PART 1

Oncology

CHAPTER 1

Breast Cancer

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OVERALL BOTTOM LINE

- Breast cancer is the second leading cause of cancer-related deaths among women aged <50 years.
- There has been an approximately 30% reduction in breast cancer mortality since 1990 as a result of screening and the increased detection of early stages of disease, and adjuvant therapy.
- Breast cancer is not a single disease. Based on molecular genetic profiling there are at least five major subtypes: luminal A, luminal B (high proliferation rate), luminal B human epidermal growth factor receptor 2 (HER2) overexpressing, HER2 overexpressing, and triple negative breast cancer (TNBC) is estrogen and progesterone receptor (ER, PR) and HER2 negative.
- Inherited germline mutations of *BRCA1* and *BRCA2* represent about 5–10% of all breast cancers. The lifetime risk of developing breast cancer increases by 80% and 60%, and ovarian cancer by 54% and 23% for *BRCA1* and *BRCA2* mutation carriers, respectively.
- The treatment of breast cancer is one of the earliest examples of using targeted treatments with the recognition of the ER and HER2 receptors serving as therapeutic targets and the development of effective drugs against these receptors.

Background

Definition of disease

- Breast cancers arise in the epithelial cells that line milk ducts or in breast alveolar lobules.
- Breast cancers consist of two major categories: invasive and noninvasive.
  - Invasive cancers include invasive ductal, lobular, mucinous, tubular, medullary, and papillary cancers.
  - Noninvasive cancers include ductal carcinoma *in situ* (DCIS) which is recognized as a pre-invasive lesion; and lobular carcinoma *in situ* (LCIS) that is recognized as a marker of increased risk of developing subsequent breast cancer in either breast.

Disease classification

Breast cancers can be phenotypically classified by their receptor status: ER and PR as measured by immunohistochemistry (IHC); by HER2/neu receptor status measured by IHC or *in situ* hybridization (ISH); or intrinsic molecular subtypes based on gene expression profiling (Table 1.1).

Mount Sinai Expert Guides: Oncology, First Edition. Edited by William K. Oh and Ajai Chari.

Companion Website: www.wiley.com/go/oh/mountsinaioncology

Table 1.1 Subtypes of breast cancer.

	Luminal A	Luminal B	Luminal HER2	HER2 enriched	Triple negative/ basal like
Frequency	~55%	~15%		~20%	~10%
Receptors					
ER	+	+	+	–	–
PR	+/–	+/–	+/–	–	–
HER2	–	–	+	+	–
Grade	Low	Mod–high	Mod–high	High	High
Ki-67[a]	Low	High	High	High	High
Mutations[b]	PI3K (49%) PTEN[c] (13%) P53 (12%)	PI3K (32%) P53 (32%) PTEN[c] (24%)		P53 (75%) PI3K (42%) PTEN[c] (19%)	P53 (84%) PTEN[c] (35%) PI3K (7%)
Treatments					
Anti-estrogens[d]	+	+	+	–	–
Chemotherapy[e]	–	+/–	+/–	+	+
HER2 directed	–	–	+	+	–
Outcome	Favorable	Interm[f]	Interm[f]	Favorable	Poor

[a] Ki-67, proliferation marker; low <10–14%; high >14%.
[b] Most frequent mutations based on The Cancer Genome Atlas (TCGA).
[c] Loss or mutation.
[d] Tamoxifen and gonadotropin-releasing hormone (GnRH) agonists in premenopausal women; fulvestrant (selective estrogen receptor degrader, SERD), tamoxifen (selective estrogen receptor modulator, SERM), aromatase inhibitors (AI) in postmenopausal women.
[e] Anthracycline (cyclophosphamide, doxorubicin (AC) with or with paclitaxel (T) or non-anthracycline-containing regimens (docetaxel, cyclophosphamide (TC)). Trastuzumab (T), pertuzumab (P), lapatinib (L), and trastuzumab emtansine (T-DM1)
[f] Intermediate.

Incidence/prevalence

- Breast cancer is the most common cancer in females in the USA and the second most common cause of cancer death in women.
- There were approximately 225 000 new breast cancer cases and approximately 40 000 deaths in 2012, with an estimated 3 000 000 women living with breast cancer in the USA. There are about 5000 cases of male breast cancer annually.
- Black women have a lower incidence of breast cancer than white women, but a higher breast cancer-specific mortality rate. This is thought to be a result of more unfavorable biology (e.g. increase in triple negative subtype) and less access to care leading to a more advanced stage of disease at diagnosis.

Economic impact

- From 1970 to 2008, the number of breast cancer deaths in women aged 20–49 years was about 226 000 and accounted for 8 million years of potential life lost.
- The total productivity loss in 2008 was $5.5 billion and individual lifetime lost earnings was $1.1 million.

Etiology

- It is unclear what causes breast cancer; ~5–10% are linked to inherited germline mutations in *BRCA1, BRCA2, TP53, PTEN*, and the *ATM* genes.
- 15–20% of women will have a positive family history (with low penetrance genes).
- Environmental factors: endogenous and exogenous estrogen, radiation exposure (i.e. mantle field radiation in Hodgkin lymphoma), daily alcohol ≥2 drinks, and obesity (body mass index (BMI) >30) increase the risks of developing breast cancer.

Pathology/pathogenesis

- Figure 1.1 describes estrogen binding to ER in cytosol, translocation to the nucleus where the complex binds to DNA and initiates transcription. The *HER2* gene on chromosome 17q12 belongs to the epidermal growth factor receptor (EGFR) family. *HER2* overamplification occurs in 20% and is associated with an increased risk of distant recurrence, poorer response to chemotherapy, and increased mortality in the absence of *HER2*-directed therapy. A monoclonal antibody to an external domain of the *HER2* receptor, trastuzumab, has changed the natural history by improving OS in both the early and advanced stage setting.
- *BRCA1* on chromosome 17q21 and *BRCA2* on chromosome 13q12.3 proteins are involved in DNA repair. An inherited germline mutation from either the maternal or paternal line increases the lifetime risk of developing breast cancer by 80% (*BRCA1*) and 60% (*BRCA2*), and ovarian cancer by 54% (*BRCA1*) and 23% (*BRCA2*).

Predictive/risk factors

- Female gender.
- Aging.
- Elevated estrogen levels: early menarche, late menopause, late parity, nulliparity, and prolonged (>10–15 years) of hormone replacement therapy (HRT).
- Benign breast conditions: atypical ductal or lobular hyperplasia, or LCIS.
- Dense breast tissue.
- A personal history of breast cancer.
- A family history of breast cancer (strongly affected by the number of female first degree relatives).
- Inherited germline mutation in *BRCA1, BRCA2, p53, ATM,* and *PTEN*.
- Obesity: BMI ≥30 kg/m^2.
- Alcohol: dose–response relationship between alcohol and risk of breast cancer.
- Prior thoracic radiation.

However, 75–80% of newly diagnosed women with breast cancer do not have any of these risk factors.

Prevention

BOTTOM LINE/CLINICAL PEARLS

The key to prevention is:

- Identification of germline genetic mutation carriers.
- Age appropriate and high risk patient screening (i.e. magnetic resonance imaging (MRI) breast screening for mutation carriers of *BRCA* genes).
- Modifiable lifestyle risk factors such as reducing daily alcohol consumption, weight management, and avoidance of obesity.

- Regular physical exercise may reduce the risk of breast cancer and reduces all cause mortality.
- Primary chemoprevention with tamoxifen in pre- and postmenopausal women, and raloxifene or aromatase inhibitors in postmenopausal women.
- Prophylactic salpingoopherectomy and mastectomy for *BRCA* germline mutation carriers.

Screening

- Mammographic screening is associated with a 15–30% decrease in breast cancer mortality, increased detection of earlier stage curable breast cancers, and an increase in breast conserving therapy (BCS). The role of ultrasound for whole breast screening is not established. Breast ultrasound is used to help clarify imaged mammographic abnormalities.
- Annual breast MRI for high risk women as defined by the following:
  - Known *BRCA* mutation carriers, start at age 25.
  - Untested and first degree relative of *BRCA* carrier, start at age 25.
  - Lifetime risk ≥20%.
  - Chest irradiation between ages 10 and 30 years.
  - Genetic syndromes (e.g. Cowden, Li–Fraumeni).
- Annual mammographic screening and clinical breast examination is indicated in women ≥50 years. The upper age limit of screening mammography has not been defined and decisions are based on functional age and comorbid conditions rather than chronologic age. There is controversy in women aged 40–49 with some policy-making organizations recommending decisions should be individualized with a thorough discussion of smaller absolute reductions in mortality and the potential harms of screening, whereas others recommend screening intervals every 1 or 2 years along with clinical breast examination. Promoting breast self-examination is controversial because overall mortality is not decreased. However, women can be empowered by performing breast self-examination but for other women it is a source of anxiety.

Primary prevention

- Breastfeeding for prolonged durations.
- Primary chemoprevention is indicated for women with a first degree relative with breast or ovarian cancer, history of thoracic irradiation, *BRCA* mutation carriers, LCIS, atypical hyperplasia or Gail Model risk assessment tool (https://bcrisktool.cancer.gov/) predicting a 5-year breast cancer risk ≥1.7%. Five years of tamoxifen, raloxifene, or the aromatase inhibitors exemestane or anastrozole reduces the risk of developing breast cancer by 50–75%.
- Prophylactic bilateral mastectomy: reduces the risk of breast cancer by 99% in *BRCA* germline mutation carriers.
- Prophylactic bilateral salpingoopherectomy: decreases risk of ovarian cancer by 99% in *BRCA* mutation carriers.

Secondary prevention

- Weight maintenance and avoid obesity.
- Reduce alcohol to ≤1 serving/day.
- There is emerging evidence that physical activity lessens the risks of developing breast cancer.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Most women present with a nonpalpable mammographic abnormality. Only about 20% of these biopsied mammographic abnormalities will be breast cancer. Up to 30–40% of the cancers diagnosed based on mammographic abnormality will be DCIS.
- 15% of women have a breast mass that is not detected on mammogram.
- Women without access or who do not choose not to have mammograms typically present with a palpable breast or axillary mass with or without skin changes and advanced stage at diagnosis.
- Women with a palpable breast lesion should undergo biopsy of the lesion regardless of whether the imaging is positive or negative.

Differential diagnosis

Differential diagnosis	Features
Proliferative benign breast changes	Ductal hyperplasia, papilloma, radial scar, sclerosing adenosis, cysts, and fibroadenoma
Atypia	Atypical ductal or lobular hyperplasia
DCIS	A precursor lesion to invasive breast cancer characterized by the size of the lesion, nuclear grade, presence and extent of comedo necrosis, architectural pattern, and ER status
LCIS	Typically, found incidentally when a breast biopsy is performed Serves as marker of increased risk of developing breast cancer in either breast
Other cancers	Sarcoma and lymphoma

DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*.

History

- Family history of breast and ovarian cancer in the maternal and paternal lineage and the age of diagnosis of these cancers.
- Age of menarche.
- Age of menopause.
- Number of years of HRT.
- Prior exposure to mediastinal radiation.
- Establish any symptoms related to the breast (e.g. bloody nipple discharge, erythema of the skin, palpable masses in the breast or axillae) or suggestive of metastatic disease including any new or persistent symptoms in any part of the body.

Physical examination

Breast imaging and a clinical breast examination are always indicated. Clinical breast examination includes upright and supine inspection of the breasts, palpation of all the four quadrants of the breast and of the lymph-bearing areas including the cervical, supraclavicular, and axillae. A complete physical examination is also indicated.

Disease severity classification

Staging is based on the TNM system of the American Joint Committee on Cancer (AJCC 8th edition; website: https://cancerstaging.org).

List of diagnostic tests

- Pathology review of a breast biopsy requires histologic type, grade, and receptor classification.
- Tumor markers: CA 27-29, CA 15-3, and carcinoembryonic antigen (CEA) are sometimes useful to monitor treatment response in the metastatic setting. They should not be used to "screen" for metastatic disease in asymptomatic women.
- If metastatic lesion is suspected, biopsy is essential to document the histology and confirm ER/PR/HER2 status. For example, in women treated for early stage breast cancer the appearance of solitary lung nodule is a primary lung cancer in up to 50–60%. Discordance between receptor status of the primary breast cancer and metastatic site occurs in up to 10–15%.
- Oncotype DX® is a 21-gene reverse transcription-polymerase chain reaction (RT-PCR) assay commercially available since 2004, used in women with HER2 negative, ER positive, node-negative, or 1–3 node-positive breast cancers. The results are a recurrence score from 1 to 100. The recurrence score predicts the 10-year risk of distant metastases in node-negative women, and may predict the 5-year risk of distant recurrence in 1–3 node-positive disease. More importantly, only the high risk recurrence score group (≥25) derives benefit from adjuvant chemotherapy in addition to anti-estrogen treatments, whereas the low risk group (0–11) derives no benefit from the additional chemotherapy. Recently, the low risk recurrence score was prospectively validated (Sparano et al. 2015). The intermediate recurrence score group (11–25) has been reported (Sparano et al. 2018). For women over the age of 50 years, recurrence scores of <25 are associated with no chemotherapy benefit whereas recurrence scores ≥25 are associated with benefit. For women ≤50 years, recurrence scores of 16–20 are associated with a 1.6% absolute benefit of chemotherapy and scores of 21–25 are associated with 6.5% absolute benefit.
- A prospective validation of Oncotype DX was recently completed in axillary node 1–3 positive but has not been reported.
- Mammoprint is based on the 70-gene risk predictor and classifies into low risk (favorable) or high risk (unfavorable) prognosis. It is indicated for both ER positive and negative breast cancers. Prospective validation of its use as a prognostic test and a predictive test (i.e. which patients respond to chemotherapy) is available.
- PAM50 is a multigene RT-PCR test, which measures 50 classifier genes and five control genes. It can be used to categorize patients into five intrinsic breast cancer subtypes that confers prognostic information: luminal A, luminal B, HER2-enriched, basal-like, and normal-like. It is in commercial use.
- Breast Cancer Index is a five-classifier of late (after 5 years) recurrences in ER positive women. Prospective validation of this test is not available.

Lists of imaging techniques

- Bilateral digital diagnostic mammography and breast ultrasound. Breast MRI as clinically indicated (see section on Screening).
- Any new or persistent symptoms require imaging as clinically indicated. If the review of systems is negative, the likelihood of finding occult asymptomatic metastases is very low in clinical stages I–IIIA and no imaging or blood tests are recommended.
- In asymptomatic stage IIIB or higher, the likelihood of finding occult metastatic disease is higher and either a computed tomography (CT) scan of chest, abdomen, pelvis, and bone scan or positron emission tomography (PET)/CT is indicated.

- If, based on symptoms, central nervous system disease is suspected a brain MRI scan with contrast is indicated and is superior to a head CT with contrast.

Treatment

Treatment rationale

The primary goal of treatment for stages I–III is personal cure (i.e. dying of a cause other than breast cancer).

- Anti-estrogen treatments tamoxifen (for pre- and postmenopausal women) and aromatase inhibitors (only for postmenopausal women) are given in all cases of ER and PR positive breast cancers.
- Chemotherapy is routinely given to women with breast cancers that are HER2 positive, TNBC, ER/PR positive with high risk Oncotype DX recurrence score or Mammoprint in histologically proven multiple axillary node-positive disease.
- The primary goal of treatment for stage IV disease is to palliate symptoms, increase quality of life, and, in some cases, increase OS.

Table of treatment

Local treatment	Comments
Breast surgery	Multiple randomized controlled trials (RCTs) show that BCS (also called lumpectomy or partial mastectomy) with whole breast radiation/boost and modified radical mastectomy show the same OS. There is slightly higher overall local recurrence with BCS; however, the individual RCT varied with respect to adequacy of surgical margins and the use of boost. Standard treatment option in stage I and II breast cancers is BCS. However, both BCS and mastectomy options should be discussed. Absolute contraindications to BCS include: • Two or more primary tumors in different quadrants of the breast or diffuse malignant appearing calcifications throughout the breast on presurgical breast imaging • Breast cancer during pregnancy • Prior history of breast radiation • History of scleroderma • Persistently positive surgical margins after attempted surgical re-excisions of the lumpectomy bed Relative contraindications include: • Centrally placed tumor with removal of the nipple–areolar complex • Relatively large tumor in a smaller breast in which asymmetry would be the result of BCS (relative to the contralateral breast) Stage IIIA (T3 or >5 cm tumors with N0 or N1) breast cancers often receive neoadjuvant chemotherapy Absolute contradictions to breast surgery include: • Direct extension to skin or chest wall, ulceration, or skin nodules (T4, any N) • Fixed or matted axillary nodes (any T, with N2–N3) • Internal mammary and supraclavicular nodal positivity For noninvasive DCIS either lumpectomy with (or without) radiation, or mastectomy are standard options
Sentinel node biopsy (SNB)	Standard practice for stage I–III (operable) breast cancers is sentinel node mapping and biopsy. SNB reduces the risk of lymphedema vs. full level I and II axillary dissection without comprising OS

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Local treatment	Comments
Breast radiation	For invasive cancers: after BCS follows whole breast radiation/boost. After mastectomy, decisions about chest wall radiation are based on increasing the number of positive axillary nodes, initial tumor size, extranodal extension, or subtype of breast cancer For noninvasive DCIS: after lumpectomy whole breast radiation/boost is the standard practice. Obviating radiation is a consideration in women over the age of 70 years with stage I breast cancer who receive anti-estrogen treatments or women who have small, low grade, ER positive DCIS
Systemic treatments	Early stage I–III breast cancers: • RCTs of postoperative adjuvant chemotherapy vs. preoperative neoadjuvant chemotherapy show comparable clinical results. The advantages of neoadjuvant therapy are downstaging to allow BCS • The benefits of chemotherapy are greater in pre- than in postmenopausal women, in ER negative or low vs. high ER expression and high vs. low grade breast cancers • The use of anthracyclines (doxorubicin) in chemotherapy regimens for stage I–III breast cancer is controversial. This is because of the small risk of developing cardiomyopathy, about ≤1% with doxorubicin-based regimens and about 3% with trastuzumab/taxane-based regimens following doxorubicin-based regimens. It is important to distinguish doxorubicin-related cardiomyopathy (causes myocardial cell death and is related to total cumulative dose) from trastuzumab-related myocardial dysfunction (does not cause myocardial cell death, is not dose-related, and 50% of patients can be retreated with trastuzumab when their left ventricular fraction improves). Several randomized trials show that outcomes are similar or better (results of one randomized trial) with non-anthracycline than with anthracycline-based regimens. Women with pre-existing cardiac problems should receive non-anthracycline-based regimens Systemic treatment decisions are based on the expression of three receptors: ER, PR, and HER2 ER and/or PR positive, HER2 negative (luminal A: see Table 1.1): • ER and/or PR positivity is defined as ≥1% positive cells. Treated with anti-estrogen treatments such as tamoxifen (pre- and postmenopausal women) or one of the aromatase inhibitors (e.g. anastrozole, exemestane, or letrozole). RCTs of 10 vs. 5 years of tamoxifen show benefits favoring treatment for 10 years. RCTs of 10 vs. 5 years of aromatase inhibitor have been completed and the results show treatment durations of more than 5 years show no differences for the low risk patients, but the high risk multiple nodal positive patients may benefit. The MA-17 trial showed a benefit for 10 years of letrozole over 5 years but the patients in that trial had all completed 4–5 years of prior tamoxifen. The majority of benefit was in contralateral risk reduction • Oncotype DX assay is a predictive test (high recurrence score predicts [25 or greater] benefit from chemotherapy) ER and/or PR positive, HER2 positive (luminal B): • These breast cancers typically receive trastuzumab-based chemotherapy regimens and then anti-estrogens. • Luminal B is also defined by ER and/or PR positive and high proliferation rate as measured by Ki-67. However, the Ki-67 assays are problematic in varying methods and interpretation of cut-points that separate high and low proliferating tumors. Therefore, Ki-67 is not considered as a standard marker. The majority of non-HER2 positive luminal B cancers, but not all, are high grade. The Oncotype DX assay is also used in this group. Many will receive chemotherapy and then anti-estrogen treatments. Identification of luminal B, non-HER positive breast cancers will be easier when PAM 50 is routinely used to subtype breast cancers

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Local treatment	Comments
	HER2 positive: • For less than 3 cm, node-negative, adjuvant paclitaxel in combination with trastuzumab results in a 3-year invasive disease-free survival of over 97% • Trastuzumab and pertuzumab with concurrent chemotherapy (either docetaxel or paclitaxel alone for six cycles every 21 days alone, docetaxel and carboplatin for six cycles every 21 days, or cyclophosphamide and doxorubicin for four cycles every 2 weeks followed by 12 weeks of weekly paclitaxel) is standard practice as neoadjuvant therapy or postoperative adjuvant therapy (Table 1.2) • Trastuzumab given for 2 years has not been shown to be superior to 1 year • The Katherine Trial is for patients with residual disease after neoadjuvant HER2 targeted containing chemotherapy. The randomization was to 1 year of trastzumab emtansine (TDM-1) or trastuzmab. TDM-1 was statistically and clinically significant and is the new standard of care • Concurrent administration of anthracycline and trastuzumab results in an unacceptably high risk of cardiomyopathy and is contraindicated TNBC: • Postoperative adjuvant or neoadjuvant chemotherapy is the only option. TNBC responding to DNA-damaging drugs such as carboplatin or cisplatin are more frequent in *BRCA1* germline mutation carriers • The hallmark of TNBC is early distant recurrences (i.e. the first 1–2 years after completing treatment). Distant recurrences after 5–6 years are rare and most women who remain disease-free will experience personal cures. This is in contrast to ER positive, luminal A cancers in which ≥50% of metastatic recurrences occur after 5 years • Carboplatin added to paclitaxel increases the pathologic complete response rate in neoadjuvant chemotherapy. A trial of carboplatin added to paclitaxel in the postoperative adjuvant setting is ongoing • Poly (ADP-ribose) polymerase (PARP) inhibitors, inhibiting homologous recombination DNA repair, are still being evaluated in TNBC Treatment of stage IV metastatic breast cancer: • OS has improved for women with metastatic breast cancer • The first site of metastatic disease is bone only in 40% • Treatment continues until progression of disease or dose-limiting side effects in most cases • For women with ER positive metastatic disease, there is no advantage in OS to starting initial treatment with chemotherapy over anti-estrogen treatments • Besides ER expression, prediction of response to a subsequent anti-estrogen treatment is based on the prior response to current anti-estrogen treatment. Progression of disease ≤6–12 months usually predicts for no or minimal response to subsequent anti-estrogen treatment • RCTs demonstrate the mammalian target of rapamycin (mTOR) inhibitor, everolimus, when combined with exemestane (Bolero-2 trial) provides superior PFS but not OS relative to exemestane alone in postmenopausal women with ER positive, HER2 negative metastatic disease who progressed on an aromatase inhibitor as the first line treatment for metastatic disease. The main side effects of everolimus include mouth sores, myelosuppression, diarrhea, and pneumonitis (rare)

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Local treatment	Comments
	• In RCTs the cyclin-dependent kinase inhibitor 4 and 6, palbociclib, in combination with letrozole as first line treatment (Paloma III trial) and in combination with fulvestrant as second line treatment (Paloma III trial) for postmenopausal, ER positive, HER2 negative, metastatic disease improves PFS. The main side effect of palbociclib is neutropenia. The OS results of palbociclib trials are not yet available. In the second line treatment of ER positive metastatic disease, in planned subset analysis in those patients with prior endocrine sensitivity, fulvestrant plus palbociclib showed an OS advantage over fulvestrant plus placebo. During the past 2 years the Monarch (ambeciclib) and Monalessa (ribociclib) trials have been published showing essentially comparable benefits in PFS in the first line (with letrozole) and second line (with fulvestrant). There are no OS results as yet • Chemotherapy remains the standard of care for metastatic triple-negative breast cancer (TNBC), however TNBC is more immunogenic than other breast cancer subtypes. The FDA approved the combination of Atezolizumab and nab-paclitaxel in November 2018 for TNBC based on the Impassion130 trial. This demonstrated an improved PFS compared to nab-paclitaxel alone and the benefit was more pronounced (25 vs. 15.5 months) for those with PDL1 expressing tumors Chemotherapy: • Clinical trials, if available and the woman is eligible, should always be considered when discussing therapeutic options • The goals of treatment are to palliate symptoms, improve quality of life, and in some cases extend OS (in particular, OS in metastatic breast cancer has improved for women with HER2 positive tumors) • There are a number of single drugs and chemotherapy combination regimens that are Food and Drug Administration (FDA) approved or commonly used for metastatic breast cancer, neoadjuvant or postoperative adjuvant (Table 1.2) • For non-HER2 positive metastatic disease, sequential use of single drugs is preferred over combinations because of fewer side effects and generally no differences in OS. The use of combination chemotherapy results in higher response rates but at the expense of more side effects

Table 1.2 FDA-approved chemotherapy drugs and regimens in breast cancer.

Drug (metastatic)[¶]		Dose (mg/m^2)	Schedule (week/cycle[a])	Major side effects
Paclitaxel (T)	IV	80	Every week	Pain, alopecia, neuropathy
Nab[a]-T	IV	260	Every 3 weeks	Neuropathy
Docetaxel (D)	IV	100 or 75	Every 3 weeks	Myelosuppression; mucositis, alopecia, hand-foot; fluid accumulation[c]
Capecitabine	oral	2000	Days 1–14 every 3 weeks	Hand-foot; diarrhea
Vinorelbine	IV	15–20	Days 1, 8 every 3 weeks Days 1, 8, 15 every 4 weeks	Constipation/ileus; neuropathy
Gemcitabine	IV	1250	Days 1, 8 every 3 weeks Days 1, 8, 15 every 4 weeks	Myelosuppression

Table 1.2 (*Continued*)

Drug (metastatic)[¶]		Dose (mg/m^2)	Schedule (week/cycle[a])	Major side effects
Eribulin[d]	IV	1.4	Days 1, 8 every 3 weeks	Myelosuppression, alopecia, peripheral neuropathy
Ixabepilone	IV	40	Every 3 weeks	Myelosuppression, hand-foot, alopecia, peripheral neuropathy
Pegylated liposomal doxorubicin[d]	IV	40	Every 4 weeks	Hand-foot
HER2 (metastatic)[¶]				
D Trastuzumab (H) Pertuzumab (P)	IV	75 6 mg/kg[e] 420 mg[f]	Every 3 weeks[b] Every 3 weeks (HP)	Myelosuppression; mucositis, hand-foot, fluid accumulation[c], and diarrhea
THP	IV	80 6 mg/kg 420 mg	Every week[b] Every 3 weeks (HP)	Myelosuppression, alopecia, peripheral neuropathy, diarrhea
TH	IV	80 6 mg/kg	Every week[b] Every 3 weeks (H)	Myelosuppression, alopecia, peripheral neuropathy
Capecitabine and lapatinib	oral	2000 125 mg	Days 1–14 every 3 weeks Daily	Myelosuppression; hand-foot; diarrhea
TDM-1	IV	3.6	Every 3 weeks	Thrombocytopenia; neuropathy
HER2 (neoadjuvant) and adjuvant				
D CarboHP	IV	75 AUC = 6 6 mg/kg 420 mg	Every 3 weeks × 6 Every 3 weeks × 17 Every 3 weeks × 6	Myelosuppression, mucositis, alopecia, hand-foot, fluid accumulation[c], and diarrhea
Doxorbicin Cyclophosphamide (C)-THP	IV	60 600 80 2 mg/kg 6 mg/kg 420 mg	Every 2 weeks × 4 (AC) Weekly × 12 (T) Weekly × 12 (H) Every 3 weeks × 14 (H) Every 3 weeks × 4 (P)	Myelosuppression, mucositis, alopecia, hand-foot, diarrhea, cardiac (~3%), leukemia (≤0.1%)
THP	IV	80 2 mg/kg 6 mg/kg 420 mg	Every week × 12 (T) Every week × 12 (H) Every 3 weeks × 14 (H) Every 3 weeks × 4 (P)	Myelosuppression, alopecia, diarrhea
THP-Fluorouracil (F) Epirubicin (E) C	V	80 2 mg/kg 6 mg/kg 420 mg 500 75 500	Every week × 12 (T) Weekly × 12 (H) Every 3 weeks × 14 (H) Every 3 weeks × 4 (P) Every 3 weeks × 4	Myelosuppression, alopecia, diarrhea Myelosuppression, alopecia, cardiac (~3%), leukemia (≤0.1%)
TH	IV	80 2 mg/kg 6 mg/kg	Every week × 12 (T) Every week × 12 (H) Every 3 weeks × 14 (H)	Myelosuppression, alopecia, cardiac (~3%), leukemia (≤0.1%)

(*Continued*)

Table 1.2 (*Continued*)

Drug (metastatic)[¶]		Dose (mg/m^2)	Schedule (week/cycle[a])	Major side effects
TNBC (neoadjuvant)				
PCarbo-AC	IV	80 AUC 6 60 600	Every week × 12 (T) Every 3 weeks × 4 (Carbo) Every 2 weeks × 4 (AC)	Myelosuppression, alopecia, mucositis, cardiac (≤1%); leukemia (≤0.1%)
AC-T	IV	60 600 80	Every 2 weeks × 4 (AC) Every week × 12 (T)	Myelosuppression; alopecia, mucositis, cardiac (≤1%); pain, peripheral neuropathy, leukemia (≤0.1%)
Adjuvant				
AC-T	IV	60 600 80	Every 2 weeks × 4 (AC) Every week × 12 (T)	Myelosuppression; alopecia, mucositis, cardiac (≤1%); pain, peripheral neuropathy, leukemia (≤0.1%)
DC	IV	75 600	Every 3 weeks × 4	Myelosuppression; alopecia, mucositis, hand-foot, fluid accumulation
CAF	IV	600 60 600	Every 3 weeks × 6	Myelosuppression; alopecia, mucositis, cardiac (≤1%), leukemia (≤0.1%)
CEF	IV	500 75 500	Every 3 weeks × 6	Myelosuppression; alopecia, mucositis, cardiac (≤1%), leukemia (≤0.1%)
C Methotrexate (M)F	IV	600 50 600	Every 3 weeks × 6	Myelosuppression; alopecia[g], mucositis, diarrhea

[¶] Treatment until disease progression or dose-limiting side effects.
[a] Nanoparticle albumin bound (Nab).
[b] Chemotherapy until maximal benefits or dose-limiting side effects, then H continues.
[c] Taking dexamethasone before, during, and after treatment mitigates fluid accumulation.
[d] Three-month median OS advantage vs. physician's choice for women with ≥2 lines of chemotherapy for metastatic disease (Embrace RCT).
[e] First loading dose is 8 mg/kg then 2 or 6 mg/kg.
[f] First loading dose is 840 then 480 mg.
[g] Partial alopecia is common, but most women do not have to wear a wig.

Prevention/management of complications

Bone metastases

- Cause pain and skeletal-related events (SRE) including spinal cord compression, pathologic fracture, necessity of radiation to provide pain relief, and hypercalcemia.
- As adjunctive treatment to women with bone metastases, either every 1 or 3 month intravenous zoledronic acid, an osteoclast inhibitor, or monthly subcutaneous denosumab, a monoclonal antibody to the RANK ligand, for a 2-year duration are standard options. In an RCT comparing monthly zoledronic acid with denosumab the only endpoint that was statistically significant in favor of denosumab was the time to multiple SRE events. For OS and, for most individuals, SRE there were no significant differences between the two drugs. In cost-effectiveness analyses,

denosumab is about 20 times the cost of zoledronic acid. The main side effects of zoledronic acid are temporally associated fevers, myalgia, arthralgia, renal and osteonecrosis (very rare). The main side effects of denosumab are asymptomatic hypocalcemia and osteonecrosis (very rare).

- Orthopedic fixation of an impending pathologic fracture is always preferred to an operative procedure after fracture. Retrospective criteria for an impending pathologic fracture in a weight-bearing bone include pain, ≥50% cortical involvement, or metastasis ≥2.5 cm. After orthopedic fixation, a course of radiation therapy is usually indicated.
- Radiation is an effective means of providing pain relief if the pain is localized to one area or region of bone and systemic treatments and pain medications do not control the pain. Repeated radiation to large areas of the bone marrow can comprise systemic chemotherapy so if at all possible should be avoided.

Brain metastases

- Increased incidence of metastatic disease to brain in HER2 positive and TNBC subtypes.
- For solitary lesions in an area of the brain that is not critical for neurologic function resection of lesion followed by whole brain radiation, or stereotactic radiation, is used for smaller (up to ≤3 cm) and up to 1–3 lesions. For ≥4 brain metastases and for multiple lesions >3 cm whole brain radiation is generally indicated.

Cardiotoxicity

Trastuzumab is associated with reversible New York Heart Association (NYHA) class III–IV cardiomyopathy in 2–4%. In contrast to anthracycline-induced cardiomyopathy (occurs in ≤1% in women who receive a total cumulative dose of 240 mg/m^2), it is not dose-dependent, does not cause myocardial cell death, the ejection improves in most cases with cardiac medications, and retreatment is possible once the ejection fraction improves.

CLINICAL PEARLS

- When there is an opportunity to try anti-estrogen treatment first, then try it. There are fewer side effects and no advantages to chemotherapy first in the initial treatment of metastatic breast cancer.
- Most women with newly diagnosed invasive cancers will experience personal cures and die of something else.
- There has been enormous progress made in drugs that target the HER2 receptor. In the absence of HER2 targeted drugs ≤20 years ago, HER2 overexpression was an independent adverse prognostic factor. However, the multitude of drugs to target the HER2 receptor and pathways has changed the natural history of this subtype by improving OS.

Special populations

Pregnancy

The treatment of breast cancer during pregnancy can be modified in such a way that the mother can receive optimal breast cancer treatment without the risk of harming the fetus/baby. The basic principles are the following: (i) This is considered as a "high risk" pregnancy by most obstetricians and close communication between the oncologist and obstetrician is essential. (ii) Routine staging studies such as CT, bone, and PET scans are contraindicated. With appropriate shielding mammograms, chest radiographs and liver ultrasounds can be performed. (iii) Chemotherapy should be avoided in the first trimester, but can be given during the second and third trimesters without harm to the fetus in terms of increased congenital abnormalities. The babies that are delivered

are normal in terms of APGAR scores and developmental milestones. (iv) If breast surgery has to be performed during pregnancy the only option is mastectomy because radiation after BCS is contraindicated. (v) There is no evidence that a pregnancy subsequent to breast cancer treatment increases the risks of recurrence or decreases OS.

Elderly

- Risk of developing breast cancer increases with aging such that the lifetime risk of "1 in 9 women" will develop it in the sixth to ninth decades of life. Consequently, over the next 25 years and beyond most breast cancers will be in elderly women. Unfortunately, there is a relative lack of knowledge about this group because most RCTs over the past 40+ years either excluded women over 65–70 years or recruited only a minority of women in this age group.
- Women of this age often have comorbid conditions, the primary one being heart disease. For example, a woman who has coronary artery disease and a myocardial infarction has a greater risk of mortality from heart disease than from a stage I or II breast cancer. This has to be taken into consideration when discussing treatment options.
- It is functional age and comorbid disease rather then chronologic age that determines OS and treatment options. Matched for performance status and end organ function, the side effects and toleration of chemotherapy are similar in younger and elderly women.
- A comprehensive geriatric assessment should be performed in women aged 65 years and older to establish functional assessment. These can be CRASH score (https://www.moffitt.org/eforms/crashscoreform) or Cancer and Aging Research Group (CARG) Chemotoxicity calculator (www.mycarg.org).
- Several RCTs performed specifically in elderly women (65+ years) have established the following: (i) radiation can be omitted from BCS in selected stage IA, ER positive women treated with anti-estrogens. (ii) standard combination chemotherapy with either anthracycline or non-anthracycline-based adjuvant chemotherapy has better clinical outcomes than single-agent capecitabine.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Women with early stage breast cancer have a better OS than those diagnosed with later stages of disease. Hence, the emphasis is on screening mammography and early detection of breast cancer.
- African American (AA) women have worse OS than Caucasians. In part, this is because of access to care, with AA women presenting at more advanced stages. However, even controlling for stage of disease at initial presentation, AA women have higher mortality rates.
- Low BMI $\leq$18 or obesity with BMI $\geq$30 is associated with poorer prognoses.
- The 21-gene Oncotype DX assay recurrence score is prognostic is for 10-year risk of distant (metastatic) recurrence in women with ER positive, node-negative breast cancers and a prospective randomized trial in ER positive, axillary node 1–3 positive disease has been completed.

Follow-up tests and monitoring

Routine surveillance for asymptomatic women after stage I–III breast cancer treatment:

- History and physical examination every 3–4 months for the first 3 years, then every 6 months for years 4 and 5, then annually thereafter. Unless they receive anti-estrogen treatment for up to 10 years, in which case every 6 months until they finish treatment.
- Mammogram 6 months after radiation for BCS and then annually.

- Periodic review of family history of cancer and referral to a genetic counselor as clinically indicated.
- Bone density every 2 years for women on aromatase inhibitors, with recommended amounts for daily calcium intake (ideally from food sources) and vitamin D3.
- All the routine preventative health care that women without a history of breast cancer receive including immunizations and periodic nonbreast cancer screening examinations.

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Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-postive advanced breast cancer. N Engl J Med 2012;367:1783–1791.

Suggested websites

American Society of Clinical Oncology (ASCO). http://www.asco.org

National Comprehensive Cancer Network (NCCN). https://www.nccn.org/professionals/physician_gls/f_guidelines.asp

National Cancer Institute (NCI). http://www.cancer.gov/

Clinical Trials. http://www.cancer.gov/about-cancer/treatment/clinical-trial

Guidelines

National society guidelines

Title	Source	Date and weblink
National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Breast Cancer	Consensus Committee made up of surgical, radiation, and medical oncologists from NCCN member institutions	Version 1.2016 http://www.nccn.org/professionals/physician_gls/f_guidelines_nojava.asp
American Cancer Society (ACS)/American Society of Clinical Oncology (ASCO) Breast Cancer Survivorship Care Guideline	Systematic literature review performed by Expert Panel	2015 http://www.instituteforquality.org/american-cancer-societyamerican-society-clinical-oncology-breast-cancer-survivorship-care-guideline
ASCO Clinical Practice Guideline: Chemo- and Targeted Therapy for Women with HER2 Negative (or unknown) Advanced Breast Cancer	Systematic literature review performed by an Expert Panel	2014 http://www.instituteforquality.org/chemo-and-targeted-therapy-women-her2-negative-or-unknown-advanced-breast-cancer-american-society
ASCO Clinical Practice Guideline Focused Update: Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer	Systematic literature review performed by an Expert Panel	2014 http://www.instituteforquality.org/adjuvant-endocrine-therapy-women-hormone-receptor positive-breast-cancer-american-society-clinical
ASCO Clinical Practice Guideline: Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer	Systemic literature review performed by an Expert Panel	2014 http://www.instituteforquality.org/systemic-therapy-patients-advanced-human-epidermal-growth-factor-receptor-2-positive-breast-cancer
ASCO Clinical Practice Guideline Update: Sentinel Lymph Node Biopsy for Patients with Early-Stage Breast Cancer	Systematic literature review performed by an Expert Panel	2014 http://www.instituteforquality.org/sentinel-lymph-node-biopsy-patients-early-stage-breast-cancer-american-society-clinical-oncology
ASCO Clinical Practice Guideline Update: Use of Pharmacologic Interventions for Breast Cancer Risk Reduction	Systematic literature review performed by an Expert Panel	2013 http://www.instituteforquality.org/use-pharmacologic-interventions-breast-cancer-risk-reduction-american-society-clinical-oncology

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Title	Source	Date and weblink
ASCO Clinical Practice Guideline Update: Breast Cancer Follow-Up and Management After Primary Treatment	Systematic literature review performed by an Expert Panel	2013 http://www.instituteforquality.org/breast-cancer-follow-and-management-after-primary-treatment-american-society-clinical-oncology
ASCO Clinical Practice Guideline Update: Role of Bone-Modifying Agents in Metastatic Breast Cancer	Literature search using Medline and Cochrane Collaboration Library performed by an Expert Panel	2011 http://www.instituteforquality.org/asco-clinical-practice-guideline-update-role-bone-modifying-agents-metastatic-breast-cancer

Evidence

Type of evidence	Title and comment	Date and weblink
Genomic study	Molecular portraits of human breast cancer **Comment:** Paradigm shifting first evidence that breast cancer can be divided into subtypes (Table 1.1) based on molecular genetic profiling	2000 http://www.ncbi.nlm.nih.gov/pubmed/10963602
RCT	Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2 **Comment:** Pivotal trial that first demonstrated that trastuzumab improved the OS for women with HER2 positive metastatic disease	2001 http://www.ncbi.nlm.nih.gov/pubmed/11248153
Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Meta-analysis	Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials **Comment:** Largely of historic interest establishes multidrug adjuvant chemotherapy with an anthracycline-based chemotherapy (compared with no chemotherapy) reduces breast cancer mortality by 30% (absolute reduction in mortality in about 12% of women < 50 years) and 20% (absolute mortality reduction of about 6% in women aged 50–69). Five years of adjuvant tamoxifen irrespective of age and use of adjuvant chemotherapy (compared to with no treatment) reduces breast cancer mortality by 30% (absolute reduction in mortality of 9%)	2005 http://www.ncbi.nlm.nih.gov/pubmed/15894097
EBCTCG Meta-analysis	Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomized trials **Comment:** Radiation after BCS confers a small, statistically significant OS benefit in addition to improved local control	2011 http://www.ncbi.nlm.nih.gov/pubmed/22019144

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(*Continued*)

Type of evidence	Title and comment	Date and weblink
RCT	Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343 **Comment:** No OS benefit to radiation, but local/regional breast recurrences were 2% and 10% with and without radiation. Omitting radiation is a viable option	2013 http://www.ncbi.nlm.nih.gov/pubmed/23690420
RCT	Adjuvant chemotherapy in older women with early-stage breast cancer **Comment:** Standard multidrug adjuvant chemotherapy was superior to single-drug oral capecitabine. Provides justification for not undertreating women aged ≥65	2009 http://www.ncbi.nlm.nih.gov/pubmed/19439741
RCT	Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer **Comment:** First trial to show paclitaxel after standard doses of doxorubicin and cyclophosphamide improves disease-free and OS	2003 http://www.ncbi.nlm.nih.gov/pubmed/12637460
RCT	Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of OS from NSABP B-31 and NCCTG N9831 **Comment:** The addition of trastuzumab to adjuvant chemotherapy results in 10% absolute improvement in OS. These results are consistent with two other RCTs	2014 http://www.ncbi.nlm.nih.gov/pubmed/25332249
RCT	Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial **Comment:** Largest trial with longest follow-up that shows anastrozole was superior to tamoxifen in time to recurrence (TTR) by about 21% (absolute difference of 4.3%) but there was no difference in OS. Consistent with the results of two other RCTs of other aromatase inhibitors (exemestane or letrozole) vs. tamoxifen	2010 http://www.ncbi.nlm.nih.gov/pubmed/21087898
RCT	Effect of preoperative chemotherapy on the outcome of women with operable breast cancer **Comment:** Established that neoadjuvant and postoperative result in similar OS	1998 http://www.ncbi.nlm.nih.gov/pubmed/9704717
RCT	Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17 Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomized controlled trial **Comment:** These two RCTs established modern treatment of DCIS with BCS, radiation, and tamoxifen for ER-positive DCIS	1998 http://www.ncbi.nlm.nih.gov/pubmed/9469327 1999 http://www.ncbi.nlm.nih.gov/pubmed/10376613

(*Continued*)

Type of evidence	Title and comment	Date and weblink
RCT	Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer **Comment:** Established the use exemestane and everolimus for treatment of postmenopausal women who progressed on aromatase inhibitor	2012 http://www.ncbi.nlm.nih.gov/pubmed/22149876
RCT	The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first line treatment of estrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-III): a randomized phase 3 trial **Comment:** With median follow-up of 38 months, 27.6 vs. 14.5 months ($p < 0.0001$) in median PFS with letrozole + palbociclib vs. letrozole, respectively in postmenopausal women with ER-positive metastatic disease, first line treatment for metastases	2019 https://doi.org/10.1007/s/10549-018 05125-4
RCT	OS with palbociclib and fulvestrant in advanced breast cancer **Comment:** With a median follow-up of 45 months, OS for fulvestrant + palbociclib vs. fulvestrant + placebo in postmenopausal women with ER-positive metastatic disease was 35 versus 28 months ($p = 0.09$), as second line treatment for metastases. However, in a preplanned subset analysis in patients that had previouly responded to endocrine therapy (79% of overall population), the median OS was 40 months for combination versus 30 months (hazard ratio 0.72; 95% CI 0.55–0.94)	2018 https://www.ncbi.nlm.nih.gov/pubmed/30345905
RCT	Trastuzumab emtansine (TDM-1) in previously treated HER/2 overexpressing breast cancer **Comment:** The EMILA trial (versus lapatinib and capecitabine) and the TH3rRESA (versus physicians choice of standard chemotherapy) led to 6–7 month median OS favoring TDM-1. The MARIANNE trial was first line chemotherapy for metastatic HER2 overexpressing breast cancer patients randomizing to paclitaxel and trastuzumab, TMD-1, or TDM-1 and pertuzumab. These treatments were comparable	2012 https://www.ncbi.nlm.nih.gov/pubmed/23020162 2017 https://www.ncbi.nlm.nih.gov/pubmed/28526538 2017 https://www.ncbi.nlm.nih.gov/pubmed/28056202
RCT	PDL-1 inhibitor in triple negative breast cancer (TNBC) **Comment:** Metastatic TNBC were randomized to nab-paclitaxel + /– atezolizumab. The median trial follow-up was 12.9 months. Overall, there was a 1.7 month statistically significant improvement ($p = 0.0025$) for combination. In a preplanned interim subgoup analysis, in the TNBC group who had PDL-1 expression of ≥1% in tumor-infiltrating lymphocytes (41% of the total trial population), the overall median survial was 25 months for combination vs. 15.5 months for nab-paclitaxel alone (stratified hazard ratio for death was 0.62 (95% CI 0.45–0.86)	2018 https://www.ncbi.nlm.nih.gov/pubmed/30345906

Image

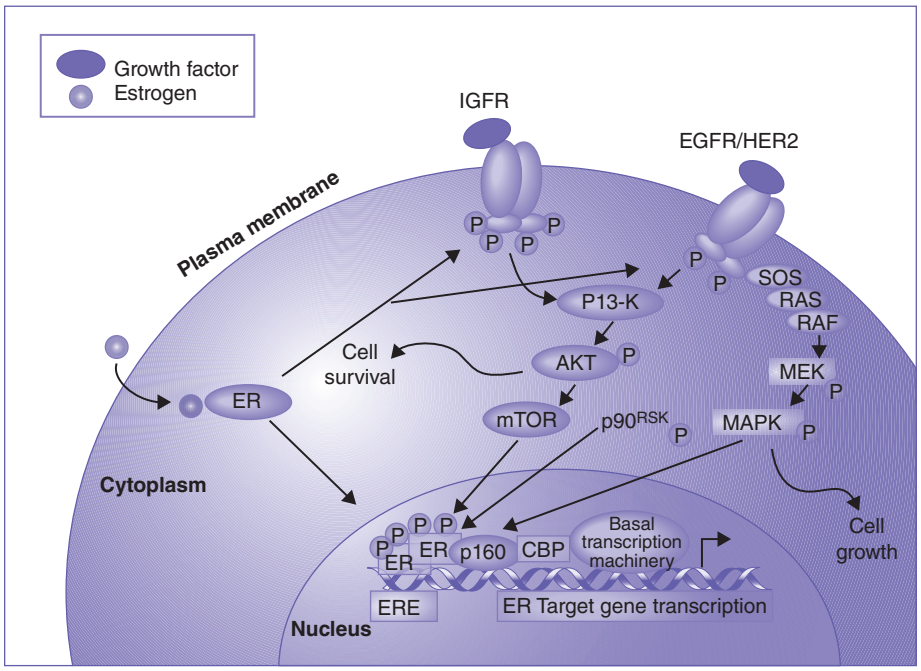

Figure 1.1 ER and HER2 pathways in breast cancer (used with permission).

Additional material for this chapter can be found online at:
www.wiley.com/go/oh/mountsinaioncology

This includes advice for patients, a case study, and multiple choice questions.