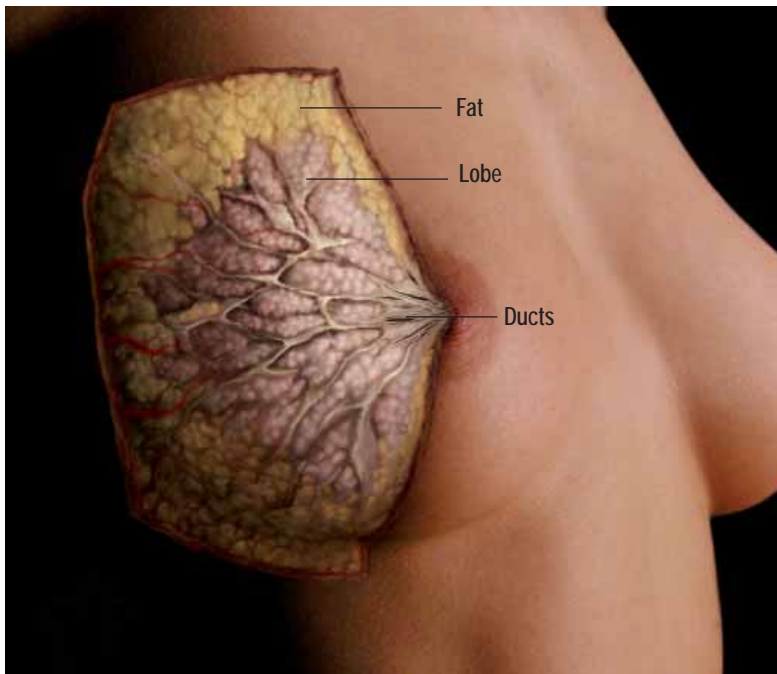
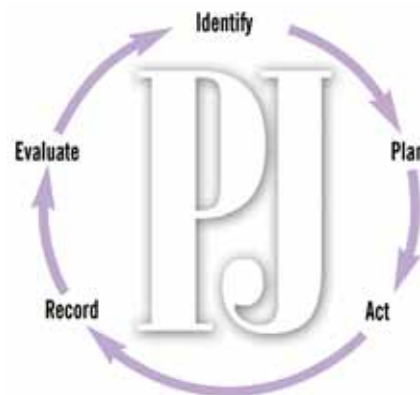


Breast cancer: an overview

In the first of two articles, Sandra Melville and Lucy Heycock outline the pathology of breast cancer and the role pharmacists can play in prevention and patient support



Anatomical Travelogue / Science Photo Library



Identify knowledge gaps

1. What are the signs and symptoms of breast cancer?
2. What are the risk factors for breast cancer and what advice could you offer on prevention strategies?
3. What is the relevance of staging and grading breast cancer?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states" and "health education and promotion" (see appendix 4 of "Plan and record").

Breast cancer affects almost 42,000 people in the UK each year and there are 12,700 deaths from the disease annually — it is the most common cause of death in women between the ages of 35 and 55 years. One in nine women in the UK will develop breast cancer and although the incidence is increasing, recent advances in prevention and screening together with new treatments have resulted in improved survival rates.^{1,2} Breast cancer also occurs in men, accounting for 1 per cent of cases in the UK. However, this series only applies to breast cancer in women.

Pharmacists, particularly in the community, are ideally placed not only to give lifestyle advice about risk reduction, but also to act as a valuable resource for patients experiencing side effects during treatment.

Structure of the breast

The mature female breast is composed of fat, connective tissue and glandular tissue, and can be divided into lobes. On average, there are 15–20 lobes in each breast and, within these, many smaller lobules, which ultimately end in dozens of tiny milk-producing bulbs. A network of ducts leading to the nipple, link these lobes and lobules. The areola around the nipple has large glands around it which produce fluid to lubricate the nipple. Connective tissue, known as stroma, supports these structures and fat fills the spaces around the lobules and ducts. There are no muscles in the breast, but muscles lie under each breast and cover the ribs.

The breast is responsive to a complex interplay of hormones (mainly oestrogen, progesterone and prolactin) that cause the tissue to

develop, enlarge and produce milk. It also contains a network of lymph vessels which connect to lymph nodes, located mainly in the armpits, near the chest wall and over the collarbone and neck region.

Risk factors

Breast cancer is an extremely complex disease. There are many types with differing histological, biological and immunological characteristics. Many women mistakenly believe that most breast cancers are hereditary but, in fact, only 5 per cent of breast cancers in the UK have a genetic link. Generally, the greatest risk factor for developing breast cancer is age, with 80 per cent of cases occurring in women over the age of 50 years. Incidence in women under 30 years of age is rare.

Panel 1 (p300) describes risk factors for developing breast cancer but it should be noted that these are relative risks and having one or more of these does not mean that a patient will develop the disease.

Oestrogen in breast cancer Levels of oestrogen vary during a woman's lifetime and will influence her breast cancer risk.

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Panel 1: Risk factors for developing breast cancer

- **Age** Incidence increases from one in 900 in those under 30 years old to one in 10 in those over 85 years.
- **Oestrogen therapy** Oral contraceptives slightly increase the risk of breast cancer. Hormone replacement therapy increases the risk of breast cancer and decreases sensitivity of mammography.³
- **Obesity** Women who are obese, particularly post menopause, are at increased risk. Adipose tissue is the main body source of oestrogen after menopause.
- **Menstrual and pregnancy history** Early menarche, late menopause, fewer pregnancies and shorter duration of breastfeeding are all associated with increased risk.
- **Race** Variations are seen with age and race. In women under 40 years old, Caucasian women are more likely than black or Asian women to develop breast cancer, while in women over 40 years black women are at increased risk compared with Caucasian or Asian women. Asian women of all ages are at a decreased risk.
- **Family history** A small proportion of breast cancers have a strong genetic link. Carrying the BRCA1 or BRCA2 gene mutation leads to a 50–80 per cent chance of developing breast cancer.
- **Height at age 14** Women who were taller than 165cm at the age of 14 years are at increased risk and those under 150cm at the age of 14 years are at decreased risk. (Women in between these heights are at average risk.)
- **Birth weight** Women who weighed over 4.43kg at birth are at increased risk and those weighing less than 3.18kg are at decreased risk.
- **Socio-economic status** There is a positive correlation between risk and socio-economic status — those of higher status are at greater risk.
- **Geographical location** Women in urban areas are at higher risk than those in rural areas.

Oestrogen stimulates the growth and division of breast tissue cells and it is believed that the greater the growth rate, the greater the risk of cancerous mutations. Oestrogen levels change dramatically during puberty, pregnancy and the menopause, and are affected by hormone replacement therapy (HRT) and the oral contraceptive pill. Elevated oestrogen levels are linked to an increased risk of breast cancer and is relevant in two-thirds of breast cancers. These are termed “oestrogen receptor positive” (or “oestrogen responsive”, see below).

The million women study³ confirmed that both current or recent use of HRT can increase the risk of developing breast cancer. The study also found that:

- Users of HRT are at a 22 per cent relative increased risk of death from breast cancer compared with women who have never used HRT
- The relative risk of breast cancer varies significantly among the different HRT types and is substantially greater in users of oestrogen-progestogen combinations than in users of other preparations

The use of HRT has to be balanced with the benefits of treatment (eg, relief of hot flushes and night sweats, prevention of osteoporosis, etc) and women should be encouraged to discuss the pros and cons fully with their GP before making a decision.

Use of the combined oral contraceptive (COC) pill slightly increases the risk of developing breast cancer. The risk is highest for women who started using these pills as teenagers. However, 10 or more years after

stopping COCs, the risk of developing breast cancer returns to the same level as women who have never taken them. In addition, the Committee on Safety of Medicines advises that a possible small increase in the risk of developing breast cancer should be weighed against the benefits and evidence of a protective effect against cancers of the ovary and endometrium. [See also p281.]

Prevention

Obesity is one of the few modifiable risk factors for the breast cancer. Recent evidence suggests that physical activity has a preventive effect on breast cancer although it is not clear if this is caused by exercise having a direct effect on hormonal and growth factor levels or simply as a result of it lowering body mass index.

There is a significant association between alcohol intake and breast cancer. There is some evidence to suggest that animal fat intake may cause a small increased risk in breast cancer, but this is not thought to play as large a role as previously thought. Breastfeeding has an association with a reduction in risk, which is another reason for promoting it to young mothers who may seek advice.

Signs and symptoms

Early breast cancer can present with any of the following:

- Breast or chest pain
- Palpable lump in breast or armpit
- Nipple inversion or discharge
- Puckering or dimpling of skin (“peau d’orange”)
- Change in size or shape of breast

Metastatic disease can present with bony pain or pathological fracture, breathlessness due to pleural effusion or jaundice.

In addition to providing lifestyle advice, pharmacists are ideally placed to promote the importance of breast awareness. Recent research carried out by Breakthrough Breast Cancer found that 80 per cent of women had not checked their breasts in the previous month and the study highlighted that the main reason was that they simply did not know how. In fact, there is no special routine for breast examination. What is important is that a woman looks at and feels her breasts so that any changes are noticed. A check can be done in any way that feels comfortable, for example in the bath or shower or when dressing or lying down. Women should be encouraged to become familiar with their breasts, how they usually look and feel, and what is normal at different times of the menstrual cycle. If a woman notices anything unusual she should report it to her GP. It is worth stressing to women that nine out of 10 lumps are not cancerous but it is vital that any breast changes are reported to their GP because early detection improves survival.

The prompt detection of breast cancer offers the best chances of survival and pharmacists can help women by encouraging those

Nine out of 10 lumps are not cancerous but it is vital that any breast changes are reported because early detection improves survival

between the ages of 50 and 70 years to participate in the NHS Breast Screening Programme so that a mammography can be performed. Mammographies can detect cancerous lesions before they are large enough to become palpable. Despite the success of this programme, which has significantly increased early detection and therefore survival rates, some areas (notably central and east London) have an uptake of appointments as low as 20 per cent.

Diagnosis

Mammography and ultrasound (performed after a mammography if necessary) can help to detect a lesion or to confirm a lesion as suspicious. Diagnosis of the disease is by biopsy and pathological assessment to confirm type (eg, adenocarcinoma, medullary, inflammatory, mucinous, Paget's), hormone receptor status and HER2 status.

For example, tests on a sample of breast cancer cells can show if they "respond" to oestrogen. Breast cancers can be divided into two types: oestrogen responsive (ER+) and non-oestrogen responsive (ER-). Establishing this status is important because it determines whether or not hormone therapy is appropriate. Whether or not a breast cancer is progesterone receptor positive also affects how a woman will respond to hormone therapy, although to a lesser extent than being ER+.

HER2 is a protein found on the surface of some cancer cells. It is made by a specific gene called the HER2/neu gene. HER2 is a receptor for a particular growth factor called human epidermal growth factor, which occurs naturally in the body. When human epidermal growth factor attaches itself to HER2 receptors on breast cancer cells, it can stimulate the cells to divide and grow. Some breast cancers have many more HER2 receptors than others. In this case, the tumour is described as being HER2-positive. It is thought that about one in five women with breast cancer will have HER2-positive tumours. These tumours have a worse prognosis than HER2-negative tumours and are more likely to respond to trastuzumab. (The treatment of breast cancer will be covered in next article, to be published on 29 September.)

If metastatic disease is suspected, computed tomography scans and bone scans are required.

Staging and grading The stage of a cancer describes its size and whether it has spread beyond its original site. The grade gives an idea of how quickly the cancer could develop. The staging system used for breast cancer in the UK is the Union International Contre Cancer (UICC) scheme and this is related to the more universal TNM (tumour, node, metastases) classification, which is based on the size of the tumour, the number of nodes and whether there are metastases (see Panel 2).

Grading is determined by the appearance of the cancer cells under the microscope. There are three grades: grade 1 (low grade), grade 2 (moderate or intermediate grade) and

Panel 2: Staging of breast cancer

UICC staging	TNM staging	Tumour, nodes, metastases
Stage 1	T1 N0 M0	Tumour <2cm, Node negative
Stage 2A	T1/2 N0/1 M0	Tumour 2–5cm, or < 2cm with 1–3 nodes
Stage 2B	T2/3 N0/1 M0	Tumour 2–5cm with 1–3 nodes or >5cm with no nodes
Stage 3A	up to T3 N1/2 M0	Tumour >5cm but free from chest wall 4–10 nodes
Stage 3B	T4 and N	Tumour >5cm and fixed to chest wall, any node state
Stage 4	M1	Distant metastases

grade 3 (high grade). The higher the grade the more abnormal the appearance of the cells and the more aggressive the cancer. Many women will know their grade of breast cancer and appreciate the significance of this, so an understanding of this terminology can provide a useful background for health care professionals involved in their care.

Types of breast cancer A breast cancer can be described as either in situ or invasive. "In situ" means there are cancerous changes in the cells but these are still limited to the lining of the glands or ducts, and have not begun to invade the surrounding tissue. "Invasive" implies that cancerous cells have broken through the lining layer and begun to penetrate the surrounding tissue from where they can gain access to the lymphatics and blood vessels for further dissemination.

Most breast cancers are adenocarcinomas, originating in the epithelia of the ducts and lobes. About 80 per cent of breast cancers are invasive at presentation. Invasive ductal carcinomas account for around 90 per cent of these. These generally present with poorly defined hard lumps, peau d'orange or nipple inversion, or both.

Invasive lobular carcinomas account for the other 10 per cent of invasive breast cancers and these tend to be harder to detect without a mammography because they are relatively diffuse tumours. Pre-invasive carcinomas account for the remaining cases of breast cancer, and are known as ductal or lobular carcinomas in situ (DCIS or LCIS).

The important considerations are:

- Size of tumour
- Grade
- Margin of clearance (distance of tumour from edge of the healthy tissue that can be surgically removed — the more tissue that can be removed, the better)
- Number of nodes involved
- Oestrogen or progesterone receptor positivity
- HER2 status

Prognosis

Outcome primarily depends on the intrinsic growth rate of the tumour (which can vary dramatically), the age at diagnosis and numerous biological parameters (eg, histology, grade, hormone receptor levels, proliferation rate and

Panel 3: Survival 15 years post diagnosis

Stage at diagnosis	Survival (per cent)
1	85
2	55
3	40
4	<5

presence of tumour suppressor gene p53) that ultimately define the natural history of the disease. Simplistically, survival at 15 years after diagnosis is linked to staging at diagnosis, as illustrated in Panel 3 (p301).

Successful treatment of early stage disease can still result in relapse, even as long as 30 years later. It is interesting that, irrespective of the length of disease-free interval, the behaviour of tumours at relapse are similar and predictable. The average survival at this point is around three years (but can vary from a few months to five years). Women who are younger than 34 years at diagnosis generally have a worse prognosis, with less than half surviving at five years and most relapsing within three years.

Predicting prognosis can be aided by using the Nottingham prognostic index (NPI). This is a formula that uses the size, stage and grade of a tumour to calculate a prognostic score:

$$\text{NPI} = (\text{tumour size} \times 0.2) + \text{grade} + \text{node status}$$

For example, for a 5cm, grade 3 tumour with two nodes, the NPI is $(5 \times 0.2) + 3 + 2 = 6$

The NPI can be used to advise patients of their chances of a cure and to help select appropriate pharmacological treatment options. For example, no chemotherapy is needed if NPI is less than 3.4. Those with a score between 3.5 and 5.4 will derive the maximum benefit from chemotherapy and for those with a score of more than 5.4, chemotherapy is essential. The lower the score, the better the prognosis.

Treatment options

Treatment of breast cancer depends on various factors, such as stage of disease, age, menopausal status, size and grade of the tumour and hormonal status. The second article in this series will look at treatments for breast cancer in more detail.

Pharmacy support

As one of the most accessible members of the health care team, the pharmacist is ideally placed to provide cancer patients with the information and support they need to get through what can be one of the most difficult times of their lives. Testimonies of women who have undergone treatment for breast cancer tell us time and again how a positive and empathic approach of health care professionals can make a real difference.

Studies show that patients often feel they are imposing on their doctor's time if they ask questions during appointments yet do not seem to have the same reservations in the pharmacy. Pharmacists can encourage women to talk about their treatment and side effects. Just having someone listen can be therapeutic in itself and also provides an opportunity for information to be gathered, which can be used to direct patients to the most appropriate sources of support. In addition, a review of patients' medication in the light of their diagnosis can sometimes highlight valuable anomalies, such as inappropriate continuation

Breast cancer awareness month

October is breast cancer awareness month. Breast Cancer Care has designed a free "breast aware" display pack. More information on the pack and how to order it can be found at www.breastcancercare.org.uk

of oral contraceptives or HRT slipping through the net on repeat prescriptions.

An understanding of current issues related to breast cancer in order to address fears fuelled by media scares (eg, stories linking antibiotic or antiperspirant use to breast cancer risk) will also be useful, as will steering people away from less trusted sources of information, such as unreliable websites, and enabling them to make more objective choices.

Signposting Local sources of help can include support groups, breast care nurse specialists, hairdressers and wig suppliers, complementary health centres and Macmillan and Marie Curie nurses. There is a common misconception that Macmillan nurses only get involved in cancer care at the palliative stage, but they can provide excellent support at any part of the disease process and may be of particular value to patients just after diagnosis when they have to digest a lot of information.

National organisations include charities such as Breast Cancer Care and Cancer Backup provide written information, telephone support and advice lines and websites. Information is available on a wide range of topics such as entitlement to state benefits as well as treatment options and symptom management. Patients often need an extra bit of encouragement to take the step to access a support group or telephone a helpline and it is worth spending a little time encouraging them to do this.

Summary

Being diagnosed with breast cancer can be bewildering and frightening. Women can experience a range of emotions including fear, anger and anxiety. They have to deal with a vast array of different health professionals and negotiate a confusing maze of health care systems. During treatment, people can often be exhausted, nauseated and unwell. They may also be trying to come to terms with the loss of a breast. Then they often lose their hair during treatment, at a time when they are already feeling at a low point. The amount of distress that this can cause to women at time in their lives when they are vulnerable should not be underestimated.

Being aware of these issues will be invaluable when someone with breast cancer comes to the pharmacy; there is a vast amount of help and advice that pharmacists can offer to provide significant psychological support as well as improved pharmaceutical care.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Plan an event for breast cancer awareness.
2. Talk to your local Macmillan nurse about how you might help support patients with breast cancer.
3. Visit www.breastcancercare.org.uk and www.breakthrough.org.uk and look at the range of leaflets available. Choose one for your pharmacy.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

References

1. The Institute of Cancer Research. Chemotherapy clinical trials. Available at www.icr.ac.uk (accessed on 2 July 2007).
2. NHS Cancer Screening Programmes. Screening for breast cancer in England: past and future. Available at www.cancerscreening.nhs.uk (accessed 2 July 2007).
3. The million women study. Available at www.icnet.uk (accessed 28 September 2007).

Resources

- Both Breast Cancer Care and Breakthrough Breast Cancer have information packs for health professionals.