidisciplinary team meeting. The core members of this team should include a consultant histopathologist, consultant cytologist, consultant radiologist, consultant surgeon, consultant medical oncologist, consultant clinical oncologist and breast care nurse. Other members include a plastic surgeon, radiographer, trials coordinator, clinical psychologist, a geneticist and administration staff. The histological factors will help to determine the appropriate treatment for the patient.

The pathologist will report of different characteristics of the tumour including:

Size

The size of the tumour is one of the most significant prognostic indicators. The smaller the cancer is, the better the prognosis.

Grade

The tumour is graded according to the cellular differentiation i.e. the degree to which the cancer cells resemble their tissue of origin (King, 1996). A commonly used grading system is the modified Bloom and Richardson system (Elston and Ellis, 1998). It uses three grades: Grade I, Grade II and Grade III. Grade I is the slowest growing cancer; a well-differentiated tumour with the cells closely resembling their tissue of origin. Grade II is a moderately differentiated tumour where the cells are less like their tissue of origin and Grade III is a poorly differentiated tumour where the cells look very unlike their tissue of origin, it is the most aggressive grade of breast cancer.

Grade alone is an important prognostic indicator. It is known that 85% of patients with a grade I tumour are alive and well at 5 years as opposed to 45% of those with a grade III tumour (Ellis *et al.*, 1992).

Vascular and lymphatic invasion

If the tumour has invaded the blood or lymphatic vessels this is a poor prognostic feature.

Lymph node status

The number of lymph nodes involved with cancer cells determines the chance of survival for that individual and is one of the most important prognostic indicators. If positive nodes are identified it will impact on the type of treatment offered.

Hormone Receptor status

The tumour is analysed to test for the presence of the steroid hormone receptors, oestrogen (ER) and progesterone (PR). The presence of such receptors will determine the effectiveness

of endocrine therapy such as tamoxifen and the aromatase inhibitors. It has been shown that those with an oestrogen receptor positive tumour have a better outcome.

For over 30 years tamoxifen has been the gold standard endocrine therapy used for oestrogen receptor positive breast cancers, and still is for pre-menopausal women. The Early Breast Cancer Trialists' Collaborative Group (1998) produced a meta-analysis which showed that if tamoxifen was taken for 5 years, it reduced the recurrence rate by 50%. However, tamoxifen is known to increase the risk of thromboembolic events and endometrial cancer.

Since 2005, the use of aromatase inhibitors has increased following the publication of several studies (Howell *et al.*, 2005; Goss *et al.*, 2003; Coombes *et al.*, 2004). The three most commonly used aromatase inhibitors are anastrozole (Arimidex), exemestane (Aromasin) and letrozole (Femara). They can be given as an upfront treatment, switching therapy after 2–3 years of tamoxifen or as extended therapy after 5 years of tamoxifen. It is important to note they are only suitable for post-menopausal women.

Endocrine therapy will be discussed in more depth in Chapter 10.

Oncogenes

Changes to the genes in a normal cell can result in cell proliferation and malignant proliferation. Proto-oncogenes are involved in stimulating the cell through the normal cell cycle resulting in proliferation, while tumour suppressor genes inhibit excessive cell proliferation. However, either mutation or amplification of proto-oncogenes, and inactivation or loss of tumour suppressor genes can result in uncontrolled cell proliferation and cancer formation (Cooke *et al.*, 1999).

Many proto-oncogenes encode for epidermal growth factor receptors, and the two most important growth factors that have been discovered so far are the human epidermal growth factor receptor – 1 (HER1) and the human epidermal growth factor – 2 (HER2). These are sometimes referred to as *c-erb1* and *c-erb2*, respectively, and are located on Chromosome 17.

HER2 has been shown to be over-expressed in 25–30% of all human breast cancers, and women whose tumours over-expresses HER2 have a shorter disease-free survival and worse overall survival (Slamon *et al.*, 1987; Slamon *et al.*, 1989).

In 2005, results of the HERA trial (Trastuzumab after Adjuvant Chemotherapy in HER2-positive Breast Cancer) were published showing a significant improvement in disease-free survival among women with HER2-positive breast cancer (Piccart-Gebhart *et al.*, 2005). It was shown that if trastuzumab was given, for 1 year, to HER2-positive patients who had completed adjuvant chemotherapy, it reduced the rate of recurrence, particularly distant recurrence by approximately 50%.

Therefore, if a patient's tumour over-expresses HER2, they will be deemed HER2-positive and will be eligible for trastuzumab (Herceptin). This will be discussed in more depth in Chapter 8.

New drugs are being developed to target epidermal growth factor receptors; for example, lapatinib (Tykerb) – a dual tyrosine kinase inhibitor – targets both HER1 and HER2. Ongoing trials are assessing effectiveness and safety (Petrelli *et al.*, 2008).

Targeted therapies are a new and exciting development in the treatment of breast cancer, and future research may result in the development of additional targeted therapies.

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Classification of stage

Staging refers to the grouping of patients according to the extent of their disease. The purpose of this grouping is as follows (Sobin and Wittekind, 2002).

- To aid the clinician in the planning of treatment;
- To give some indication of prognosis;
- To assist in the evaluation of the results of treatment;
- To facilitate the exchange of information between treatment centres;
- To contribute to the continuing investigation of human cancer.

Several classification systems are in use, most commonly the UICC (International Union Against Cancer) TNM system and the Nottingham Prognostic Indicator.

The TNM system

The TNM system was developed in France between 1943 and 1952 and is used for all tumour types, not solely breast. The TNM system is based on three main components:

- 1 T** – the extent of the primary tumour;
- 2 N** – the absence or presence and extent of regional lymph node metastasis;
- 3 M** – the absence or presence of distant metastasis.

The TNM system is summarised in Table 1.1. The TNM classification categories can be relatively complex and, for convenience, they can be condensed to make a more manageable stage group that gives an indication for survival. There are five stages, as shown in Table 1.2.

To put this in practice, a woman who presents with a 3-cm tumour with a moveable node in her ipsilateral (same side) axilla, but has no evidence of metastatic disease, is said to have a T2 N1 M0 invasive breast cancer, which is stage IIB. The lower the stage, the better is the prognosis.

Nottingham Prognostic Indicator

The Nottingham Prognostic Indicator (NPI) is an integrated prognostic index that combines tumour size, lymph node status and grade. The index is calculated by $0.2 \times$ the tumour size (cm) + grade (1–3) + lymph node status (1 = no nodes; 2 = 1–3 nodes; 3 = 3 or more nodes are involved). This separates patients into three prognostic groups: good (score <3.40), moderate (score 3.4–5.4) and poor (score >5).

Adjuvant! Online

Adjuvant! Online is a website that is aimed to help health professionals and patients discuss the risks and benefits of adjuvant treatment for early breast cancer (chemotherapy and endocrine therapy). Information is entered about the patients and their tumours (for example: age of patient, tumour size, grade, nodal involvement, etc.). A printout from the website illustrates the estimated risk of cancer-related mortality or relapse without

Table 1.1 TNM classification

Stage	Characteristics
T-primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: Tis (DCIS): Ductal carcinoma in situ Tis (LCIS): Lobular carcinoma in situ Tis (Paget): Paget's disease of the nipple, no tumour
T1	Tumour 2.0 cm or less in greatest dimension T1mic: Microinvasion 0.1 cm or less in greatest dimension T1a: More than 0.1 cm, but not more than 0.5 cm in greatest dimension T1b: More than 0.5 cm, but not more than 1 cm in greatest dimension T1c: More than 1 cm, but not more than 2 cm in greatest dimension
T2	Tumour more than 2 cm, but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension Tumour of any size, with direct extension to chest wall or skin
T4	T4a: Extension to chest wall T4b: Oedema (including peau d'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast T4c: Both 4a and 4b, as above T4d: Inflammatory cancer
N-nodal status	
NX	Regional lymph nodes cannot be assessed (e.g. previously removed)
N0	No regional lymph node metastasis
N1	Metastasis in moveable ipsilateral axillary node(s)
N2	Metastasis in fixed ipsilateral axillary node(s) N2a: Metastasis in axillary lymph nodes fixed to one another or to other structures N2b: Metastasis in only clinically apparent internal mammary lymph node(s) and in the absence of clinically evident axillary lymph node metastasis
N3	Metastasis to ipsilateral internal mammary lymph node(s) N3a: Infra-clavicular N3b: Internal mammary and axillary N3c: Supra-clavicular
M-distant metastasis	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

systematic adjuvant therapy and with systemic therapy. The website is available to view on <http://www.adjuvantonline.com>.

CONCLUSION

Chapter 1 has given an overview of breast cancer, including the anatomy and physiology of the breast, and has also looked at the symptomatic diagnostic pathway. This overview will

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Table 1.2 Five stages of the TNM classification.

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

hopefully provide a good knowledge base for healthcare professionals caring for women with breast cancer.

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