# Breast cancer

Breast cancer is by far the most common cancer in women and the second most common cause of death from cancer in the UK. It is also a significant cause of morbidity. Most breast cancers arise from either:

- The epithelial lining of ducts and are called ductal.
- The epithelium of the terminal ducts of the lobules and are called lobular.

Carcinoma can be invasive or in situ. Most cancers arise from intermediate ducts and are invasive.

Paget's disease of breast is an infiltrating carcinoma of the nipple epithelium and represents about 1% of all breast cancers.

Inflammatory carcinoma occurs in a small minority of all cases with a rapidly growing, sometimes painful mass enlarging the breast and causing the overlying skin to become red and warm. There may be diffuse infiltration of tumour.

Because male breast cancer occurs at a relatively very low incidence, the literature, research, clinical trials, and development of new treatment options for men with breast cancer primarily focus on female breast cancer. [1]

## How common is breast cancer? (epidemiology) [2] [3]

- Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-2018).
- 99% of breast cancer cases in the UK are in females, and 1% are in males.

- Approximately 50,000 new cases of breast cancer are diagnosed each year in the UK, around a quarter of these following screening mammography.
- Breast cancer incidence is strongly related to age, with the highest incidence rates being in older people.
    - In the UK in 2016-2018, on average each year around a quarter of new cases (24%) were in people aged 75 and over.
    - Age-specific incidence rates rise steadily from age 25-29, more steeply from age 35-39 in females and from age 60-64 in males.
    - The highest rates are in the 90+ age group for females and the 85 to 89 age group for males.
- For females, breast cancer age-standardised incidence rates in the UK increased by 24% between 1993-1995 and 2016-2018. For males, breast cancer age-standardised incidence rates in the UK remained stable between 1993-1995 and 2016-2018.
- The most common specific location for invasive breast cancers in the UK is the upper-outer quadrant of the breast (2016-2018).
- Breast cancer incidence rates in England in females are 14% lower in the most deprived quintile compared with the least, and in males are similar in the most deprived quintile compared with the least (2013-2017).

See also the separate Male Breast Cancer article.

## Risk factors for malignancy[4]

- Previous history of breast cancer.
- Risk increases with age; ≤5% of cases present before age 35 years, ≤25% before 50 years.
- Family history of breast cancer in a first-degree relative. Between 6% and 19% of women will have a family history but this may be due to chance, shared environmental or lifestyle risk factors, or increased genetic susceptibility.

- Genetic factors:[5]
    - The BRCA1, BRCA2 and TP53 mutations carry very high risk but only about 5% of all breast cancers are largely attributable to inherited mutations in specific genes.
    - BRCA1 mutation on chromosome 17: the lifetime risk of breast cancer for women with this mutation is 65-85%, and the lifetime risk of ovarian cancer is 40-50%; men with this mutation may also be at increased risk of breast cancer.
    - BRCA2 mutation on chromosome 13: for women with this mutation, the lifetime risk of breast cancer is 40-85%, and the lifetime risk of ovarian cancer is 10-25%; for men with this mutation, the lifetime risk of breast cancer is 6%.
- Never having borne a child, or having a first child after the age of 30 years.
- Not having breastfed (breastfeeding is protective).
- Early menarche and late menopause.
- Radiation to the chest (even quite small doses).
- The Western-style diet, obesity and the consumption of alcohol also contribute to the rising incidence of breast cancer.[4]
- Hormone replacement therapy (HRT):[6]
    - HRT with oestrogen alone is associated with little or no change in the risk of breast cancer.
    - HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer.
    - Any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT.

- Combined oral contraception:[7]
    - There is a small increase in the risk of having breast cancer diagnosed in women taking the combined oral contraceptive pill.
    - However, this relative risk may be due to an earlier diagnosis and the cancers are more likely to be localised to the breast.
    - The most important factor for diagnosing breast cancer appears to be the age at which the contraceptive is stopped rather than the duration of use.
    - Any increase in the rate of diagnosis diminishes gradually during the 10 years after stopping and disappears by 10 years.

Breast augmentation is not generally associated with increased risk of breast cancer.[8]

# Breast cancer symptoms (presentation)[3]

Most patients present having felt a lump, which is most often painless but may be associated with pain. Other presenting symptoms include nipple change, nipple discharge and skin contour changes. Breast pain/mastalgia alone is a very uncommon presentation. Intraduct carcinoma may present as a bloody discharge from the nipple.

### History

Organised screening, education programmes and improved consciousness of the female population have substantially changed the type of patients seen nowadays compared with a few decades ago and the neglected tumour is much rarer than it was.

Patients presenting with a lump in the breast will be aware of the possible diagnosis and will be very anxious. This should be taken into account when taking the history and discussing management.

Most patients present having found a painless lump in the breast. Other symptoms include a lump under the arm, lump in other regional lymph nodes and with retraction or inversion of the nipple. A suspicious mass may have been found at routine mammography.

Metastases may cause pain in bones or even pathological fractures. Metastases at other sites - for example, the liver, lung or brain - may cause symptoms.

Intraduct carcinoma may present as a bloody discharge from the nipple. The lump of breast cancer is usually painless. Occasionally, patients (usually elderly but not always) will still present with a fungating mass that has obviously been neglected for a long time.

### Examination

See the separate Breast Lumps and Breast Examination article.

### Screening [9]

- The NHS Breast Screening Programme in England provides 3-yearly routine breast screening to women.
- Breast screening uses mammography radiography to detect small changes in the breast before other symptoms or signs of breast cancer develop.
- If breast cancer is found at an early stage, there is an increased chance of breast-conserving surgery and a better prognosis for long-term survival.
- Invitations for routine mammography screening are sent out to women aged 50–70 years (from the age of 50 years up to their 71st birthday) in England, Northern Ireland, Scotland, and Wales.
- Not every woman will receive an invitation as soon as she is in the screening age range, but she should receive her first invitation for routine screening within 3 years of her 50th birthday.
- Women older than the maximum age for screening can continue to receive breast screening by self-referral to a local breast screening service.
- Women at increased risk of breast cancer (for example, with a strong family history) may be eligible for breast screening before the age of 50 years.

# Referral for breast cancer

Referral guidance is available and should be carefully followed. The National Institute for Health and Care Excellence (NICE) guidance for specialist referral states:[10]

- Refer people, using a suspected cancer pathway referral (for an appointment within two weeks), for breast cancer if they are aged 30 and over and have an unexplained breast lump with or without pain, or are aged 50 and over with any of the following symptoms in one nipple only: discharge, retraction or any other changes of concern.
- Consider a suspected cancer pathway referral in people with skin changes that suggest breast cancer, or for those aged 30 and over with an unexplained lump in the axilla.
- Consider non-urgent referral in people aged under 30 with an unexplained breast lump with or without pain.

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**Editor's note**

Dr Krishna Vakharia, 16th October 2023
**Suspected cancer: recognition and referral** [10]
NICE has recommended that a person should receive a diagnosis or ruling out of cancer within 28 days of being referred urgently by their GP for suspected cancer.

### Management of women at high risk of breast cancer

The risk of breast cancer is multifactorial but some women will have a high risk because of a genetic predisposition or, rarely, as a consequence of radiotherapy at a young age. Women with a family history suggestive of a genetic predisposition to cancer should be referred to local genetics services for formal assessment. See also the separate Familial Breast Cancer article.

# Investigations

Guidelines on the clinical assessment and techniques for accurate diagnosis have been produced. Investigations should take place in secondary care.

Initial investigations include:

- Oestrogen and progesterone receptor status.
- Epidermal growth factors including, for example, human epidermal growth factor receptor 2 (HER2) status.
- Routine blood tests including LFTs.
- CXR.

### Diagnostic radiography [4] [11]

Initial imaging includes bilateral mammography and ultrasound of the breast and regional lymph nodes.

Ultrasound is very effective (especially in younger women). It is particularly useful when breast tissue is dense. In young patients it can be diagnostically more useful than mammography.

MRI of the breast should not be used routinely in the pre-operative assessment of people with biopsy-proven invasive breast cancer or ductal carcinoma in situ (DCIS). MRI should be offered to people with invasive breast cancer:

- If there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment.
- If breast density precludes accurate mammographic assessment.
- To assess the tumour size if breast-conserving surgery is being considered for invasive lobular cancer.

### Genetic testing [11]

Genetic testing for BRCA1 and BRCA2 mutations should be offered to women aged under 50 years with triple-negative breast cancer (tests negative for oestrogen receptors, progesterone receptors, and excess HER2 protein), including those with no family history of breast or ovarian cancer.

### Diagnostic procedures

Various procedures are used, including:

- Fine-needle aspiration (FNA):
    - High accuracy combined with mammography.
    - Negative results do not exclude carcinoma.
    - False negatives are high (especially if the lesion is small). False positives are very low.
- Core needle biopsy (image-guided):
    - The method of choice and should be obtained before any surgery.[4]
    - Ultrasound or stereotactic mammographic guidance can be used.
- Open biopsy (needle localisation):
    - Radio-opaque needles used to guide biopsy.
    - It can usually be done under local anaesthetic.
    - There are fewer false negatives.
- Excision biopsy (entire lesion removed) or incisional biopsy (part of lesion removed).

### Staging investigations[11]

NICE recommends pre-treatment ultrasound evaluation of the axilla for people having investigations for early invasive breast cancer and, if abnormal lymph nodes are identified, ultrasound-guided needle sampling.

Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. Sentinel lymph node biopsy is the preferred technique.

### Advanced breast cancer[12]

For the diagnosis and assessment of advanced breast cancer, NICE recommends:

- Combination of plain radiography, ultrasound, CT and MRI to assess presence and extent of visceral metastases.
- Bone windows on CT, MRI or bone scintigraphy to assess presence and extent of metastases in the bones of the axial skeleton.
- Bone scintigraphy and/or plain radiography to assess proximal limb bones for the risk of pathological fracture in patients with evidence of bone metastases elsewhere.
- MRI to assess bony metastases if other imaging is equivocal for metastatic disease or if more information is needed (eg, if there are lytic metastases encroaching on the spinal canal).
- Positron emission tomography fused with computed tomography (PET-CT) only to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.

On recurrence, consider reassessing oestrogen receptor (ER) and HER2 receptor status if a change in receptor status will lead to a change in management.

## Differential diagnosis

The differential diagnosis includes fibroadenoma and other varieties of benign breast disease, including breast cysts. See also the separate Breast Lumps and Breast Examination and Benign Breast Disease articles.

## Staging

Staging is based on the T (primary tumour) N (regional lymph nodes) M (presence of metastases) classification.[4]

Breast cancer is staged as follows:

- Stage 0: non-invasive breast cancer (ductal carcinoma in situ): the cancer remains localised in the ducts (Tis, N0, M0).
- Stage IA: the tumour is small, is invasive and has not spread to the lymph nodes (T1, N0, M0).

- Stage 1B: spread to the lymph nodes and the cancer in the lymph node is larger than 0.2 mm but less than 2 mm in size. There is either no evidence of a tumour in the breast, or the tumour in the breast is 20 mm or smaller (T0 or T1, N1mi, M0).
- Stage 2A - any one of:
    - No evidence of a tumour in the breast but the cancer has spread to 1 to 3 axillary lymph nodes. No spread to distant parts of the body. (T0, N1, M0).
    - Tumour is 20 mm or smaller and has spread to 1 to 3 axillary lymph nodes (T1, N1, M0).
    - Tumour is larger than 20 mm but not larger than 50 mm and has not spread to the axillary lymph nodes (T2, N0, M0).
- Stage 2B - either one of:
    - Tumour is larger than 20 mm but not larger than 50 mm and has spread to 1 to 3 axillary lymph nodes (T2, N1, M0).
    - Tumour is larger than 50 mm but has not spread to the axillary lymph nodes (T3, N0, M0).
- Stage 3A - either one of:
    - Tumour of any size has spread to 4 to 9 axillary lymph nodes or to internal mammary lymph nodes. It has not spread to other parts of the body (T0, T1, T2, or T3; N2; M0).
    - Tumour larger than 50 mm that has spread to 1 to 3 axillary lymph nodes (T3, N1, M0).
- Stage 3B: tumour has spread to the chest wall or caused swelling or ulceration of the breast, or it is diagnosed as inflammatory breast cancer. It may or may not have spread to up to 9 axillary or internal mammary lymph nodes. It has not spread to other parts of the body (T4; N0, N1, or N2; M0).
- Stage 3C: tumour of any size that has spread to 10 or more axillary lymph nodes, the internal mammary lymph nodes, and/or the lymph nodes under the collarbone. It has not spread to other parts of the body (any T, N3, M0).

- Stage 4 (metastatic): tumour of any size and has spread to other organs, such as the bones, lungs, brain, liver, distant lymph nodes, or chest wall (any T, any N, M1).

Invasive breast cancer can be defined as early breast cancer (stage 1 or 2), locally advanced disease (stage 3) and advanced disease (stage 4).

## Breast cancer treatment and management[4] [7] [11]

- Treatment should be patient-centred, taking into account patients' individual needs and preferences.
- Surgery and radiotherapy aim to remove the tumour mass, whilst adjuvant drug therapy (drug treatment following surgery) aims to reduce the risk of disease recurrence and the risk of developing invasive disease.
- Neoadjuvant drug therapy (drug treatment before surgery) aims to reduce the size of the tumour to allow breast-conserving surgery to be possible and to reduce axillary lymph node involvement.
- Both breast reconstruction options (immediate reconstruction or delayed reconstruction) should be offered when applicable.
- In women with invasive breast cancer in only one breast who have not received treatment, including the use of neoadjuvant chemotherapy, NICE recommends the use of the PREDICT tool to estimate prognosis and the absolute benefits of adjuvant therapy.[13]

EndoPredict (EPclin score), Oncotype DX Breast Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and lymph node-negative (including micrometastatic disease) early breast cancer, only if they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index, and the information provided by the test would help the decision on whether or not to have adjuvant chemotherapy.[14]

One trial with 10,273 women showed that chemotherapy may be avoided in about 70% of women with hormone receptor-positive tumours (HER2-negative). The Oncotype DX test was used to determine how active a tumour is by looking at 21 genetic markers in biopsied tumour cells. It then gave a score from 1 to 100 for risk of metastasis or recurrence.

Treatment decisions are clear for women whose score is lowest (10 or below) or who score 26 or above. However, the majority of women fall between these two points and so treatment decisions are more difficult.

In the trial, 6,711 fell between the high and low risk recurrence scores and they were randomly assigned to receive either hormone therapy or hormone therapy and chemotherapy as part of the Trial Assigning Individualised Options for Treatment (TailorX). The authors concluded that chemotherapy can be spared in:[15]

- All women older than 50 years with hormone receptor-positive and HER2-negative breast cancer with a recurrence score up to 25 - about 85% of women in this age group.
- All women younger than 50 with a recurrence score of 0 to 15 - about 40% of the women in this age group.

A study involving 1,836 women found that, among patients with high-risk, HER2-negative early breast cancer and germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants, adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy was associated with significantly longer survival free of invasive or distant disease than placebo.[16]

NICE has provided recommendations for the use of a number of drugs that may be considered as options (monotherapy or combination therapy) in various circumstances for the treatment of breast cancer. The list of approved drugs includes trastuzumab, pembrolizumab, ribociclib, fulvestrant, sacituzumab, tucatinib, olaparib, alpelisib, atezolizumab, palbociclib, neratinib, abemaciclib, pertuzumab, eribulin, everolimus, denosumab, bevacizumab, lapatinib, and gemcitabine.[17]

**Ductal carcinoma in situ (intraepithelial neoplasia)** can be treated with conservation surgery, if clear resection margins can be achieved. There is no accepted consensus on an adequate margin but margins ≤2 mm are considered inadequate. Adjuvant whole breast irradiation afterwards reduces the risk of local recurrence but has no effect on survival.

## Early and locally advanced breast cancer treatment

For operable breast cancer, treatment involves surgery to the breast (breast-conserving surgery or mastectomy) and to the axillary lymph nodes, with or without radiotherapy to reduce local recurrence rates. This is often followed by adjuvant drug therapy to eradicate the micro-metastases that cause relapses.

### Radiotherapy

- Radiotherapy is recommended after breast-conserving surgery with clear margins, as it reduces local recurrence rates.
- However, radiotherapy may be omitted if risk of local recurrence is very low and the woman is willing to take adjuvant endocrine therapy for a minimum of five years.
- Radiotherapy is also recommended after mastectomy in patients with node-positive invasive breast cancer or involved resection margins.
- It should also be considered in patients with node-negative T3 or T4 invasive breast cancer.

### Adjuvant drug therapy

Adjuvant drug therapy may include chemotherapy, endocrine therapy, biological therapy, or bisphosphonate therapy. The decision to use adjuvant drug therapy is based on the risks and benefits of treatment, disease prognosis and predictive factors such as ER, progesterone receptor (PR), and HER2 status of the primary tumour.

- **Chemotherapy**: adjuvant chemotherapy using an anthracycline (eg, doxorubicin, epirubicin, daunorubicin, mitoxantrone) with a taxane (eg, paclitaxel, docetaxel) is recommended if sufficient risk of disease recurrence.

- **Biological therapy**:
  - Trastuzumab should be offered to patients with tumour size T1c and above HER2-positive invasive breast cancer, in combination with surgery, chemotherapy, or radiotherapy.
  - It should also be considered in patients with a smaller tumour size (T1a or T1b) depending on their comorbidities, prognosis, and possible toxicity with concomitant chemotherapy.
  - Cardiac function should be regularly assessed in patients receiving trastuzumab, and caution in patients with underlying cardiac disease.
- **Endocrine therapy**:
  - Tamoxifen should be used as initial adjuvant endocrine therapy in men and pre-menopausal women with oestrogen-receptor-positive invasive breast cancer.
  - In addition, ovarian function suppression with a gonadotropin-releasing hormone (GnRH) should be considered in pre-menopausal women, taking into account the risk of temporary menopause. Ovarian function suppression may be most beneficial in women who are at sufficient risk of disease recurrence to have been offered chemotherapy.
  - In postmenopausal women with oestrogen-receptor-positive invasive breast cancer who are at medium or high-risk of disease recurrence, an aromatase inhibitor (eg, anastrozole, exemestane, letrozole) should be given as first-line therapy. Alternatively, tamoxifen should be given if an aromatase inhibitor is not tolerated or is contra-indicated, or if the risk of disease recurrence is low.

- **Extended endocrine therapy** (total duration longer than five years):
    - An aromatase inhibitor (unlicensed indication) should be offered to postmenopausal women with oestrogen-receptor-positive invasive breast cancer at medium or high risk of disease recurrence who have been taking tamoxifen for two to five years.
    - Extended therapy should also be considered in postmenopausal women at low risk of disease recurrence.
    - Extended tamoxifen therapy for longer than five years can also be considered, both in pre-menopausal and in postmenopausal women with oestrogen-receptor-positive invasive breast cancer.
- **Endocrine therapy for ductal carcinoma in situ**:
    - Following breast-conserving surgery, endocrine therapy should be offered to women with oestrogen-positive ductal carcinoma in situ, if radiotherapy is recommended but not given.
    - If radiotherapy is not recommended, the use of endocrine therapy should also be considered.

- **Bisphosphonate therapy**:
    - Zoledronic acid and sodium clodronate have been shown to improve disease-free survival and overall survival in postmenopausal women with node-positive invasive breast cancer. However, there is insufficient evidence to recommend their use in premenopausal women.
    - Intravenous zoledronic acid (unlicensed indication) or oral sodium clodronate (unlicensed indication) should be offered to postmenopausal women with lymph-node-positive invasive breast cancer.
    - Treatment should be considered in those with lymph-node-negative invasive breast cancer who are at high risk of recurrence.
    - Bisphosphonate therapy is also recommended in women at high risk of osteoporosis due to the use of aromatase inhibitors in postmenopausal women, or in women with treatment-induced premature menopause.
    - Denosumab is recommended by NICE as an alternative option for preventing skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) for people with bone metastases.[18]

**Neoadjuvant drug therapy**

Neoadjuvant drug therapy may involve the use of chemotherapy or endocrine therapy.

- **Neoadjuvant chemotherapy**:
    - Should be offered to reduce tumour size in patients with oestrogen-receptor-negative invasive breast cancer. In patients with oestrogen-receptor-positive invasive breast cancer, chemotherapy should be considered.
    - In patients with HER2-positive invasive breast cancer, neoadjuvant chemotherapy should be offered in combination with trastuzumab and pertuzumab.
    - A chemotherapy regimen containing both a platinum (eg, cisplatin, carboplatin, oxaliplatin) [unlicensed indication] and an anthracycline should be considered in patients with triple-negative invasive breast cancer (oestrogen-receptor-negative, progesterone-receptor negative and HER2-negative).
- **Endocrine therapy**:
    - If chemotherapy is not indicated, neoadjuvant endocrine therapy should be considered as an alternative in postmenopausal women with oestrogen-receptor-positive invasive breast cancer.
    - Chemotherapy and endocrine therapy are equally effective in postmenopausal women in terms of breast conservation and shrinking of the tumour.
    - Although chemotherapy is more effective than endocrine therapy at shrinking the tumour in pre-menopausal women, some tumours may respond to endocrine treatment.

**Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence** [19]

Abemaciclib is a selective inhibitor of cyclin-dependent kinases 4 and 6. This leads to disruption of cancer cell proliferation.

NICE has recommended abemaciclib with endocrine therapy as an option for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer in adults whose disease is at high risk of recurrence.

Those defined as having a high risk of recurrence are patients with clinical and pathological features of:

- At least four positive axillary lymph nodes; or
- 1 to 3 positive axillary lymph nodes, and at least one of the following criteria:
    - Grade 3 disease (defined as at least 8 points on the modified Bloom-Richardson grading system or equivalent); or
    - Primary tumour size of at least 5 cm.

Adjuvant treatment aims to reduce the risk of cancer returning after surgery. Clinical trial evidence showed that adjuvant treatment with abemaciclib plus endocrine therapy increased how long people were free of disease compared with endocrine therapy alone.

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**Pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer** [20]

The National Institute for Health and Care Excellence (NICE) has advised that pembrolizumab is an option with chemotherapy for neoadjuvant treatment and then continued alone as adjuvant treatment after surgery for adults with triple-negative early breast cancer at high risk of recurrence or in locally advanced breast cancer.

It has been shown that by adding pembrolizumab to chemotherapy before surgery (neoadjuvant) and then continuing with pembrolizumab alone after surgery (adjuvant), there is an increased chance the cancer will disappear. It also increases the time before any cancer comes back again.

**Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy** [21]

- NICE have recommended olaparib (alone or with endocrine therapy) as an option for the adjuvant treatment of HER2-negative high-risk early breast cancer that has been treated with neoadjuvant or adjuvant chemotherapy in adults with germline BRCA1 or 2 mutations.

- Olaparib is a PARP inhibitor. In the absence of functional BRCA- PARP inhibition results in an antineoplastic effect on cancer cells.
- Evidence has shown that when compared to placebo, those taking olaparib after neoadjuvant or neoadjuvant chemotherapy have a decreased chance of their cancer returning or getting worse. This increases the length of time people live.

### Advanced breast cancer treatment [12]

Treatment of advanced breast cancer depends on the patient's treatment history, disease severity, and oestrogen receptor and HER2 status.

#### Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments [22]

NICE has recommended the option of trastuzumab deruxtecan with **managed access** for treating HER2-positive unresectable or metastatic breast cancer but only after they have had one or more anti-HER2 treatments.

It has been shown to increase the time before someone's cancer gets worse. It is still uncertain as to whether this medication will prolong life. For this reason, it is under managed access so evidence can be gathered whilst in use.

#### Endocrine therapy

For the majority of patients with oestrogen-receptor-positive advanced breast cancer, endocrine therapy is recommended as first-line treatment.

Aromatase inhibitors should be offered to postmenopausal women with no previous history of endocrine treatment, or to those previously treated with tamoxifen. Tamoxifen in combination with ovarian function suppression should be offered as first-line treatment to pre-menopausal and perimenopausal women with oestrogen-receptor-positive advanced breast cancer not previously treated with tamoxifen.

Ovarian function suppression should be offered to pre-menopausal and perimenopausal women who have had disease progression despite treatment with tamoxifen. Tamoxifen should be offered as first-line treatment to men with oestrogen-receptor-positive advanced breast cancer.

**Chemotherapy**
Chemotherapy should be offered as first-line treatment in patients with oestrogen-receptor-positive advanced breast cancer that is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement. Once chemotherapy treatment is completed, endocrine therapy should be offered.

**Biological therapy**
Trastuzumab is recommended for the treatment of HER2-positive advanced breast cancer. It is used in combination with paclitaxel in those who have not received chemotherapy for metastatic breast cancer, and as monotherapy for patients who have received at least two chemotherapy regimens for metastatic breast cancer.

**Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy:**[23] NICE recommends that abemaciclib plus fulvestrant is recommended as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer in adults who have had endocrine therapy only if exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor.

**Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer:**[24]

Pembrolizumab is a monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor. This potentiates an immune response to tumour cells:

- NICE has advised that pembrolizumab plus chemotherapy (paclitaxel or nab-paclitaxel) is recommended as an option for treating triple-negative, locally recurrent unresectable or metastatic breast cancer in adults who have not had chemotherapy for metastatic disease.
- It is recommended only if the tumours express PD-L1 with a combined positive score (CPS) of 10 or more and an immune cell staining (IC) of less than 1%.

- This is an option for those who cannot have atezolizumab combination treatment. Clinical trials have shown that pembrolizumab combination increases how long people have before their cancer gets worse and how long they live.

**Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer:** [25]
NICE has recommended alpelisib plus fulvestrant as an option for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer in adults.

- It can only be used if their cancer has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.
- This combination could be a life-extending treatment at the end of life.

**Sacituzumab govitecan for treating unresectable triple-negative advanced breast cancer after 2 or more therapies** [26]
NICE has recommended sacituzumab govitecan is an option for treating unresectable triple-negative locally advanced or metastatic breast cancer in adults after two or more systemic therapies, at least one of which was for advanced disease.

Clinical trial evidence has shown that sacituzumab govitecan increases how long people have before their disease gets worse and how long they live compared with chemotherapy. It can therefore be considered to be a life-extending treatment at the end of life.

**Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy** [27] NICE has recommended palbociclib plus fulvestrant as an option for treating hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer in adults who have had endocrine therapy if exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor.

Currently, treatment for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer after endocrine therapy includes exemestane plus everolimus, and the CDK4/6 inhibitors abemaciclib (plus fulvestrant) and ribociclib (plus fulvestrant) if exemestane plus everolimus is the most appropriate alternative.

New clinical evidence has shown that palbociclib plus fulvestrant works in a similar way to abemaciclib and ribociclib and can, therefore, be another alternative.

This combination has shown that it could increase how long people live.

**Bisphosphonates**
The use of bisphosphonates should be considered in patients with metastatic breast cancer to reduce pain and prevent skeletal complications of bone metastases.

# Managing breast cancer complications [12]

### Lymphoedema

- Assess patients with lymphoedema for treatable underlying factors before starting any lymphoedema management programme.
- Offer all patients with lymphoedema complex decongestive therapy (combination of different treatments, including bandaging, compression garments, manual lymphatic drainage, exercise, and self-care) as the first stage of lymphoedema management.
- Consider using multilayer lymphoedema bandaging (MLLB) for volume reduction as a first treatment option before compression hosiery.
- Provide patients with lymphoedema with at least two suitable compression garments.

### Cancer-related fatigue

- Assessment to identify any treatable causative factors, and offer appropriate management as necessary.
- Provide information about and timely access to an exercise programme for all patients with advanced breast cancer experiencing cancer-related fatigue.

### Bone metastases

- Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain.
- Use external beam radiotherapy to treat patients with bone metastases and pain.
- An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery.

### Brain metastases

- Offer surgery followed by whole brain radiotherapy to patients who have a single or small number of potentially resectable brain metastases, a good performance status, and no or well-controlled other metastatic disease.
- Offer whole brain radiotherapy to patients for whom surgery is not appropriate, unless they have a very poor prognosis.
- Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy.
- Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate.

### Psychological difficulties [28]

Breast cancer may be associated with various psychological difficulties, which may include severe anxiety and depression. The experience of a life-threatening illness, such as cancer, requires a person to consider an array of emotional, medical, social and existential needs.

Specific to breast cancer, research shows that the experience of diagnosis and treatment of breast cancer may result in considerable distress. The diagnosis of invasive breast cancer may cause a time of uncertainty, that brings fear and emotional difficulties, with challenges to a woman's identity, self-esteem, body image and relationships.

### Arm and shoulder mobility problems [11]

People who are having surgery for breast cancer are at high risk of developing shoulder problems if they have any of the following factors:

- Pre-existing shoulder conditions, eg, history of shoulder surgery, shoulder trauma injury (fracture or shoulder dislocation), frozen shoulder, osteoarthritis or rheumatoid arthritis affecting the shoulder.
- Non-specific shoulder pain, stiffness, decreased function.
- Body mass index (BMI) over 30.
- Axillary node clearance or radiotherapy to the axilla or supraclavicular nodes planned.

Provide advice about upper limb exercises and offer supervised support when performing upper limb exercises if high risk of developing shoulder problems after surgery for breast cancer.

Refer to physiotherapy for individual assessment and treatment if persistent reduction in arm and shoulder mobility after breast cancer surgery or radiotherapy.

### Menopausal symptoms

Some treatments used in the management of breast cancer, such as tamoxifen or ovarian function suppression may lead to menopausal symptoms or early menopause.

Women diagnosed with breast cancer should discontinue HRT because of possible tumour stimulation and interference with adjuvant endocrine therapy. HRT should not be offered routinely to women with menopausal symptoms if they have a history of breast cancer.

However, in exceptional circumstances, HRT can be offered to women with severe menopausal symptoms once the associated risks have been discussed.

SSRI antidepressants may be offered to relieve menopausal symptoms such as hot flushes in women with breast cancer who are not taking tamoxifen. Clonidine hydrochloride, venlafaxine (unlicensed indication) and gabapentin (unlicensed indication) are sometimes used for the treatment of hot flushes in women with breast cancer.

# Breast cancer in pregnancy[29]

- Breast cancer is the most prevalent malignancy diagnosed in pregnancy, accounting for up to 21% of all pregnancy-related malignancies.
- Treatment is possible but not simple, because it creates a conflict between the care of the mother and the potential for serious adverse effects on the fetus..
- Treatments like radiotherapy and chemotherapy are toxic to the fetus and termination of pregnancy (TOP) may be considered depending upon the mother's preference, stage of the disease, the current gestation and the mother's chance of survival.
- It may be possible to defer treatments other than surgery depending upon stage.
- Chemotherapy should not be given in the first trimester but after that it can cause intrauterine growth restriction or premature labour.

# Follow-up

- After adjuvant treatment (including chemotherapy and/or radiotherapy, where indicated) is completed, discuss with patients where they would like follow-up to be undertaken. They may choose primary, secondary or shared care.
- Patients should follow an agreed care plan written with the patient by a healthcare professional. Copies should be sent to the GP and held by the patient. It should include:
    - Designated named healthcare professionals.
    - Dates for review of any adjuvant therapy.
    - Details of surveillance mammography.
    - Contact details for immediate referral to specialist care.
    - Contact details for support services - for example, support for patients with lymphoedema.

## Prognosis[2]

- 75.9% of women diagnosed with breast cancer in England survive their disease for ten years or more, it is predicted (2013-2017).
- 80.6% of women in England diagnosed with breast cancer between ages 15-44 survive their disease for ten years or more, compared with 57.1% of women diagnosed aged 75-99 (2013-2017).
- 10-year survival is highest in women aged 55-64 (87.2%) (2013-2017).
- Breast cancer survival has doubled in the last 50 years in the UK.
- Compared with female breast cancer, male breast cancer has a lower survival and higher mortality.[30]
- For breast cancer, like other cancer sites, survival trends reflect a combination of changes in treatment and stage distribution. These factors themselves can vary by age, sex and deprivation.

Clinical parameters can be used in scoring systems that can give a relatively accurate estimation of the probability of recurrence or death from breast cancer.[13]

## Breast cancer prevention

- Some women will have concerns about the development of breast cancer because of family history. See the separate Familial Breast Cancer article.
- Consider modification of risk factors, particularly in high-risk patients.

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