Learning Objective: Upon completion of this course, you will be able to describe the care of patients with breast cancer, including approaches to prevention, assessment of risk factors, screening and diagnosis methods, current treatment modalities, survivorship, and end-of-life issues.

Learning Objectives:

• Describe the pathophysiology and clinical manifestations of breast cancer.
• Discuss the epidemiology and risk factors of breast cancer.
• Summarize methods of screening, detecting, and diagnosing breast cancer.
• Explain the process of staging breast cancer.
• Describe the different types and categories of breast cancer.
• Compare various modes of treatment for breast cancer.
• Describe the possible side effects of treatment modalities.
• Discuss the psychological implications of having breast cancer.
• Summarize the major components of follow-up and survivorship care for breast cancer.
• Explain the unique concerns for end-of-life care for breast cancer patients and their immediate circle.

Breast cancer is the most common cancer among women in the United States and the second most common cause of cancer death in women (ACS, 2015a). Healthcare providers frequently manage women with breast cancer in the acute and chronic stages of the disease within the clinical setting. This course will discuss the pathophysiology, epidemiology, diagnosis, treatment, and survivorship aspects of managing patients with breast cancer.
PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The breast is made up of lobules (glands that produce milk), ducts (tiny tubes that carry lobules to the nipple), and stroma (connective and fatty tissue that surrounds the lobules and ducts, including blood and lymph vessels). Most of the lymph vessels in the breast lead to lymph nodes under the arm (axillary nodes).

Breast cancer normally arises in the epithelial cells that line the ducts and lobes of the breast, which are in constant turnover. These cells are generated continuously by a basal membrane and normally divide, migrate, and differentiate in a tightly controlled process. Cancer forms when internal (genetic alterations) or external (e.g., environmental and hormonal) factors interfere and the cells undergo an abnormal spectrum of changes, from hyperplasia to preinvasive to invasive and metastatic cancer.

If the cancerous cells are confined to the ducts or lobules, the cancer is called noninvasive or in situ. Breast cancer that has spread through the walls of the ducts or lobules into the surrounding fatty and connective tissue is referred to as invasive or infiltrating.

The most common sign of breast cancer is a **painless, hard lump with irregular edges**. However, two thirds of lumps are not cancerous but may be fluid-filled cysts, fibroadenomas (benign tumors), or pseudo lumps. Cysts can be aspirated if painful and are generally found not to be malignant. Fibroadenomas need to be biopsied to determine whether they are malignant. Pseudo lumps are breast lumps that may be caused by previous breast surgery, fat necrosis (dead fat), trauma from previous breast cancer treatment, or silicone that has migrated from an implant or injection site.

Warning signs of breast cancer may not be the same for everyone. Women should be aware of changes in the look and feel of their breasts as well as changes in the nipple or discharge from the nipple. Possible **warning signs** of breast cancer include:

- Lump, hard knot, or thickening inside the breast or underarm area
- Swelling, warmth, redness, or darkening of the breast
- Change in the size or shape of the breast
- Dimpling or puckering of the skin
- Itchy, scaly sore or rash on the nipple
- Pulling in of the nipple or other parts of the breast
- Nipple discharge that starts suddenly
- New pain in one spot that does not go away
Warning signs of breast cancer. (© 2016, Susan G. Komen. Used with permission.)

EPIDEMIOLOGY

Breast cancer strikes more women in the world than any other type of cancer except skin cancer. Breast cancer occurs in both women and men, although male breast cancer is rare. In 2013, over 3 million women were living with a diagnosis of breast cancer in the United States (NCI, 2016a). Breast cancer is the second major cause of cancer deaths for women of all ethnicities in the United States, following lung cancer.
According to the American Cancer Society (ACS), in the United States, approximately 246,660 new cases of invasive breast cancer were predicted to be diagnosed in 2016 in women and 2,600 in men. About 40,890 people (men and women) are expected to die from the disease. It is estimated that women today have a 1-in-8 chance of developing breast cancer in their lifetime (ACS, 2016a).

### Incidence

Historically, in the 1980s and 1990s, breast cancer incidence rates in the United States increased as a result of the implementation of screening mammograms, which identified many cancers that previously would not have been detected (ACS, 2015a). Data from 2003 to 2012 show that breast cancer incidence rates were stable in white women and increased slightly (by 0.3% per year) in black women, resulting in similar rates in blacks and whites (ACS, 2016a).

Breast cancer incidence and mortality rates vary widely among racial/ethnic groups, among age groups, and among populations in different geographic areas.

- Globally, incidence is highest among white women who live in industrialized countries.
- From 2008 to 2012, overall breast cancer incidence rates in the United States increased among non-Hispanic black (0.4% per year) and Asian/Pacific Islander (1.5% per year) women.
- During this same period, rates were stable among non-Hispanic whites, Hispanics, and American Indians/Alaska Natives.
- For the first time, breast cancer rates for non-Hispanic white and black women converged in 2012, reflecting a steady increase in incidence in black women and relatively stable rates in white women. At this time, incidence is highest in these two groups and lowest in Hispanic whites (ACS, 2015a).

By age, the great majority of women diagnosed with breast cancer are 45 years old or older. However, young black women (under age 40) have a higher incidence of breast cancer than their white counterparts and a less favorable prognosis. Their tumors are more aggressive, difficult to treat effectively, and usually larger and more advanced at the time of diagnosis (NCI, 2014a).

Approximately 1% of all breast cancer cases diagnosed each year are in men. In 2016, invasive breast cancer is estimated to be diagnosed in 2,600 men. Breast cancer is far less common in men than women, with a lifetime risk of about 1 in 1,000. Men are more commonly diagnosed with advanced breast cancer because of decreased awareness and delayed diagnosis and treatment (ACS, 2015a). The number of cases of breast cancer reported in men relative to the population has been stable over the past 30 years (ACS, 2016b). Routine screening mammograms are not recommended for men due to the rarity of the disease in males (ACS, 2015a).
Mortality

Young black women (age 40 or younger) have the highest breast cancer mortality rate of any ethnic group in the United States. Asian Americans/Pacific Islanders have the best survival rates (ACS, 2015a; NCI, 2014a). The reasons for these disparities are not clearly understood, but socioeconomics, genetics, environmental exposure, and limited access to healthcare likely all contribute. American Indians/Alaska Natives not only have the lowest incidence of breast cancer but also one of the lowest mortality rates. However, it is important to note when interpreting these statistics that it is possible that many cases of breast cancer may go unreported, particularly among rural women with limited access to healthcare.

While statistics are helpful, the bulk of our current statistical knowledge is based on white women of European descent. Although research on more diverse populations is increasing in the United States, the understanding of genetic risk among racial and ethnic groups is still being uncovered. For example, women with Ashkenazi Jewish ancestry have a higher risk of having a genetic mutation linked to breast cancer (Lynch et al., 2015).

RISK FACTORS

Breast cancer is a complex disease whose development is influenced by many factors; some of these risks can be modified and others cannot. The two most prominent risk factors are female gender and increasing age.

Nonmodifiable risk factors include the following:

- Age (65 and over)
- Female gender
- Race/ethnicity
- Family history
- Personal history of previous breast, endometrial, ovarian, and colon cancer
- Primary genetic mutations (gene mutations BRCA1, BRCA2)
- Other breast cancer susceptibility genes
- Benign breast conditions (e.g., atypical hyperplasia, radial scar, fibroadenoma)
- History of ductal or lobular carcinoma in situ
- High-dose radiation to the chest area at a young age (childhood cancer treatment or mantle radiation for Hodgkin disease or non-Hodgkin lymphoma before age 30)
- Dense breast tissue
- High bone mineral density
- Type 2 diabetes (independent of obesity)
• Reproductive factors
  o Early menarche (before age 12) and late menopause (after age 55)
  o Never having a pregnancy
  o Having first child after age 30
  o High levels of sex hormones
  o DES (diethylstilbestrol) exposure (during a pregnancy or in utero for daughters of mothers exposed during their pregnancy)

Modifiable risk factors include the following:

• Radiation exposure, such as repeated fluoroscopies (scoliosis or tuberculosis) or radiotherapy for Hodgkin disease (see note below under “Ionizing Radiation”)

• Postmenopausal hormone therapy (combination estrogen and progesterone)

• Lifestyle factors, such as:
  o Being overweight or obese, especially weight gain after the age of 18
  o Alcohol and drug consumption
  o Long-term, heavy smoking
  o Lack of physical exercise
  o Shift work (i.e., that disrupts sleep patterns)

• Reproductive factors
  o Recent use of oral contraceptives
  o Having first child after age 30

(ACS, 2016a)

Family History and Genetic Risk

Family history of breast cancer is a multifaceted risk factor. In general, a woman with a first-degree relative (such as a mother, sister, or daughter) with the disease has about twice the risk of developing breast cancer as a woman without such family history. In general, the more first-degree relatives a woman has with breast cancer, the greater her risk. In addition, if breast cancer diagnosis occurs at a young age in first-degree relatives, the risk is greater. These are key factors that suggest the possibility of an inherited type of breast cancer.

INDICATORS OF INHERITED BREAST CANCER

• History of breast cancer in maternal or paternal relatives

• Multiple cases of breast cancer in the same family
• Women diagnosed at a younger age (less than 50 years old)
• Ovarian cancer in the family
• Male breast cancer in the family
• Breast and ovarian cancer in the same woman
• Ashkenazi Jewish heritage
• Occurrence of bilateral or multiple ipsilateral breast cancers in a family member


Genetic mutations that have been identified include breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2). BRCA1 and BRCA2 genes are associated with familial breast and ovarian cancers and are implicated in the majority of hereditary breast cancers in the United States and Europe. About 5% to 10% of all breast cancers are caused by the BRCA1 and BRCA2 inherited gene mutations.

### GENETIC DISORDERS RELATED TO INCREASED RISK FOR BREAST CANCER

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene (mutation)</th>
<th>Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer (HBOC)</td>
<td>BRCA1, BRCA2</td>
<td>Breast (female and male), fallopian tube, ovarian, peritoneal, prostate, pancreatic</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome (LFS)</td>
<td>TP53</td>
<td>Adrenal, breast, colon, glioma, leukemia, lymphoma, neurofibrosarcoma, osteosarcoma</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>PTEN</td>
<td>Breast, endometrial, non-medullary thyroid, kidney, colorectal</td>
</tr>
<tr>
<td>Ataxia telangiectasia (A-T) (also referred to as Louis-Bar syndrome)</td>
<td>ATM</td>
<td>Breast, endometrial, gastric, glioma, skin</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome (PJS)</td>
<td>STK11</td>
<td>Colorectal, gastric, pancreatic, breast, ovarian</td>
</tr>
<tr>
<td>Neurofibromatosis 1</td>
<td>NF1</td>
<td>Peripheral nerve sheath, astrocytoma, glioma, pheochromocytoma, possibly breast</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>BLM</td>
<td>Breast, colon, cervix, esophagus, larynx, lymphoma</td>
</tr>
</tbody>
</table>

Source: Adapted from Lynch et al., 2015.

While BRCA1 and BRCA2 account for only approximately 5% of all breast cancer cases annually in the United States, those individuals inheriting these gene mutations have a 50% to 87% lifetime risk of developing invasive breast cancer. Studies of BRCA1 and BRCA2 mutations have revealed that persons of Ashkenazi Jewish descent have an increased incidence of these gene mutations. In fact, up to 2% of Ashkenazi Jewish women were found to have BRCA1 gene mutation (ACS, 2015a).
The discovery of genetic mutations brings forward the importance of obtaining accurate patient family history and referral for genetic counseling and testing when appropriate. Those known to have genetic mutations require very diligent monitoring and present the possibility of prophylactic measures such as bilateral mastectomy and/or oophorectomy.

**CRITERIA FOR BRCA GENETIC TESTING**

Criteria for evaluating patients for BRCA gene testing generally include the following:

- Ashkenazi Jewish heritage
- Breast, colorectal, or endometrial cancer diagnosed prior to age 50
- Bilateral breast cancer (personal or family history)
- Two primary cancers or clustering of breast and ovarian cancer in the family history
- Multiple cancers in the family occurring at a young age
- Rare cancer(s) occurring at any age
- Two or more primary types of BRCA1 or BRCA2-related cancers in a single family member
- Family history of male breast cancer

Source: Lynch et al., 2015.

The National Comprehensive Cancer Network has made available recommended criteria for genetic testing (see “Resources” at the end of this course).

**Exposure to Ionizing Radiation**

Exposure to radiation either through accidental occupational events or through radiation therapy for Hodgkin lymphoma, non-Hodgkin lymphoma, childhood cancers (e.g., Wilm’s tumor), postpartum mastitis, or arthritic conditions has a definite link to increased breast cancer risk (ACS, 2015a).

 Radiation increases the risk of breast cancer both by directly damaging DNA and by disrupting normal cellular and intracellular processes. The risk may be the highest for long-term Hodgkin disease survivors who received chest irradiation prior to age 30 as part of treatment. The risk appears to be both dose and age related. The risk for developing breast cancer from chest radiation is higher if the radiation exposure occurs during adolescence, when breast tissue is still developing (ACS, 2015a).

Thus, those who have been exposed to large amounts of radiation either inadvertently or therapeutically should be very closely monitored for development of breast cancer through a modified schedule of more frequent physical exams and medical imaging. Fortunately, advances
have been made in the field of radiation oncology. The delivery of radiation therapy is now much more precise, making it possible to deliver ideal doses to intended areas while sparing adjacent organs.

MEDICAL IMAGING

According to the National Cancer Institute, the small amount of radiation exposure received from common diagnostic procedures such as mammograms does not pose a significant risk (NCI, 2014b). Mammography equipment is highly regulated by the U.S. Food and Drug Administration (FDA). Machines today deliver a higher picture quality with a much lower dose of radiation (approximately 0.1 to 0.2 rads per scan).

Thus, the level of exposure to X-rays with mammography does not significantly increase breast cancer risk for women who have regular screening. However, prudence should be exercised in decisions about surveillance using medical imaging on women with known gene abnormalities or high previous exposure that predispose them to cancers.

Reproductive Factors and Estrogen

Reproductive factors associated with increased risk for breast cancer include early puberty, late menopause, childlessness, and delayed childbearing. All of these factors represent exposure to unopposed estrogen, particularly estradiol.

The landmark Nurses Health Study showed that in women with higher endogenous estrogen levels there is a strong association with hormone receptor–positive breast cancer, especially in postmenopausal women. The risk can be as much as twice that of women with lower estradiol levels (Rossouw et al., 2002).

Exposure to synthetic hormones in the form of oral contraceptives and/or postmenopausal hormone replacement therapy also increases the risk of breast cancer (ACS, 2014a). The awareness of this finding with subsequent decrease in use of these exogenous hormones in postmenopausal women likely contributed to the drop in incidence of breast cancer, as mentioned above.

Childbearing trends have changed over the past 40 years, with many women delaying childbirth until after age 30. However, the younger a woman is when her first childbirth occurs, the lower her breast cancer risk. Women who never become pregnant or who give birth to their first child after age 30 have an increased risk of breast cancer. Some studies have shown a protective effect from breastfeeding, while other studies have not. One explanation for this decreased risk is that early pregnancy and breastfeeding transforms the breast cells into their final mature phase. Breast cells that are fully mature may be less influenced by the effect of carcinogens (Hartmann & Loprinzi, 2012).

Cumulative exposure to estrogen over a women’s lifetime appears to have an impact on her risk for breast cancer. This exposure may be influenced from the cumulative history of her menstrual
cycle. Both early onset of menarche (<12 years) and later age at menopause (>55 years) may increase her exposure to endogenous hormones, which may ultimately increase breast cell proliferation and the possibility of cancer growth promotion (ACS, 2014a).

Starting in the 1940s and continuing for a period of 20 years, some pregnant women were given the drug diethylstilbestrol (DES) to lower the risk of miscarriage. Women exposed to DES have a 30% higher risk of developing breast cancer compared to women with no exposure to DES. In addition, research also shows that women born to mothers who took DES during pregnancy have a slightly higher risk of developing breast cancer as adults (ACS, 2015a).

Environmental and Lifestyle Factors

Environmental and lifestyle factors are gaining much attention in recent years related to breast cancer risk. These factors include diet, exercise, alcohol use, and exposure to other environmental agents.

DIET AND WEIGHT

One area of interest under study has been the influence of dietary fat intake on breast cancer incidence. Although there seems to be some association with high-fat diets, the results of numerous analyses have been inconsistent and additional research is needed.

However, being overweight or obese after menopause does increase a woman’s risk for breast cancer. One explanation may be that before menopause the ovaries produce most of the estrogen in the body, and fat tissue produces a small amount of estrogen. After menopause (when the ovaries stop making estrogen), most of a woman’s estrogen comes from fat tissue. Having more fat tissue after menopause can increase the chance of getting breast cancer by raising estrogen levels (Hartmann & Loprinzi, 2012). An added factor is that women who are overweight or obese tend to have higher blood insulin levels. Higher insulin levels have also been linked to breast cancer (ACS, 2014a).

EXERCISE

How exercise affects a woman’s risk for breast cancer is a new area of research. Many studies show that a lack of regular exercise can increase breast cancer risk. According to the ACS (2014a), evidence is growing that regular physical exercise can help reduce breast cancer risk. In the Women’s Health Initiative, 1.25 to 2.5 hours per week of brisk walking reduced risk by 18%.

Exercise may have an effect on the levels of estrogen and progesterone in the body. It may also reduce risk because regular exercise promotes a healthy weight. In postmenopausal women, reduced body fat means lower estrogen levels. Exercise may also boost the natural immune response, which can be protective against cancer (Hartmann & Loprinzi, 2012).
ALCOHOL CONSUMPTION

Over 40 large epidemiological studies since 1995 have provided consistent evidence that alcohol consumption significantly increases the risk of breast cancer, most specifically hormone receptor–positive type. The important mechanism involved appears to be higher estrogen and androgen levels with alcohol consumption, among other factors. When compared to nondrinkers, women who have one alcoholic drink a day have a very small increase in risk. Those who have two to three drinks daily have a 20% higher risk compared to women who do not drink alcohol (ACS, 2015a; ACS, 2014a).

SMOKING

For many years, researchers did not link smoking with breast cancer. However, recent research studies conducted on larger groups of women are showing a slightly increased risk for breast cancer among smokers. In addition, women are at an even higher risk the earlier they start smoking. The longer and the more a woman smokes, the higher her risk for breast cancer. Recent studies have also shown that long-term exposure to second-hand smoke also increases a woman’s risk for breast cancer (ACS, 2014a).

NIGHT-SHIFT WORK

Recent findings have indicated that night-shift work may increase breast cancer incidence. It is thought that melatonin production by the pineal gland, which aids in sleep and usually peaks between the hours of 1:00 a.m. and 2:00 a.m., has a protective effect against breast cancer, although the exact mechanism is not known. Thus, nocturnal work results in decreased levels of melatonin, as workers are exposed to light during normal sleeping hours (Wang et al., 2015). More studies are needed to understand this risk factor.

ENVIRONMENTAL EXPOSURES

Epidemiological and experimental studies have shown that women who are exposed to ionizing and non-ionizing radiation, pesticides, polycyclic aromatic hydrocarbons (benzene), and metals may have an increased risk of developing breast cancer (Fenga, 2016).

INCONCLUSIVE HYPOTHESES

Various other environmental causes for breast cancer have been studied but have not been definitely shown to cause any risk (ACS, 2015a). Exposure to hazardous materials such as solvents, dyes, and radioisotopes may increase general cancer risk. However, the evidence that exposure to these materials directly increases breast cancer risk is inconclusive (Hartmann & Loprinzi, 2012).
Other commonly discussed risk factors—including breast implants, abortion, antiperspirants, and hair dyes—have not been proven to be associated with an increased risk for breast cancer (ACS, 2014a).

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Factor</th>
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<tbody>
<tr>
<td>&gt;4.0</td>
<td>• Biopsy-confirmed atypical hyperplasia</td>
</tr>
<tr>
<td></td>
<td>• Age (65+ vs. &lt;65 years, although risk increases across all ages until age 80)</td>
</tr>
<tr>
<td></td>
<td>• Certain inherited genetic mutations for breast cancer (BRCA1 and/or BRCA2)</td>
</tr>
<tr>
<td></td>
<td>• Mammographically dense breasts</td>
</tr>
<tr>
<td></td>
<td>• Personal history of breast cancer</td>
</tr>
<tr>
<td>2.1–4.0</td>
<td>• High bone density (postmenopausal)</td>
</tr>
<tr>
<td></td>
<td>• High endogenous estrogen or testosterone levels</td>
</tr>
<tr>
<td></td>
<td>• High-dose radiation to chest</td>
</tr>
<tr>
<td></td>
<td>• Two first-degree relatives with breast cancer</td>
</tr>
<tr>
<td>1.1–2.0</td>
<td>• Ashkenazi Jewish heritage</td>
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<tr>
<td></td>
<td>• Early menarche (&lt;12 years)</td>
</tr>
<tr>
<td></td>
<td>• Height (tall)</td>
</tr>
<tr>
<td></td>
<td>• High socioeconomic status</td>
</tr>
<tr>
<td></td>
<td>• Late age at first full-term pregnancy (&gt;30 years)</td>
</tr>
<tr>
<td></td>
<td>• Late menopause (&gt;55 years)</td>
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<tr>
<td></td>
<td>• Never breastfed a child</td>
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<tr>
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<td>• No full-term pregnancies</td>
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<tr>
<td></td>
<td>• Obesity (postmenopausal)/adult weight gain</td>
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<td></td>
<td>• One first-degree relative with breast cancer</td>
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<tr>
<td></td>
<td>• Personal history of endometrial, ovarian, or colon cancer</td>
</tr>
<tr>
<td></td>
<td>• Recent and long-term use of menopausal hormone therapy containing estrogen and progestin</td>
</tr>
<tr>
<td></td>
<td>• Recent oral contraceptive use</td>
</tr>
<tr>
<td></td>
<td>• Alcohol consumption</td>
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</table>

PREVENTION STRATEGIES FOR WOMEN AT HIGH RISK

Women at high risk of developing breast cancer, such as those with BRCA mutations, may want to consider preventive surgery or the use of drugs to reduce their risk of developing breast cancer. Women considering decisions about prophylactic surgery or chemoprevention should be offered a second opinion, and all risks should be discussed, including changes in body image and long-term fertility.

Prophylactic Surgery

Women at very high risk of breast cancer may decide to have a prophylactic (preventive) mastectomy. This surgery removes one or both breasts. Removing both breasts before cancer is diagnosed reduces the risk of breast cancer by 90% or more. Prophylactic salpingo oophorectomy (surgical removal of the fallopian tubes and ovaries) reduces the risk of both breast and ovarian cancers in women who carry BRCA mutations.

Not all women who elect to have these surgeries would have gone on to develop breast cancer. Those considering prophylactic surgery should discuss the benefits, risks, and limitations with her provider. Additional surgeries may be needed as well, based on the option to have breast reconstruction after mastectomy.

Chemoprevention

The use of drugs to reduce the risk of disease is called chemoprevention. At this time, the FDA has approved two drugs for the prevention of breast cancer in high-risk women: tamoxifen and raloxifene. Tamoxifen can be used in both premenopausal and postmenopausal women, however raloxifene is only approved for use in postmenopausal women. These drugs lower the risk of both invasive breast cancer and ductal carcinoma in situ.

Women taking these drugs need to weigh the risks and benefits, including side effects. The most common side effect is menopausal symptoms. Premenopausal women taking tamoxifen can also experience menstrual changes. Serious side effects are not as common but may include blood clots and endometrial cancer.

Source: ACS, 2015a.

SCREENING AND DETECTION

Screening recommendations have changed recently and are the point of much discussion and controversy. The American Cancer Society recommends regular screening starting at age 45 (see “Mammography Screening Guidelines” below) (ACS, 2015b).

Alternatively, in 2009, the U.S. Preventive Services Task Force (USPSTF), in a groundbreaking decision, changed their recommendations to state that women should start screening at age 50. Their current recommendations state that women ages 50 to 74 be screened every two years with a mammogram. For women with an average risk for breast cancer, most of the benefit of
mammography results from biennial screening from ages 50 to 74 years. However, they also recommended that women under age 50 partner with their healthcare provider to decide whether to have a mammogram earlier based on individual history and the risks and benefits of the test (USPSTF, 2016).

These recommendations are for women at average risk of breast cancer, i.e., women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (e.g., BRCA), or a history of previous radiotherapy to the chest at a young age. Women should also discuss the potential benefits, limitations, and harms associated with breast cancer screening with their primary care provider.

Breast Self-Examination (BSE)

One of the biggest changes is that breast self-examination is no longer recommended as a regular screening method for average-risk women. However, it is important for health professionals to discuss the potential benefits and limitations. BSE is recommended for women of all ages who are at high risk for developing breast cancer. Although results of research indicate that BSE as a screening method has not been shown to improve survival, the fact is that many women (or their partners) discover their own breast cancers (ACS, 2014a).

For average-risk women, general breast awareness is recommended, which includes regularly taking note of any breast changes (such as shape or feel) while getting dressed or showering. Women should be aware of how their breasts look and feel and report any changes to their healthcare provider for a clinical examination. Finding a breast change does not always indicate breast cancer (ACS, 2014a).

Clinical Breast Examination (CBE)

The ACS no longer recommends CBE in conjunction with screening mammography for average-risk and asymptomatic women based on lack of clear benefits (ACS, 2015a). If breast cancer is suspected, a CBE should be performed by a physician or nurse practitioner skilled in the technique. The exam includes a visual inspection of the breasts, noting any changes in shape, size, and appearance. Breast tissue, nipples, and axillae are also palpated for lumps, abnormalities, and enlarged lymph nodes (ACS, 2014a).

Mammography

Mammography screening is the most widely used method of breast cancer detection and is considered the “gold standard.” It remains the only breast screening imaging modality associated with a reduction in breast cancer mortality.

Screening mammography aims to detect possible breast cancer in large populations of women who have no symptoms of the disease. A screening mammogram is a breast X-ray that is performed to detect suspicious masses or changes in breast tissue in women who have no signs
or symptoms of breast cancer. It requires two views of each breast—one from above (the cranial-caudal view) and one from an inside angle of each breast (the mediolateral-oblique view).

Many medical facilities now offer the use of digital mammography, which is a superior technology for dense breast tissue. Three-dimensional (3D) digital breast tomosynthesis also has the potential for benefiting many patients by slightly increasing mammographic cancer detection rates while significantly decreasing the screening false positive callback rate.

**Diagnostic mammography** aids in the diagnosis of an individual’s suspicious lesion and is more complex. A diagnostic mammogram may be used to investigate a lump or thickening, a suspicious finding, or another symptom of breast cancer that was previously detected by self-examination, clinical breast examination, or screening mammogram. A diagnostic mammogram may include more extensive views and magnification in an effort to better view the lump or abnormality. The radiologist may mark the site of the lesion prior to the scan.

Signs of cancer on a mammogram may include dense mass with irregular borders, suspicious clusters of microcalcifications, tissue distortion, and asymmetrical breasts. Any symptom of breast cancer should be thoroughly investigated until a definitive diagnosis is reached, and mammography is an appropriate part of that investigation.

**EFFECTIVENESS OF MAMMOGRAPHY**

Mammography is most effective in postmenopausal women and has been shown to reduce the risk of dying from breast cancer in women over age 50. In this age group, mammography can detect slow-growing (indolent) breast tumors, which are less likely to be fatal, at least two years before they reach palpable size.

It is less clear whether mammography screening for women under 50 significantly reduces breast cancer mortality in this age group. Premenopausal women have dense breasts, which may make detection by mammography more difficult. Also, breast cancer in younger women tends to be more aggressive, with a higher mortality rate. Thus, the fast-growing tumors in this younger age group may appear between mammography screens, making them less likely to be caught early.

There is also debate about the value of mammography screening for women over 75. This population is fast expanding as the “Baby Boomer” generation ages. Currently, the USPSTF (2016) states that “among women 75 years or older, evidence of benefits of mammography is lacking.” The ACS supports regular mammogram screening for women as long as their overall health is good and they have a life expectancy of 10 years or more. The ACS also continues to recommend mammograms as an effective and valuable tool for decreasing death from breast cancer, despite their limitations (ACS, 2014a).

**MAMMOGRAPHY SCREENING GUIDELINES**

The majority of breast cancers occur in postmenopausal women, which is why mammography was initially recommended to screen women over age 50. However, some screening guidelines have expanded to include women ages 40 to 49, as well as women in their 30s who are at high
risk for breast cancer. When determining when to begin screening, individuals should discuss their status and history with their primary care providers to determine the best screening schedule for them.

The **ACS guidelines**, updated in 2015, state the following:

- Women ages 40 to 44 should have the choice to start annual breast cancer screening with mammograms if they wish to do so. The risks of screening as well as the potential benefits should be considered.
- Women age 45 to 54 should get mammograms every year.
- Women age 55 and older should switch to mammograms every two years or have the choice to continue yearly screening.
- Screening should continue as long as a woman is in good health and is expected to live 10 more years or longer.
- All women should be familiar with the known benefits, limitations, and potential harms associated with breast cancer screening. They should also be familiar with how their breasts normally look and feel and report any changes to a healthcare provider right away.

The **National Cancer Institute**, and some—but not all—medical organizations also recommend that women begin annual mammography screening at age 45 and even earlier if their family history, genetic predisposition, or previous medical treatment puts them at high risk of developing breast cancer. (Women are considered at high risk of breast cancer if they have either a BRCA1 or BRCA2 mutation, a family history of breast cancer in either a first- or second-degree relative on either the maternal or paternal side, or due to other factors.)

The **USPSTF** (2016) recommends screening mammography every two years for women ages 50 to 74. After age 74, they also recommend that individuals partner with their healthcare providers to consider patient risk factors along with the benefits and harm of screening.

**The ACS and USPSTF offer differing recommendations on when to begin screening.** After the professional and public reaction to its 2009 guidelines, USPSTF removed their recommendation against screening for women ages 40 to 49 but maintained the statement that biennial screening in this age group be individualized (see above).

When making decisions about screening schedules, women and their healthcare providers should keep in mind that breast cancers in younger women (under 50) tend to be faster growing, even though they are not as common as those in older women. Thus, annual screening would make sense for the younger women, while biennial screening is reasonable for older women. Currently, guidelines state that women with a parent, sibling, or child with breast cancer are at higher risk for breast cancer and therefore may benefit more than average-risk women from beginning screening in their 40s.
MAMMOGRAPHY RISKS

For those women who have breast implants, clear imaging can be problematic depending on how the implant is placed. There is also a small risk of implant rupture due to mammography. Therefore, women with implants should inform their primary care provider and the technician of this fact ahead of time. They should also seek out a facility experienced in performing mammography on breasts with implants.

CASE

Susan, a 46-year-old white female with one child, age 20, comes in to the clinic for her annual exam. While having her vital signs taken, Susan reports to nurse Helene that she discovered a small lump on her right breast last week and that it is concerning her. Her last mammogram was two years ago and was normal. Her family history is negative for breast cancer. She states she is “fearful of too many mammograms,” as she heard “it can actually cause more breast cancer.”

After listening to her concerns, nurse Helene reassures Susan that regular screening mammograms are safe and do not increase the risk of breast cancer in average-risk women. She encourages Helene to discuss the lump with her doctor as well as the potential benefits and harms of screening. Next, Helene reports their conversation to Susan’s doctor and records it in the medical record.

FINDING AN FDA-CERTIFIED MAMMOGRAPHY FACILITY

Mammography facilities are the most carefully regulated type of radiologic imaging facility. The Mammography Quality Standards Act of 1992 established baseline quality standards for equipment, personnel, and practices in these facilities. FDA-certified facilities are listed by zip code on the FDA website. (See “Resources” at the end of this course.)

Other Imaging Studies

Mammography is currently the only technique suitable for widespread breast cancer screening. While mammography has a false-negative rate well below 10% for older women, in women with dense breast tissue, the false-negative rate can be up to 15%. Thus, for some women, further evaluation with additional methods may be recommended.

Other imaging studies in use include magnetic resonance imaging, ultrasonography, ductogram, molecular breast imaging, and other experimental imaging tests. These are generally used as an adjunct to mammography and primarily for diagnostic rather than screening purposes. However, MRI may be used for screening high-risk women in addition to mammography, and MBI may be used for screening women with dense breasts in addition to mammography.

Existing research has not established these techniques as stand-alone alternatives to mammography for routine breast cancer screening.
MAGNETIC RESONANCE IMAGING (MRI)

MRI uses a powerful magnetic field and radio waves (not radiation) to produce detailed images of tissue structures in the breast and has proved ultrasensitive in detecting breast cancer in high-risk women. To improve the clarity of detail showed by breast MRI, intravenous contrast material (gadolinium) may be injected just prior to or during the exam.

MRI has a high rate of false-positive results, which can lead to unnecessary breast biopsies. MRI is also far more expensive than mammography and much more time consuming, making it inappropriate for screening large populations. Future improvements in quality, technique, and cost-effectiveness may lead to better utilization of this tool.

The ACS (2015a) recommends that women with a lifetime risk of at least 20% include breast magnetic resonance imaging (MRI) as an adjunct to annual mammography screening starting at age 30.

ULTRASOUND

Ultrasonography (ultrasound) uses high-frequency sound waves to detect breast abnormalities. Ultrasound does not involve breast compression or radiation exposure. When sound waves encounter solid lumps in the breast, they bounce back. Fluid-filled cysts, which are normally not cancerous, do not impede the sound waves. In this way, ultrasound helps distinguish between cysts and solid tumors that may be cancerous. Ultrasound may assist in evaluating dense breast tissue that can obscure masses or abnormalities on a mammogram. Some facilities may use whole breast ultrasound as a screening modality.

Ultrasound is used mainly as an adjunct to mammography to help further characterize a suspicious lesion found on mammography or by physical exam. For example, if a cyst has complex features, ultrasound may be used to guide procedures such as fine-needle aspirates. Also, for women who are pregnant and have an area of suspicion, ultrasound is the first-line imaging method of choice in order to avoid fetal harm that may occur as a result of exposure to radiation from a mammogram (ACS, 2014a).

DUCTOGRAM

A ductogram (or galactogram) may be used to diagnose the cause of unusual nipple discharge. During this test, a very thin metal tube is inserted into the opening of a duct in the nipple that the discharge is coming from. A small amount of contrast material is administered, which outlines the shape of the duct on X-ray and can reveal tumors inside the duct. Fluid may be collected and checked for signs of infection or cancer cells.

MOLECULAR BREAST IMAGING (MBI)

MBI is a newer nuclear medicine imaging test for detecting breast cancer. It uses gamma detectors that measure uptake of Technetium (99mTc) sestamibi in tumors relative to normal
breast tissue. This technique is also known as a Miraluma. The test is being used along with mammograms to screen women with dense breasts.

EXPERIMENTAL BREAST IMAGING TESTS

New tests are currently being studied for breast imaging. These tests are in the earliest stages of research. Many of these tests are used with women who have dense breast tissue.

**Optical imaging tests** pass light into the breast and measure the amount of light that returns or passes through the tissue. The technique does not use radiation and does not require breast compression. Current studies are looking at combining optical imaging with other tests like MRI or 3D mammography to help diagnose breast cancer.

**Positron emission mammography (PEM)** uses sugar attached to a radioactive particle to detect cancer cells. The PEM scanner is approved by the FDA. This test is similar to a PET scan. The PEM scan may be better able to detect small clusters of cancer cells within the breast. Currently, this test is being researched with women with a diagnosis of breast cancer or other breast problems to detect which lumps are cancer.

**Electrical impedance imaging (EIT)** scans the breast for electrical conductivity. The science behind this test is based on the concept that breast cancer cells conduct electricity differently from normal cells. The test passes a very small electrical current through the breast and then detects it on the skin of the breast using electrodes taped to the skin. EIT does not use radiation or compress the breasts. This test is approved by the FDA to help classify tumors found on mammograms, however it is not approved for breast cancer screening.

Source: ACS, 2016c.

DIAGNOSIS OF BREAST CANCER

The diagnostic process may include a complete physical exam, assessment of risk factors, further mammographic evaluation, additional imaging tests, laboratory tests, and biopsy of the suspicious area. Biopsy is the most definitive step in the process, establishing whether the abnormality is benign (noncancerous) or malignant (cancerous), since no definitive diagnosis can be made without microscopic evaluation. If the diagnosis is breast cancer, the pathologist defines the type of cancer and whether it is invasive or noninvasive (in situ).

**Biopsies**

When a breast abnormality has been detected by mammography, the next diagnostic step is biopsy. A biopsy involves removal of a small sample of tissue in the suspicious lesion for analysis in the laboratory. There are different types of biopsies, and each has advantages and disadvantages. Biopsies are performed by surgeons, radiologists, and/or pathologists and evaluated by cytopathologists (pathologists who specialize in cancer).
Along with identifying cancerous cells, a biopsy can provide information about the type of cancer as well as hormone receptor status (ER, PR, and HER2), which is important in the process of recommending treatment strategies.

There are two categories of biopsies for breast tumors: needle biopsies and surgical (open) biopsies. **Needle biopsies** are generally outpatient procedures and include:

- Fine-needle aspiration biopsy
- Ultrasound-directed needle biopsy
- Vacuum-assisted core biopsy
- Stereotactic core-needle biopsy

**Surgical biopsies** include:

- Needle-localization biopsy
- Excisional biopsy

**NEEDLE BIOPSIES**

**Fine-needle aspiration (FNA) biopsy** uses a small hollow needle to aspirate fluid or cells from a palpable breast lump or mass. It is performed without anesthesia, sometimes in a physician’s office. If clear fluid can be aspirated from the lump, it is diagnosed as a benign cyst. However, if the fluid is bloody or if fluid cannot be aspirated, the cells in the needle are transferred to a slide and sent to the pathology laboratory for review.

The accuracy of the procedure depends on the experience of the person performing the procedure. The incidence of false-positive diagnosis is very low (1% to 2%), but the incidence of false-negative diagnosis is as high as 10%. Another disadvantage of the procedure is that because only cells are obtained and not tissue, it is more difficult to distinguish between noninvasive (in situ) and invasive cancer.

**Ultrasound-directed needle biopsy** is actually an FNA of a nonpalpable lump or mass that can be seen on an ultrasound screen. The ultrasound sensor (also called a transducer) is rolled over the breast until the lesion becomes visible on the screen, identifying the precise area for needle insertion. It is not a reliable method for evaluating microcalcifications (tiny specks of calcium) in the breast.

**Vacuum-assisted core biopsy** may be done using a special biopsy system. During this procedure, a small incision is made and a hollow probe is introduced and guided to the site of the abnormal area of the breast with X-rays, ultrasound, or MRI. Breast tissue is extracted through the probe. Multiple tissue samples may be removed through one small incision.

**Stereotactic core-needle biopsy** uses computerized mammography equipment to obtain tissue samples from nonpalpable abnormalities in the breast that can be seen on a mammogram, such as microcalcifications. The patient is positioned either sitting up or lying on her stomach, depending
on the equipment used. If she is lying on her stomach, the breast hangs down through an opening in a special table. The radiologist compresses the breast with mammography plates then pinpoints the area of concern using mammography. After the area is injected with a local anesthetic, the physician makes a tiny cut and inserts a biopsy probe (large hollow needle). The probe removes several small cores of tissue from the area, which are then sent to the pathologist.

This procedure generally takes less than an hour. In addition to mammogram, ultrasound, and MRI can be used to guide a core biopsy. To minimize post-biopsy pain, women are advised to wear a snug-fitting bra and apply ice packs as needed (Hartmann & Loprinzi, 2012).

SURGICAL BIOPSIES

Surgical biopsies are outpatient procedures but are usually done in the hospital or an ambulatory surgery center rather than a physician’s office.

Needle-Localization Biopsy

Needle-localization biopsy is a combined-specialty procedure, requiring coordination between the radiologist and radiology facility and the surgeon and the facility where the actual biopsy will be performed. The placement of the localization needle is usually done with local anesthesia since the patient’s cooperation during the procedure and subsequent transport to the operating room is necessary.

The goal is to pinpoint a mammographic finding, either microcalcifications or a small nonpalpable tumor that is to be excised. Using a mammography machine, the radiologist locates the area of concern and inserts a hollow needle into that area. A thin wire is inserted through the needle into the lesion. Then the needle may be withdrawn, leaving the wire in place. The needle may also be left in place to maintain the security of the wire’s position.

The patient is next taken to the operating room (OR). This often requires moving from one outpatient facility to another. Once the patient is in the OR, the biopsy may be done under local anesthesia, general anesthesia, or conscious sedation. Using the mammogram films (or in the case of digital mammography, the electronic image), the surgeon removes the needle if it is still in place and uses the wire as a guide to identify the tissue to be removed. This localization helps to avoid unnecessary removal of healthy tissue.

The specimen is anatomically oriented using two suture tags of distinct lengths; “long = lateral, short = superior” is a common system. The tagging code is recorded on the documentation that accompanies the tissue. These markings allow the pathologist to envision the specimen within the breast. This is especially crucial if additional breast tissue must be excised but a breast-conserving procedure is planned.

After the tissue is removed (and often while the patient is still in the OR), the tissue, accompanied by the preoperative X-rays, is sent to be X-rayed to ensure that it matches...
the suspicious area on the mammogram and to help orient the pathologist. From radiology, the tissue is sent to pathology for examination.

Needle localization is used in patients for whom a stereotactic biopsy procedure is not suitable. It is also necessary if either ductal carcinoma in situ (DCIS) or cancer is diagnosed by a stereotactic core biopsy and a part of the breast must be removed.

**Excisional Biopsy**

Excisional biopsy (also known as a lumpectomy or wide local excision) is performed by a surgeon, who removes an entire lump or mass plus a small margin of the surrounding normal tissue. It is the most common type of surgical biopsy.

Biopsy tissue may be sent as “fresh,” meaning it is not placed in a preservative solution and is intended for immediate examination by the pathologist. It must be moved quickly to its intended destination to avoid deterioration. A specimen may also be sent for examination in preservative solution. In this case, it need not be transported with the same sense of urgency.

**Laboratory Tests**

If a breast lesion is large and/or locally advanced—especially if any lymph nodes are involved—then the suspicion factor for distant metastases is raised and must be ruled out. The physician may order a number of blood tests to assess for signs of metastasis. For example:

- Serum alkaline phosphatase
- Calcium levels

Elevated serum alkaline phosphatase may signal liver or bone metastases. Hypercalcemia may indicate advanced cancer.

**Imaging Studies for Metastases**

The lungs are a common site for breast cancer metastases. Therefore, a chest X-ray is generally ordered during the diagnostic process. CT scans of the liver and brain are recommended only if metastases are suspected in those areas. Bone scans are done only if laboratory tests suggest the presence of bony metastases or if there are other known areas of metastases coupled with clinical presentation of bony pain. Positron emission tomography (PET) scans have proved more effective in detecting soft tissue metastases than metastatic bone lesions. However, the PET/CT combination is replacing CT in detecting soft tissue metastases because of its increased effectiveness (ACS, 2014a).
TUMOR GRADE

Tumor grade is an additional part of the pathology examination of the breast tissue. The grade is based on how normal or abnormal the cells appear when examined microscopically. The lower the grade, the better the prognosis.

The grade is based on three features of the tumor: tubule formation, nuclear grade, and mitotic activity. Each of these features is given a score of 1 to 3.

- **Tubule formation.** Normal breast ducts are shaped like small tubes. Cancer cells tend to change and look more distorted as cancer progresses. A tissue sample that shows more than 75% tubular structures is scored with a 1. Tubular composition of 10% to 75% is scored with a 2. If less than 10% of the cells have tubular form, the score is 3.

- **Nuclear grade.** The nuclear grade is based on how the nucleus of each cell appears. A sample that contains mostly regular and normally shaped nuclei (well-differentiated) is given a score of 1. A score of 2 is assigned to cells that show a moderate increase in size and variability. Tissue samples that contain cells that have a greater variation of size and structure of the nuclei (poorly differentiated) are given a score of 3.

- **Mitotic activity.** Mitosis is the process of cell division. The score for mitotic activity reflects the number of cells that are dividing within the total of the cells observed. A score of 1 indicates slow growth, 2 indicates intermediate growth, and 3 indicates fast growth.

The scores of each of these measurements are added together to obtain an overall tumor grade (a total score ranging from 3 to 9 points).

- **Grade 1** (3–5 points): Low-grade or well differentiated
- **Grade 2** (6–7 points): Intermediate-grade or moderately differentiated
- **Grade 3** (8–9 points): High-grade or poorly differentiated

Source: NCI, 2013a.

Biomarker Tests

Biomarkers are substances (i.e., hormone receptors or growth factors) that are present in cancer cells and help the cancer grow and spread. Testing for biomarkers can indicate specific characteristics of tumors that may help determine which adjuvant treatment would be most effective in treating and preventing recurrence of the cancer.

The standard of care is to test breast tumors for hormone receptor status, including estrogen receptors (ER) and progesterone receptors (PR), along with human epidermal growth factor receptor 2 (HER2/neu) oncogene at the time of initial diagnosis (ACS, 2014a). Cancer treatments
target these specific biomarkers by inhibiting the growth factors or blocking the hormone receptor to stop or slow the cancer growth.

**ER AND PR TESTING**

ER and PR biomarker tests are performed at the time of initial biopsy. When breast tumors are found to be ER- and/or PR-positive, the pathologist will also report on the percentage of tumor cells with receptors and the degree of receptor positivity.

In the case of ER- and/or PR-positive status, the cancer cell proliferation is stimulated by either the presence of estrogen and/or progesterone and can be treated with hormone therapies (e.g., tamoxifen or aromatase inhibitors), which are designed to interfere with the hormone stimulation of the cancer cells. These types of tumors are more common in postmenopausal women.

Tumors that are ER- and/or PR-negative do not obtain benefit from hormone therapy and need to be treated with other modalities.

A relatively new tool available to help guide treatment in ER-positive/HER2/neu-negative breast cancer patients is gene profile testing (e.g., Oncotype DX and MammaPrint). Performed on paraffin-embedded tissue samples, the gene profile testing provides individualized prediction of chemotherapy benefit and 10-year distant recurrence to inform adjuvant treatment decisions in certain women with node-negative, early-stage invasive breast cancer (ACS, 2014a).

Because of the recurrence score component, physicians and patients are able to make more informed decisions, lowering the amount of unnecessary chemotherapy, thereby sparing patients potential side effects. The most appropriate time for Oncotype DX to be utilized is after surgically obtained pathology by immunohistochemistry shows ER-positive status and before adjuvant chemotherapy has begun. The efficacy of the Oncotype DX was clinically validated in over 4,000 patients across 13 studies and is now included in both National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines.

**Oncotype DX** test is most often used for tumors that are small (1 cm or less) and have not spread to lymph nodes, however it can be also be used for more advanced tumors. The test looks at 21 genes in cells from tumor samples to determine a recurrence score, which is a number between 0 and 100:

- Tumors with a recurrence score of 17 or below have a low risk of recurrence if they are treated with hormone therapy. Women with these cancers would probably not benefit from chemotherapy.
- Tumors with a score of 18 to 30 are at intermediate risk of recurrence. Some women with these cancers might benefit from chemotherapy.
- Tumors with a score of 31 or more are at high risk of recurrence. Women with these cancers are likely to benefit from chemotherapy in addition to hormone therapy.
MammaPrint test can be used to help determine how likely breast cancers are to recur in a distant part of the body after initial treatment. The test looks at the activity of 70 different genes to determine if the cancer is low risk or high risk. To date, this test has not been studied to see if the results are useful in guiding treatment.

HER2 TESTING

HER2/neu is a gene normally found in breast tissue; it is involved with cell division. In about 20% to 30% of women with breast cancer, HER2 is amplified or overexpressed. Purely HER2-positive breast cancer tends to be more aggressive, does not respond to hormone therapy, and may not be as responsive to conventional treatment as HER2-negative cancer. Studies have shown that women with this breast cancer subtype have an increased risk of relapse and shorter survival rate without HER2-directed therapy. Targeted therapies such as trastuzumab (Herceptin) and lapatinib (Tykerb) are proving successful, which is why establishing HER2 status at the onset of diagnosis is so important (ACS, 2014a). (See also below under “Herceptin.”)

Two FDA-approved methods to test for HER2 are immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). IHC utilizes a special staining process on fresh or frozen tissue obtained from breast biopsy to detect HER2 protein overexpression on the cell membrane surface. If IHC is not strongly positive, then the sample is sent for the more definitive FISH test. FISH quantifies the number of gene copies in the cell nucleus and requires a modern epifluorescence microscope equipped with high-quality fluorescence filters.

The American Society of Clinical Oncology/College of American Pathologists practice guidelines were established for HER2/neu testing for breast cancer. These guidelines emphasize the importance of using a laboratory that is accredited and meets proficiency requirements. There is still room for improvement in the standardization of all methodologies. If there is any doubt about test results, testing should be redone.

A third, newer test approved by the FDA for HER2/neu that is being used increasingly is chromogenic in situ hybridization (CISH). CISH uses conventional bright-field microscopy in its evaluation, enabling detection of HER2/neu gene copies with conventional peroxidase reaction. CISH testing is faster and easier to perform than FISH and also does not require any special equipment that does not already exist in routine histopathology labs. Most pathologists are not familiar with the fluorescence microscopy required in FISH, so CISH is a practical alternative that is easier and less time-consuming to learn.

Researchers continue to seek more effective treatments for breast cancer based on molecular genetic characteristics of tumors that fail to respond to existing therapies. A number of other biomarkers are being studied as possible targets for new drug development.

**CASE**

Nancy has just been diagnosed with ER- and PR-positive cancer, and she has already had surgery to remove the tumor. She is unsure about her next steps for treatment and has scheduled a visit with her nurse practitioner, Angela, to discuss her options. The oncologist working with
Nancy has mentioned to Angela that the patient is very angry about her diagnosis and afraid of the side effects of hormonal treatments.

When Angela meets with Nancy, her goals for education include:

- Exploring the patient’s emotional state. She begins by stating, “Receiving a diagnosis of cancer is scary; it is normal to feel upset and angry about what is happening to your body. Let’s start by talking about your biggest fears at the moment.”

- Asking the patient to verbalize what she knows. This may help clarify fears.

- Reviewing the treatment options and discussing the facts about hormonal treatment, including risks and benefits.

- Asking the patient what information she would like to have to further understand her diagnosis and treatment.

- Recommending a peer support group or mentor to help ease the patient’s fears about treatment and side effects.

As Angela wraps up her visit with Nancy, she also asks whether Nancy has any other questions that have not covered together and schedules a follow-up phone call for one week later to check in with Nancy to see how she is doing.

STAGING

Staging describes the extent of cancer in the body. The stage is based on whether the cancer is invasive or noninvasive, the size of the tumor, lymph node involvement, and metastasis to other parts of the body. The stage of a cancer (on a scale of 1 to 4, with 4 being the most advanced) describes how advanced the disease is and helps determine the course of treatment. Many breast cancers today are detected at stage 1 or 2. In situ cancer, usually ductal carcinoma in situ (DCIS), is called Stage 0.

There are several different staging systems in use. This section discusses one of the most widely used systems, the American Joint Committee on Cancer **TNM System** for breast cancer, which is one of the oldest classification systems. The \( T \) refers to tumor size, \( N \) refers to the axillary lymph node involvement, and \( M \) refers to any distant metastasis. The treatment team uses this system to evaluate the stage of the disease and plan treatment. Once the TNM status is known, the cancer can be assigned a clinical stage.

**T—Tumor Size**

The smaller the tumor, the lower the risk of cancer recurrence and the higher the chance of survival. If it seems likely that the cancer has spread beyond the breast and lymph nodes, the oncologist may order additional blood tests, X-rays, ultrasound, CT scans, and/or bone scans to check for cancer in other organs.
TUMOR SIZE (T) CLASSIFICATIONS

<table>
<thead>
<tr>
<th>Staging Number</th>
<th>Diameter of Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor (occult primary)</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (DCIS, LCIS, or Paget’s disease of the nipple with no tumor)</td>
</tr>
<tr>
<td>T1</td>
<td>≤2 cm (3/4 inch) in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>&gt;0.1 cm but ≤0.5 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>&gt;0.5 cm but ≤cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>&gt;1 cm but ≤2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;2 cm but ≤5 cm (2 inches) in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>&gt;5 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size growing into the chest wall or skin (includes inflammatory breast cancer)</td>
</tr>
</tbody>
</table>

Source: ACS, 2016d.

N—Lymph Nodes

Lymph nodes are small oval structures that filter lymph as it flows through lymphatic vessels and on to the blood stream. These nodes act to filter out particulate matter, especially bacteria and cancer cells, from entering the blood stream. They may in time become the avenue through which cancer spreads to other parts of the body.

LYMPH NODE (N) CLASSIFICATIONS

<table>
<thead>
<tr>
<th>Staging Number</th>
<th>Node Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed (previously removed)</td>
</tr>
<tr>
<td>N0</td>
<td>No sign of cancer in the nodes</td>
</tr>
<tr>
<td>N0(i+)</td>
<td>Micrometastases found by IHC of &lt;200 cells and &lt;0.2 mm</td>
</tr>
<tr>
<td>N0(mol+)</td>
<td>Negative by IHC, but cells detected using PCR*</td>
</tr>
<tr>
<td>N1</td>
<td>Cancer has spread to 1 to 3 axillary (underarm) lymph node(s), and/or tiny amounts of cancer are found in internal mammary lymph nodes (those near the breast bone) on sentinel lymph node biopsy</td>
</tr>
<tr>
<td>N1mi</td>
<td>Micrometastases (tiny areas of cancer spread) in 1 to 3 lymph nodes under the arm; the areas of cancer spread in the lymph nodes are ≤2 mm across (but ≥200 cancer cells or ≥0.2 mm across)</td>
</tr>
<tr>
<td>N1a</td>
<td>Cancer has spread to 1 to 3 lymph nodes under the arm with at least one area of cancer spread &gt;2 mm across</td>
</tr>
</tbody>
</table>
N1b  Cancer has spread to internal mammary lymph nodes, but this spread could only be found on sentinel lymph node biopsy (it did not cause the lymph nodes to become enlarged)

N1c  Both N1a and N1b apply

N2  Cancer has spread to 4 to 9 lymph nodes under the arm, or cancer has enlarged the internal mammary lymph nodes (either N2a or N2b, but not both)

N2a  Cancer has spread to 4 to 9 lymph nodes under the arm, with at least one area of cancer spread >2 mm

N2b  Cancer has spread to one or more internal mammary lymph nodes, causing them to become enlarged

N3  Any of the following:

N3a  Either cancer has spread to 10 or more axillary lymph nodes, with at least one area of cancer spread >2 mm, or cancer has spread to the lymph nodes under the clavicle (collar bone), with at least one area of cancer spread >2 mm

N3b  Either cancer is found in at least one axillary lymph node (with at least one area of cancer spread >2 mm) and has enlarged the internal mammary lymph nodes, or cancer involves 4 or more axillary lymph nodes (with at least one area of cancer spread >2 mm) and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy

N3c  Cancer has spread to the lymph nodes above the clavicle with at least one area of cancer spread >2 mm

*A newer technology, PCR is a molecular test that detects very small numbers of cells (<200) that cannot be seen even by IHC (immunohistochemistry) staining. Neither these tiny areas, sometimes called isolated tumor cells, nor micrometastases detected by IHC change the staging of breast cancer at this time. Experts are studying micrometastases and PCR results with patient outcomes in hopes of finding an application for staging in the future.

Source: ACS, 2016d.

**M—Metastasis**

Metastasis (spread) of the cancer beyond the breast and underarm (axillary) nodes is classified as shown in the table below. Generally, the smaller the cancer, the less likely it is to have spread. The most common sites for breast cancer metastasis are the bone, brain, lungs, and liver.

<table>
<thead>
<tr>
<th>METASTASIS (M) CLASSIFICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staging Number</strong></td>
</tr>
<tr>
<td>Mx</td>
</tr>
<tr>
<td>M0</td>
</tr>
</tbody>
</table>
Small numbers of cancer cells are found in blood or bone marrow (found only by special tests), or tiny areas of cancer spread (≤0.2 mm) are found in lymph nodes away from the breast

Spread to distant organs is present (the most common sites are bone, lung, brain, and liver)

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<table>
<thead>
<tr>
<th>TNM STAGING FOR BREAST CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>IIA</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>IIB</td>
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<tr>
<td></td>
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<tr>
<td>IIIA</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>IIB</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>

*T1 includes T1mic (microinvasion ≤0.1 cm in greatest dimension)

Source: ACS, 2016d.

Stage designation may change if postsurgical imaging studies reveal the presence of distant metastases provided that the studies are carried out within four months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy (chemotherapy or hormone therapy given prior to surgery for breast cancer).

**TYPES OF BREAST CANCER**

Carcinoma of the breast is not just one disease but a group of different types of cancer that originate either in the ducts or the lobules of the breast. Each type has different effects on individual patients depending on age, general health, access to healthcare, comorbidities, and stage of the cancer at diagnosis.
There are two basic categories of breast disease: **invasive** (also called infiltrating) and **noninvasive** (also called in situ). Each can occur in either the ducts or the lobules of the breast. If noninvasive cancer breaks through the cell wall and invades the surrounding tissues, the cancer may metastasize to distant organs, becoming a potentially fatal malignancy (ACS, 2014a).

![Parts of the breast and the lymph nodes and lymph vessels near the breast.](image)

**Invasive Breast Cancers**

**INVASIVE DUCTAL CARCINOMA**

Invasive ductal carcinoma accounts for about 80% of cases and is the most common form of breast cancer (ACS, 2014a; Hartmann & Loprinzi, 2012). Originating in the ducts of the breast, invasive ductal carcinoma breaks through the wall of the duct into the breast tissue. It commonly forms a hard lump, which feels much firmer than fibroadenomas (benign breast lumps). On a mammogram, it usually appears as a mass edged with tiny spikes (spiculation).
INVASIVE LOBULAR CARCINOMA

Invasive lobular carcinoma originates in the lobules of the breast, where the milk is produced before it enters the ducts of the breast. It accounts for about 10% of breast cancer cases (ACS, 2014a). It generally does not form a lump but more of a thickened area. Lobular carcinoma is also more difficult to see on a mammogram than ductal carcinoma. A number of research studies have linked invasive lobular breast cancer with use of hormone replacement therapy.

Noninvasive/In Situ Breast Cancers

DUCTAL CARCINOMA IN SITU (DCIS)

The most common type of noninvasive carcinoma (83%) occurs in the ducts of the breast and is called ductal carcinoma in situ. About 40% to 60% of DCIS cases go on to become malignant. Widespread use of screening mammography has dramatically increased the number of known cases of DCIS since 1973, particularly in premenopausal women. DCIS now accounts for approximately 20% of all new breast cancer diagnoses in the United States (ACS, 2014a).

Ninety percent of DCIS is seen on a mammogram as microcalcifications. Benign calcifications tend to be round or oval, uniform in density, and scattered in the breast tissue. Suspicious microcalcifications may vary in shape, size, form, and density and are usually clustered in a linear or segmental pattern. Based on the mammogram, the radiologist classifies the
calcifications as benign, probably benign, indeterminate, or suspicious. Although mammograms can detect calcifications, only a biopsy can determine whether they are DCIS.

Diagnosis of DCIS depends on the pathologist’s interpretation of biopsy results and may be controversial. Second opinions are important because appropriate treatment depends on an accurate diagnosis. Patients seeking a second opinion should arrange to take their tissue slides and tissue blocks containing cell samples to a second pathologist. In general, a diagnosis of DCIS carries an excellent prognosis.

**Determining Treatment for DCIS**

How best to treat DCIS remains controversial. Some women choose watchful waiting to avoid immediate surgery. However, many choose the same treatment used for invasive cancer, which could include surgery (lumpectomy or mastectomy), radiation therapy, and possibly hormonal therapy to prevent recurrence, depending on hormone status.

Three key factors in determining treatment for DCIS are: 1) the extent of disease in the breast or the size of the DCIS as measured by the pathologist; 2) the status of the margins of the biopsy tissue; and 3) the grade of the DCIS. Grade is the most important of these and refers to the structure of the cancer cells and their growth patterns.

- **Histologic grade** describes how closely the cancer cells resemble normal cells. Low-grade tumor cells look more like normal cells and grow more slowly than high-grade cells, which look irregular and unlike normal cells. High-grade tumor cells in DCIS are thought to be more likely to become invasive over time.

- **Nuclear grade** refers to the rate at which the cells proliferate (divide to form more cells). Cells that proliferate rapidly are faster growing and more aggressive than those that divide more slowly. The nuclear grade is based on the percentage of cells that are dividing.

Although high-grade DCIS is more likely to become invasive, it can be controlled more effectively than low-grade DCIS, which can be more widespread within the breast. Mastectomy over lumpectomy may be recommended if any of the following conditions apply:

- There are two or more areas in the breast with DCIS >5 cm apart (multicentric), or there are diffuse, malignant-appearing microcalcifications in the breast

- There are persistent positive margins after surgical lumpectomy that attempted to remove all of the DCIS

- The patient is not a candidate for radiation therapy, which usually follows lumpectomy
• The patient has extremely dense breast tissue, which may make detection of recurrence difficult

• A BRCA gene mutation is present in the patient (Hartmann & Loprinzi, 2012)

Sentinel lymph node biopsy may be recommended for those patients with extensive DCIS who choose mastectomy. If cancer cells are found in the sentinel node(s), axillary dissection can also be completed at the same time as the mastectomy (Harlow & Weaver, 2016).

Research is ongoing both in the laboratory and in clinical trials for DCIS, with the goal of identifying and minimizing treatment for low-risk DCIS lesions while improving treatment of high-risk DCIS lesions to reduce recurrence rates and prevent development of invasive disease (Collins et al., 2016).

LOBULAR CARCINOMA IN SITU (LCIS)

Lobular carcinoma in situ, which accounts for about 11% of in situ breast diagnosis, is characterized by a clustering of unusual cells in the lobules of the breast and is also referred to as lobular neoplasia (ACS, 2016e). LCIS is considered abnormal cell growth but is not classified as a cancer.

Women with a diagnosis of LCIS have an increased risk of developing future invasive cancer in either breast, not only in the breast containing the LCIS. Pleomorphic LCIS (cells look more atypical) is associated with an even higher risk for developing invasive breast cancer, and as such, physicians may recommend surgery to remove this type of LCIS.

According to the American Cancer Society, no immediate treatment is recommended, but close surveillance of both breasts via yearly CBE and mammograms is warranted for most women with LCIS. Additional options may include bilateral prophylactic mastectomy and the use of chemoprevention (ACS, 2016e).

Atypical Carcinomas

Some unusual types of breast cancer are more difficult to diagnose and treat. These include triple-negative breast cancer, inflammatory carcinoma, Paget’s disease of the breast, and breast cancer during pregnancy or lactation.

TRIPLE-NEGATIVE BREAST CANCER

Women whose tumors are ER-negative, PR-negative, and HER2/neu-negative are said to have triple-negative breast cancer. This is a rare subtype of breast cancer more common among young women and those of African or Hispanic ancestry. It is highly aggressive, with distinct patterns of metastasis, and does not respond to hormone therapy or targeted therapy.
Most BRCA1-associated breast cancers are triple negative. Brain and other visceral metastases are more common in triple-negative breast cancer than are bone metastases.

**INFLAMMATORY CARCINOMA**

Inflammatory breast cancer (IBC) is the most malignant form of breast cancer and accounts for about 1% to 3% of all breast cancers in the United States. Some experts think IBC may be more common but underreported because it can be difficult to diagnose (ACS, 2014a). IBC is usually classified as stage IIIB or stage IV, indicating that it has metastasized to distant sites at the time of diagnosis.

This aggressive subtype may be mistaken for an infection because it is characterized by swelling, pain, and reddened, warm skin over the breast. The inflamed appearance is caused by invasion of cancer cells into the subdermal lymphatic channels. If antibiotics do not rapidly change the appearance, biopsy should be performed.

Like triple-negative breast cancer, IBC is more common in young African American women than in white women. It is also more commonly found in overweight or obese women.

Once a uniformly fatal disease with only an 18-month survival rate from time of diagnosis, IBC can now be treated more effectively. Research and a multidisciplinary team approach to treatment offer hope of a 5-year survival rate of approximately 40% (ACS, 2014b). Neoadjuvant chemotherapy is the standard of care. For those women whose tumors are HER2-positive, trastuzumab (Herceptin) is added to the regimen.

**PAGET’S DISEASE OF THE BREAST**

Paget’s carcinoma is a very rare cancer, accounting for only 1% of breast cancer cases. It primarily affects the nipple, presenting as itching or burning with superficial erosion or ulceration. In some cases, there is no breast mass. Like inflammatory breast cancer, Paget’s disease of the breast is often misdiagnosed, in this case as dermatitis, delaying proper diagnosis.

If cancerous changes are confined to the nipple, the prognosis is excellent. If a breast mass is present, the cancer may have spread to the axillary nodes or beyond. Treatment may include lumpectomy or simple mastectomy, depending on the extent of disease. Lumpectomy followed by radiation therapy is recommended to reduce the risk of recurrence (ACS, 2014a).

**BREAST CANCER DURING PREGNANCY OR LACTATION**

Breast cancer during pregnancy or breastfeeding is rare, but it can occur. Even though the tumor may be felt, both the woman and her primary care provider may mistake it for normal pregnancy-related changes in the breast, delaying diagnosis. This delay means that in two thirds of cases, the cancer has spread to the lymph nodes before it is discovered.
Depending on the stage of the pregnancy at the time of diagnosis, some women may choose to terminate the pregnancy before beginning treatment. Other women may choose to have a mastectomy during pregnancy and follow up with chemotherapy after the baby is born. However, studies have shown chemotherapy can be delivered safely during the second and third trimesters. Radiation treatment is not given during any stage of pregnancy due to the high risk of fetal harm (ACS, 2014c).

Understandably, younger women who have not started or completed their families may be concerned about their subsequent fertility as well as increased mortality by becoming pregnant after breast cancer. Most research so far has shown that pregnancy is possible and safe for both the fetus and the mother after early breast cancer treatment in young women without increasing the risk of recurrence. It is important for women to discuss fertility prior to treatment in order to plan for best outcomes (ACS, 2013).

TREATMENT OF BREAST CANCER

For many years, breast cancer was assumed to be a localized disease, and the treatment of choice was also localized: a radical mastectomy. However, when it was shown that these often disfiguring and debilitating surgeries were not improving survival or decreasing recurrence rates, this practice was abandoned.

As technology gets ever more sophisticated at detecting cancer cells, the view of breast cancer as a systemic disease gains more support. Thus, treatment of breast cancer today generally includes some combination of localized (surgery and radiation therapy) and systemic treatments (chemotherapy, hormonal therapy, targeted biological therapies, or immunotherapy).

Surgery is often the primary treatment for breast cancer, followed by radiation therapy. Depending on a number of factors, chemotherapy and/or hormone therapy may be administered over weeks or months. The medical oncologist may recommend one or more of these therapies, depending on the patient’s age and the stage and other characteristics of the tumor.

The goal of systemic treatment is to destroy any cancer cells that have moved beyond the breast to other areas of the body and to achieve long-term remission of the cancer. Medical scientists previously thought that a tumor had to reach a certain size before cancer cells moved into the bloodstream and traveled to other parts of the body. However, research has shown that cancer cells can migrate out of the breast very early in the development of a tumor. This is why systemic therapies (chemotherapy, biological therapy, immunotherapy, and/or hormone therapy) are recommended for premenopausal women with breast cancer even if there is no evidence of cancer in the lymph nodes.

Radiation therapy, chemotherapy, hormone therapy, and targeted biological therapy are referred to as adjuvant therapy, or therapies given after surgical intervention. However, there are situations when the sequencing of surgery and the administration of systemic therapies may need to be modified.

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Some practitioners prefer to administer chemotherapy and/or hormone therapy before surgery to remove the tumor, which is called **neoadjuvant therapy**. Neoadjuvant therapy may shrink large tumors, thereby enabling patients to have a lumpectomy rather than a mastectomy. It also enables the oncologist to evaluate a drug’s effectiveness in an individual patient.

Timing of neoadjuvant therapy also has implications for lymph node assessment (see below). Current practice is to perform sentinel lymph node biopsy (SLNB) before systemic therapies (Harlow & Weaver, 2016). If no cancer cells are found in the sentinel node(s), the patient can avoid axillary lymph node dissection and reduce the risk of lymphedema, a painful, disfiguring, chronic swelling that can affect the entire arm and hand.

**Surgical Treatment**

Surgery is a cornerstone of treatment for breast cancer. Whether it precedes or follows systemic therapy, however, depends on a number of factors, including the stage of the cancer, the age of the patient, and the preferences of the treatment team. Women with breast cancer may have a lumpectomy or one of three types of mastectomy (surgery to remove the breast).

Depending on the patient’s age, general health, and the size, type, and stage of the tumor, she may need only surgery and perhaps radiation therapy. But many women, especially those who have not reached menopause, may need to consider adjuvant systemic therapy: chemotherapy, hormonal therapy, or targeted biological therapy such as trastuzumab (Herceptin).

For almost two decades, conflicting studies and meta-analysis have created controversy on whether timing breast cancer surgery according to the patient’s menstrual cycle results in a better outcome. An extensive review of the Cochran Database by a research team in 2011 concluded that timing of surgery in regard to menstrual cycle phase did not show significant effect on survival in breast cancer patients. Konoff-Cohen and colleagues (2016) recently confirmed these findings with the results of a meta-analysis.

**LUMPECTOMY**

Also called segmental mastectomy or breast-conserving surgery (BCS), lumpectomy is the removal of the tumor and a narrow margin of the surrounding tissue. The margin is taken to increase the chance that all of the cancer cells are removed. This type of surgery allows as much of the breast tissue as possible to remain. Because tumors are now detected at an earlier stage and often are smaller in size, lumpectomy is a common procedure.

Lumpectomy may not produce a good cosmetic result for a woman who has a large tumor in her small breast. However, large tumors sometimes can be reduced prior to surgery either by neoadjuvant chemotherapy, endocrine therapy, or biologic therapy (e.g., HER2-directed) making lumpectomy a viable option. This also shows whether the tumor is responding to the specific therapy.
Current options for treatment include lumpectomy followed by 5 to 6 weeks of daily radiation therapy, five days a week, to destroy any remaining cancer cells that could cause recurrence or metastasis. Additional options may include accelerated partial breast irradiation and proton beam radiation (see also below under “Types of Radiation”). Radiation therapy reduces the locoregional recurrence rate and risk of breast cancer death (EBCTCG, 2011).

Some women, particularly older women with very small, slow-growing tumors (<1 cm), may choose not to have radiation therapy (NCI, 2016b).

**MASTECTOMY**

Mastectomy is a general term for removal of the breast. A mastectomy may be performed when a lumpectomy is not possible or based on the preference of the woman. There are three types of mastectomy: simple, modified radical, and radical.

- **A simple** mastectomy involves the removal of the breast tissue, skin, areola, and nipple, but not the lymph nodes. This procedure is generally used when axillary lymph nodes do not need to be removed, as evidenced by a negative sentinel node examination.

- **A modified radical** mastectomy involves the removal of the entire breast, including the skin, areola, and nipple, along with the axillary lymph nodes, but leaves the chest wall muscles intact.

- **A radical** mastectomy involves removal of the entire affected breast, the underlying chest muscles, the lymph nodes under the arm (axillary node dissection), along with some additional fat and skin. Radical mastectomies are rarely used today. This type of mastectomy is generally limited to cases when cancer has spread to the chest wall muscles.

Some women with cancer in one breast may choose to have the other breast removed at the time of their mastectomy. This is called a bilateral mastectomy, and removal of the other breast is considered a prophylactic (preventive) measure. Prophylactic mastectomy reduces the risk of breast cancer recurrence, but it is not an absolute guarantee because of the systemic nature of the disease.

**CASE**

Clara is a 50-year-old nulliparous, perimenopausal woman who was diagnosed with high-grade, nondiffuse DCIS. She has requested a visit with the nurse practitioner a week after a visit with her physician in which she was informed of her diagnosis and given treatment options. Clara was presented with the option to have a mastectomy with no further treatment (and immediate reconstruction, if she so desired) or lumpectomy followed by six weeks of radiation therapy. Unsure which to choose, she wants to discuss her options in more detail and ask for a referral for a second opinion. Clara raises the concern about time off from work required to recover from surgery, although she liked the statistical evidence, which shows that 90% of women did not recur after a mastectomy for DCIS.
Stefanie, the nurse, explains to Clara that recovery from mastectomy surgery usually takes about 7 to 10 days for the immediate surgical recovery and about 4 to 6 weeks for a fuller recovery, depending on the type and extent of reconstruction. With the other option, breast-conserving surgery, she would need to recover both from the more minor surgery, followed by radiation treatments five days a week for about six weeks. While noninvasive, this option causes fatigue during treatments that may persist for weeks beyond completion of the course.

After this discussion, Clara states she feels a mastectomy would be best in her situation. Stefanie gives her names of some possible surgeons and urges Clara to have all her questions answered before making her final decision.

LYMPH NODE ASSESSMENT AND REMOVAL

Lymph nodes are part of the immune system and linked by tiny vessels within the entire lymphatic system. Lymph nodes and the lymph vessels drain the excess fluid that is not absorbed by blood vessels. Lymph nodes filter out foreign substances such as bacteria and cancer cells as part of the body’s immune system.

In addition to breast surgery, surgeons will examine the underarm lymph nodes for cancer cells using either an axillary lymph node dissection or sentinel lymph node biopsy. Lymph node assessment is performed for two reasons: 1) to tell whether the cancer has spread beyond the breast, and 2) to remove any cancerous nodes. Oncologists use this information in staging the tumor and as a basis for planning optimal treatment (NCI, 2016b).

**Axillary lymph node dissection (ALND)** involves removal of a large number of axillary lymph nodes for examination by a pathologist. Formerly a part of all breast cancer surgeries, axillary dissection has been replaced in many cases by a newer procedure called sentinel lymph node biopsy.

**Sentinel lymph node biopsy (SLNB)** is also called sentinel lymph node dissection. This newer procedure offers a less traumatic alternative for determining whether the cancer has spread beyond the breast. The SLNB procedure focuses on finding the specific lymph nodes (sentinel nodes) that are first to receive drainage from the breast tumor.

SLNB is most appropriate for women with early-stage breast cancer with clinically negative axillary nodes. For women who have axillary nodes identified positive for cancer cells with the SLNB, ALND completion should be performed. Physical examination, imaging studies, and tumor size help determine the most appropriate type of lymph node sampling.

SLNB results in fewer complications and less lymphedema than ALND. The procedure is usually done at the same time as either lumpectomy or mastectomy. Before the tumor is removed, a radioactive substance is injected into the area surrounding the tumor. About an hour later, in the operating room, the surgeon injects a special dye near the tumor and makes a small incision in the underarm area. By tracking the path of the dye and the radioactive substance, the surgeon can identify and remove the sentinel node (or up to three nodes) where cancer cells from a breast tumor would reach first.
The node(s) are sent to the pathology laboratory for examination while the patient is still in surgery. If no cancer cells are found in the sentinel node(s), no further nodes are removed—only the tumor itself. If cancer cells are found, however, the remaining nodes are removed and analyzed using standard axillary dissection technique (Harlow & Weaver, 2016).

In a landmark study, the National Surgical Adjuvant Breast and Bowel Project B-32 established that SLN resection proved to be 97% accurate in predicting whether clinically node-negative patients had cancer in their remaining lymph nodes. As time progressed, reanalysis of these same patients showed that overall survival, disease-free survival, and regional control were statistically equivalent in clinically node-negative women with breast cancer who had SLN resection compared with those who had conventional ALND (Harlow & Weaver, 2016).

SIDE EFFECTS

Potential side effects of surgery include lymphedema in the arm and hand, numbness, pain, reduced range of motion, and infection of the arm and chest on the affected side.

**Lymphedema**

Lymphedema is the interstitial collection of protein-rich fluid due to disruption of lymphatic flow. It is a common complication of axillary node dissection and radiation therapy. Breast cancer treatment is the leading cause of secondary lymphedema (NCI, 2015a).

When the patient has both axillary surgery and radiation, the risk of lymphedema increases. Women who have both SLNB and radiation therapy are also at increased risk for developing lymphedema. Most women who develop lymphedema will do so within three years of surgery, but it is important that patients understand it remains a lifetime risk (Dominick et al., 2013; NCI, 2015a).

**Signs and symptoms** of lymphedema include:

- Fullness, aching, pain, or heaviness in the arm
- Feeling of tightness of the skin of the arm and hands
- Reduced range of motion of the affected arm
- Clothing or rings that no longer fit on the affected side (NCI, 2015a)

The risk and extent of developing lymphedema depend on whether and how many lymph nodes are removed and whether or not radiation treatment is added to surgery. Women who are overweight or obese are also at higher risk for the development of lymphedema (Dominick et al., 2013; NCI, 2015a).
It is critical to recognize lymphedema at the earliest possible stage to educate the patient and initiate treatment to prevent worsening of the condition. The table below describes the stages of lymphedema based on severity.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reversible lymphedema: soft, pitting edema that can be completely resolved by prolonged elevation of the limb</td>
</tr>
<tr>
<td>2</td>
<td>Spontaneously irreversible lymphedema: clinically evident pitting edema, positive Stemmer sign (a thickened skin fold at the base of the second toe or second finger)</td>
</tr>
<tr>
<td>3</td>
<td>Lymphostatic elephantiasis: severe fibrotic response, tissue volume, papillomas, cysts, fistulas, and hyperkeratosis; recurrent infections</td>
</tr>
</tbody>
</table>

Source: NCI, 2015a.

Risk of lymphedema is lifelong after breast cancer surgery or radiation therapy, especially when axillary lymph nodes are involved. Therefore, patients need to reduce risks of developing the disorder through precautionary measures such as:

- Controlling their weight
- Avoiding arm constriction (no restrictive clothing or blood pressure cuffs on the affected side)
- Avoiding punctures (no injections, IVs, blood draws, or acupuncture on the affected side)
- Using compression garments as appropriate
- Avoiding extreme temperatures, such as with hot tubs
- Keeping the arm clean and dry; applying moisturizer daily
- Avoiding resting the arm below the heart or sleeping on the affected arm
- Wearing gloves when gardening or using household cleaners
- Avoiding carrying heavy over-the-shoulder bags or purses on the affected side
- Monitoring for signs and symptoms of infection (fever, swelling, redness, pain, and heat) and seeing a physician for evaluation immediately (NCI, 2015a)

It is imperative that nurses and healthcare providers instruct patients on the above symptoms to report and precautionary measures to take both before and after surgery as well as reviewing this during treatments and follow-up appointments.
While there is no cure, **treatment** for lymphedema is available and is best started at the first sign of swelling. The goal of treatment is to decrease the swelling as much as possible and maintain the limb at its smallest size. This helps prevent or eliminate infections and minimize discomfort. Treatments include complete decongestive therapy, manual lymph drainage, and compression, as prescribed by a physical therapist, occupational therapist, or other certified lymphedema specialist.

### CASE

Susan comes into the infusion suite for her second cycle of chemotherapy, removing her sweater to allow Agnes, the oncology nurse, access to her Medi-port. While preparing to access Susan’s port, Agnes notices some mildly reddened abrasions to the forearm on Susan’s mastectomy side. She compares both arms and notes mild swelling to the hand of her affected side. Susan states, “My rose bush got me while I was pruning it. I washed the scratches and put Neosporin on it as soon as I came in.”

Upon questioning, Susan admits her affected arm has been “feeling heavy” and that she had to remove her ring because “it felt a little tight.” Agnes reminds Susan these are classic signs of early lymphedema, which could possibly have been brought on by the injury to her skin and should be addressed promptly. Agnes also reminds Susan of the importance of covering up to protect her skin integrity while gardening but acknowledges she did well in caring for the abrasions right away when they did occur.

Agnes reinforces teaching by instructing Susan to avoid carrying her large purse over her affected shoulder as well as avoiding clothing with tight or restrictive arm holes. Susan verbalizes understanding and gratefully accepts Agnes’s offer of online resources to help her further understand and care for lymphedema.

Agnes then contacts the physician, reports her assessment, and asks if the physician would like to examine the patient and make a referral for an evaluation by a certified lymphedema therapy specialist.

### RECONSTRUCTIVE SURGERY

For the majority of women with breast cancer, body-image change is a very important issue. Whether or not to have reconstructive surgery or use a breast prosthesis after a mastectomy is a highly personal decision.

Breast reconstruction is a surgical procedure performed by a plastic surgeon and may require a longer recovery than mastectomy alone. Reconstruction can be performed at the same time as a mastectomy (immediate reconstruction), or it can be done later (delayed reconstruction). Immediate reconstruction may not be possible if the tumor is advanced and radiation is recommended. With immediate reconstruction, chemotherapy treatments are usually delayed for at least 2 to 3 weeks after surgery.
Breast reconstruction may be contraindicated for women who have diabetes, smoke, are obese or very thin, or have blood circulation problems (ACS, 2014d).

There are options available with reconstructive surgery, but they are not all appropriate for every candidate. Basically, there are two categories: implant-based reconstruction and autologous tissue reconstruction (e.g., DIEP flap or TRAM flap [see “Autologous Tissue Reconstruction” below]).

For both implant-based and autologous reconstruction, the areola and nipple can be reconstructed using a specific surgical technique and tattooing, which can look quite realistic. However, patients should be aware there will be no return of erogenous feeling to the reconstructed nipple.

**Patient Education**

Although a diagnosis of cancer can feel like an urgent situation, there usually is time to talk about, research, and consider treatment options. Ideally, once a definitive diagnosis is made and the need for a mastectomy is determined, the patient will discuss reconstruction options with the breast surgeon and the plastic surgeon. Women who are exploring their options for surgery should be encouraged to have someone with them and to take notes when consulting with the breast and plastic surgeons.

Some examples of important questions and points for the patient to consider include:

- Am I a candidate for breast reconstruction?
- When is the best time to have this done?
- What type of reconstruction is the best for me and why?
- How long will I be in the hospital? How long is total recovery time?
- What are the risks involved?
- Will I need help at home after surgery?
- What are some of the possible complications?
- Can I see pictures of reconstructive surgeries that show the final results?
- What is the average cost? Does insurance usually cover this?
- Will my new breast look and feel different from my other breast?
- When will I be able to exercise again? Are there any restrictions?
(Hartmann & Loprinzi, 2012)

It is very helpful for patients to view photos of what breasts may be like post-reconstruction in order to have a realistic expectation of possible outcome. It is also beneficial for them to speak to other women, such as in an in-person or online support group, about their experiences, both positive and negative.
Healthcare professionals can help keep the lines of communication open by asking leading questions, providing referrals, and recommending support groups. A great resource to direct patients to who are considering reconstructive options is the American Cancer Society website (see “Resources” at the end of this course).

**Implant-Based Reconstruction**

As a first step in the reconstruction process, most women need to undergo tissue expansion to stretch the skin for placement of an implant. The process begins with the insertion of a temporary implant called a tissue expander. Breast expanders and eventually the implants may be subpectoral (under the muscle) or prepectoral (on top of the muscle). The expander either stretches the skin and/or helps make a pocket under the pectoralis muscle for the implant. The implant can be placed at the time of mastectomy or later if delayed reconstruction is chosen.

Over a period of months, sterile saline is injected into the tissue expander in order to slowly stretch the skin of the chest where the implants will be placed. After the tissue expansion is complete, a second surgery removes the tissue expander and a breast implant is placed. Breast implants may be filled with either saline or silicone gel. Nipple reconstruction can also be accomplished with the new breast mound after a period of healing is allowed.

**Implant safety.** A frequent question that arises with women considering implant-based reconstruction is whether or not silicone implants are safe. It is important for nurses and other healthcare providers to know the history of this controversy as well as the current evidence to address this fear.

Due to adverse publicity surrounding the anecdotal reports of leaking silicone implants as a possible cause for autoimmune disorders, a moratorium was placed on their use in 1992. However, subsequent epidemiologic studies and meta-analysis found no proof of increased risk for connective tissue disease, autoimmune disorders, or rheumatologic diseases with silicone or saline-filled silicone implants (Janowsky et al., 2000). In light of the evidence, the FDA lifted the restriction on usage of silicone breast implants in 2006, with the requirement that all approved implant devices continue to be studied in the post-market setting by the companies that produce them (U.S. FDA, 2013).

**Potential complications from implants.** Women considering implant-based reconstruction after mastectomy need to be informed of possible complications that can arise. Apart from a decrease or loss of sensation or a “rubbery” feeling to the breast, additional complications include infection, formation of scar tissue (capsular contracture), and spontaneous deflation of the implant or expander (NCI, 2013b).

The most common complication in patients who have implant-based reconstruction is capsular contracture. This is caused by a scar that forms around the implant and contracts, causing pain and a change in the breast shape or contour. Implants can break (rupture) or cause infection or pain. Routine mammograms to check any remaining breast tissue for...
Both deflation and contracture may cause the need for additional surgery to correct the problems. Up to 50% of breast implants used for reconstruction need to be removed, modified, or replaced in the first 10 years (ACS, 2014d). Due to the increased risk of capsular contraction for women who need radiation therapy after breast surgery, patients generally should be advised that delayed autologous tissue reconstruction is a more appropriate choice for them.

**Autologous Tissue Reconstruction**

This type of reconstruction uses a woman’s own tissue to create a new breast mound. A transverse rectus abdominis myocutaneous (TRAM) flap takes tissue from the lower abdomen to create the new breast. There are two main types of TRAM flap procedures: the pedicle flap and the free flap.

With the pedicle TRAM flap, the entire rectus abdominis muscle, along with the fat and skin tissue, is tunneled under the skin to the chest area, where it is brought through the mastectomy incision. In the free TRAM flap procedure, the surgeon takes only a portion of the rectus abdominis muscle, along with skin and fat from the abdomen, and reattaches the tissue to blood vessels in the chest wall using microsurgery.

The DIEP (deep inferior epigastric perforator) flap uses fat and skin from the same area as the TRAM flap but does not use the muscle to form the breast shape. This results in less skin and fat in the lower abdomen. This method uses a free flap, where the tissue is completely excised from the abdomen and then moved to the chest. A microscope is needed to connect the tiny blood vessels. With this procedure, there is less risk of a bulge or hernia because no muscle is taken. A related procedure, known as a SIEA (superficial inferior epigastric artery) flap, uses the same tissues but different blood vessels.

Less commonly, tissue from the back (latissimus flap) or tissue from the buttocks or thighs can be used to create the reconstructed breast. Once the reconstructed breast tissue has healed, nipple reconstruction can take place.

The gluteal free flap or gluteal artery perforator (GAP) flap is newer type of breast reconstruction that uses tissue from the buttocks to create the breast shape. This procedure may be an option for women who cannot or do not wish to use the abdominal sites due to thinness, previous abdominal surgeries, or other reasons. The method is much like the free TRAM flap mentioned above. The skin, fat, and blood vessels are incised from the buttocks and then moved to the chest. Like all of the free flaps, a microscope (microsurgery) is needed to connect the tiny vessels.

**Potential complications from autologous tissue reconstruction.** Even though autologous tissue reconstruction uses a woman’s own body tissue, complications can still occur. To decrease risk of complications, presence of diabetes, vascular disease,
smoking are often seen as contraindications to autologous reconstruction, especially for the TRAM flap procedure.

Depending on the donor tissue site, complications that may occur include infection, bleeding, deep vein thrombosis, pulmonary emboli, bulging or hernia, pain and weakness from the donor site, necrosis resulting in flap failure, seroma, scarring, and unsatisfactory cosmetic results (NCI, 2013b).

EXTERNAL PROSTHESES

Some women may prefer to forego reconstructive surgery altogether and choose an external prosthesis. Many prosthetics, or breast forms, are available today for both lumpectomy and mastectomy patients. They can look quite natural under clothing and serve to help a woman feel balanced in her appearance. There are also a number of products available to accommodate breast forms, such as mastectomy bras, active wear, lingerie, and swimwear (see also “Patient Information and Support” later in this course). Breast forms may also be worn on a temporary basis between mastectomy and reconstruction surgeries, especially when prolonged treatment time is required during the interim.

Radiation Therapy

Radiation therapy uses high-energy particles or rays, which produce at least three main effects:

- Inducing apoptosis, or programmed cell death, by invoking the preexisting signaling cascade through radiation damage, which results in cell self-destruct.
- Causing permanent cell-cycle arrest or terminal differentiation; when cancer cells are blocked from moving beyond a cell cycle, they are no longer able to proliferate.
- Inducing cells to die as they attempt cell division; the DNA is damaged, which results in an unsuccessful mitotic phase, causing cell death.

There are several reasons radiation therapy is utilized in treating breast cancer:

- After breast-conserving surgery (BCS), to decrease local recurrence rate
- To reduce the risk of recurrence after mastectomy when:
  - The breast tumor is >5 cm
  - Axillary lymph nodes tested positive for cancer cells
  - Margins of the tumor site are narrow and test positive for cancer cells
- In recurrent disease, to control metastasis
- To palliate symptoms of metastatic disease (ACS, 2014c)
TYPES OF RADIATION THERAPY

Radiation therapy continues to play a major part in breast conservation therapy, as women who have lumpectomy alone may have up to a 40% recurrence rate (Davidson, 2016).

External Beam Radiation

The most common way radiation therapy (RT) is delivered in breast cancer patients is through external beam radiation. RT can be delivered in various schedules. A common schedule has been to deliver external beam radiation therapy once per day, 5 days per week, for 5 to 6 weeks starting one month after surgery. If a patient is also receiving chemotherapy, radiation therapy is typically started 3 to 4 weeks after completion of therapy.

The daily schedule can present a challenge for patients, especially if they have to travel a distance to reach an RT facility. Travel expense, transportation, employment issues, and even childcare can all contribute to difficulty in complying with the RT schedule. Scheduling radiation appointments early in the day or at the same time each day assists patients with their work/life schedules. Many women continue to work throughout radiation therapy. For patients with such concerns, a social worker can assist in developing the plan of care, encouraging the patient to seek assistance from friends and family and referring to local support groups.

Newer approaches, such as hypofractionated radiation therapy, administer larger doses over a shorter time span (3 weeks vs. 5 to 6 weeks) for women with negative lymph nodes after BCS. The hypofractionated radiation schedule appears to be just as effective as standard therapy in preventing recurrence and is more convenient for patients (ACS, 2014a). Researchers are currently studying the safety and effectiveness of delivering radiation to a smaller field, i.e., partial breast radiotherapy, over a shorter period as well (Davidson, 2016).

External beam radiation can also be given interoperatively at the time a lumpectomy is performed on early-stage breast cancer. In this approach, a single, large dose of radiation is directed at the lumpectomy site before the incision is closed.

In proton beam therapy, a particle accelerator generates a highly charged beam consisting of positively charged protons. The approximately 5-millimeter beam can be finely controlled in its width, height, and depth so that it is directed specifically within the three-dimensional contours of a breast tumor. Unlike the photons used in traditional radiation therapy, the beam doesn’t exit through the body, so other tissues are spared (e.g., heart).

Internal Radiation/Brachytherapy

Another form of radiation therapy is internal radiation, or brachytherapy. Brachytherapy uses radioactive pellets or seeds that are temporarily placed in the breast tissue adjacent
to the cancerous area or in the space where the tumor was removed. This method is often used in conjunction with external beam RT to give an “extra boost” in patients after BCS.

Brachytherapy targets radiation only to the area of the breast around the location of the tumor prior to surgery (generally the lumpectomy cavity, plus 1 to 2 centimeters beyond the surgical edge). Brachytherapy is given over a period of 4 to 5 days and minimizes radiation exposure to other parts of the body. The rationale behind breast brachytherapy is to intensify treatment to the area most at risk for recurrence. Brachytherapy has fewer side effects, better cosmetic results, and improved overall quality of life during the treatment period.

EFFECTIVENESS OF RADIATION THERAPY

In a large meta-analysis involving over 10,000 women in 17 different trials (EBCTCG, 2011), it was found that compared to women who received BCS alone, those who also received RT:

- Had significant reduction in 10-year risk of recurrence, with an absolute risk of 15.7%
- Had a significant decrease in 15-year risk of breast cancer death, with an absolute risk of 3.4%

These results confirm the importance of the addition of RT after BCS to reduce not only the risk of local recurrence but also distant recurrence resulting in death.

SIDE EFFECTS OF RADIATION THERAPY

There are both short- and long-term side effects that are possible with radiation treatment. The two most common short-term side effects are fatigue and skin changes to the irradiated area. In most cases, neither effect is noticeable until at least halfway through the six weeks of treatment.

Fatigue is the most common side effect in women undergoing radiation treatment and may last for several weeks after treatment. The level and length of the fatigue is as varied as the individuals experiencing it. Teaching patients to anticipate some level of fatigue along with various strategies to conserve energy is important during this time.

Skin reactions to radiation can range from a mild “sunburn” effect to severe rash and swelling. It is important to teach patients to protect the radiated skin from exposure to harsh soaps and lotions, avoid sun exposure, and protect their skin from extreme temperatures (such as a hot bath or hot shower). Other side effects may include skin irritation, soreness, peeling, blistering, and decreased sensation or hypersensation (ACS, 2014c).

Patient self-care strategies for skin care include:

- Wash the radiated area gently with warm (not hot) water and a mild soap such as Ivory, Pears, or Neutrogena.
• Do not shower more than once per day; limit baths to twice weekly for less than 30 minutes per bath.

• Avoid rubbing, scrubbing, or scratching the skin.

• Be careful not to wash off the ink markings needed for radiation therapy.

• Wash off any lotions or creams from sites prior to RT, as their presence can intensify burns.

• Gently pat skin dry after bathing.

• Avoid deodorant or talcum powder on the radiated side.

• Wear soft clothes and use cotton sheets.

• Avoid adhesive tape, bandages, or other types of sticky tape on the treatment area.

• Avoid chlorinated swimming pools and hot tubs during radiation treatment.

• Always protect the radiated area from exposure to the sun or tanning beds, even after treatment ends.

• Promptly report pain, swelling, exudate, or other skin changes to one’s primary care provider.

More serious (uncommon) side effects include swelling in the arm, lung damage, nerve damage (brachial plexopathy), heart damage, and increased chance of rib fracture (Hartmann & Loprinzi, 2012).

Brachial plexopathy can be either an acute (short-term) or delayed (long-term) side effect of external beam RT, especially when the axillary lymph nodes are involved in the treatment field. Brachial plexopathy is caused by nerve toxicity due to radiation damage to the nerve structure, although the exact pathogenesis is not known. In acute brachial plexopathy, symptoms may include numbness and weakness in the fingers and hands as well as weakness of the bicep and/or shoulder of the affected side.

In delayed brachial plexopathy, occurring months to many years after RT, it is postulated that damage is due to vasculitis with sclerotic occlusions of small supplying vessels, demyelination, and fibrosis of the nerve plexus. Symptoms can include paresthesias, hypoesthesias, weakness, and impaired reflexes, but not necessarily pain. Some patients, however, can experience severe pain and even paralysis of the affected arm.

There is also a slight risk of developing pneumonitis (a transient lung inflammation) following chest wall irradiation. The risk can be greater depending on the exact field that is radiated. Healthcare professionals should instruct patients undergoing RT to report a persistent dry cough, shortness of breath on exertion, the inability to take a full breath, chest pain, fever, malaise, or weight loss. Lung problems can occur anywhere from 4 weeks to 12 months after treatment.
Other short-term side effects of internal radiation include redness, bruising, breast pain, infection, weakness, rib fracture, and breakdown of fat tissue in the breast (ACS, 2014a).

LONG-TERM COMPLICATIONS

Radiation therapy can also have serious long-term complications. As mentioned earlier, radiation therapy increases the risk of lymphedema, which is chronic and can appear even years after treatment.

Recent data suggests technical advances in radiation therapy techniques, including the use of proton beam therapy, have reduced the incidence of cardiovascular complications compared to past methods. However, caution is still in order, as it appears there remains a higher risk in women with left-sided as opposed to right-sided tumors, indicating that risk is not completely eliminated. Furthermore, radiation injury to the heart may not manifest for up to 10 years following RT treatment (Zagar et al., 2016).

Radiation therapy for breast cancer can also slightly increase the risk of secondary malignancies, including leukemia, lung cancer, a small risk of contralateral second breast cancer, esophageal cancer, or a rare type of cancer called angiosarcoma. These cancers may develop 10 or more years after treatment in the tissue that has been radiated (NCI, 2016b).

CASE

Esther, a 70-year-old who had standard radiation therapy after BCS for left-sided breast cancer, comes in for her 3-month follow up with the radiation oncologist. The nurse notices that Esther seems short of breath walking from the waiting area to the exam room. She also notes the patient has a frequent, dry cough and a 5-lb. weight loss since her last visit. Her temperature is 99.8 °F, while her other vital signs are unremarkable. Esther complains of difficulty “getting a full breath of air” and states her cough “started about two weeks ago; I thought I had a bug, but it just won’t go away.” The nurse reports these findings to the physician and notes them in the medical record.

After she examines Esther, the physician orders a chest X-ray, cardiac echo, and pulmonary function test to rule out radiation pneumonitis versus heart failure versus infection. The office ancillary staff assist Esther in scheduling her tests and another follow-up appointment to receive test results in two weeks. She is advised to call sooner if her cough becomes productive and/or she develops a fever of 100.5 °F or greater.

Endocrine Therapy

Decades of research indicate that the female hormone estrogen is linked to the development of a certain type of breast cancer and to the likelihood of its recurrence. That is why in the past, surgical removal of the ovaries (oophorectomy) often caused breast cancers to regress, and oophorectomy is still offered to estrogen receptor–positive (ER-positive) patients with extensive disease.
Today, however, the primary long-term treatment for ER-positive breast cancer is the use of drugs that interfere with the production of estrogen, which reduces the chance of recurrence or metastasis of ER-positive breast cancer. Two groups of drugs that affect estrogen production in the body are called selective estrogen response modulators and aromatase inhibitors (ACS, 2014a).

About 20% of all new breast cancer cases occur in women younger than 50 years of age, and 60% of these cases are ER-positive. Options for premenopausal patients who are ER-positive include treatment with SERM, ovarian ablation, or a combination of ovarian suppression in combination with a SERM. Treatment with aromatase inhibitors are recommended for postmenopausal women with ER/PR-positive breast cancer. Aromatase inhibitors are contraindicated in premenopausal women (Kounalakis & Finlayson, 2016).

SELECTIVE ESTROGEN RESPONSE MODIFIERS (SERMs)

Selective estrogen response modulators include tamoxifen (Nolvadex), goserelin (Zoladex), fulvestrant (Faslodex), toremifene (Fareston), and raloxifene (Evista). Only tamoxifen, fulvestrant, and toremifene have been approved for adjuvant breast cancer treatment. Goserelin is sometimes used in certain types of metastatic breast cancer.

Since the 1960s, tamoxifen (Nolvadex) has been prescribed for women with ER-positive breast cancer to reduce the risk of cancer in the opposite breast. Tamoxifen does not benefit women with ER-negative cancer. Currently, the standard is to recommend tamoxifen treatment, 20 mg daily, for 5 years. Recommendations for women with aggressive tumors are to take tamoxifen up to 10 years if well tolerated.

Long-term research revealed there is additional benefit from administering tamoxifen up to 10 years. Prior research results showed that 5 years of tamoxifen resulted in a reduction in breast cancer death by one third over a 15-year period following diagnosis. Ten years of tamoxifen therapy reduces breast cancer recurrence and death rates by an additional 25% from year 10 onward (Kounalakis & Finlayson, 2016; Gray et al., 2013).

Unlike chemotherapy, tamoxifen does not cause hair loss or nausea, but it does have side effects that can alter quality of life and even be life threatening. The most common side effects are hot flashes, vaginal dryness, induced menopause, sexual dysfunction, depression, and mood swings. While rare, in some women tamoxifen can cause cataracts, fractures, blood clots in the lungs or legs, stroke, and/or endometrial (uterine) cancer (ACS, 2014a). Many women also report changes in memory and concentration, which is commonly referred to as “brain fog” or “chemo brain.”

Depending on the age of the patient and tumor characteristics, the oncologist may recommend chemotherapy and/or radiation therapy as well as tamoxifen. The preferred sequencing for tamoxifen is initiation of the medication after chemotherapy is complete (Hartmann & Loprinzi, 2012).

Goseraline acetate (Zoladex) is used in pre- or perimenopausal women with ER-positive advanced disease. It is injected into the subcutaneous abdominal tissue either every 28 days or
every 3 months if given in the depot form. Adherence to the treatment schedule is important with Zoladex, especially in the nondepot form.

**Fulvestrant (Faslodex)** is indicated for postmenopausal women with metastatic ER-positive breast cancer that has failed first-line, anti-estrogen therapy. It is administered IM once monthly and comes in a prefilled syringe. The 5 ml injection is usually split and administered to each buttock.

**Toremifene (Fareston)** is indicated in the treatment of metastatic breast cancer in postmenopausal women with either ER-positive or unknown status. Typical dosing is one 60 mg tablet daily with or without food. Trials comparing toremifene with tamoxifen in patients with untreated metastatic breast cancer demonstrated comparable action and side-effect profile but no specific advantage over tamoxifen.

**Raloxifene (Evista)** is a newer drug than tamoxifen. It was approved in 1997 to prevent osteoporosis after menopause. However, early studies of raloxifene also suggested that the drug reduced the risk of breast cancer without the risk of uterine cancer that tamoxifen carries, but with a similar risk of blood clots. Subsequent studies confirmed these findings, so raloxifene is sometimes prescribed to reduce the risk of breast cancer in women who do not have breast cancer but are at high risk for developing the disease and who are postmenopausal with an intact uterus. The usual dose is 60 mg per day for 5 years; however longer or indefinite duration can be prescribed if osteoporosis is also present.

**AROMATASE INHIBITORS (AIs)**

Aromatase is an enzyme produced in body fat and other tissue, particularly the breast. After menopause, when the ovaries no longer produce estrogen, aromatase converts hormones called androgens, produced by a woman’s adrenal glands, into estrogen. This conversion serves as the body’s main source of estrogen after menopause and therefore raises the risk of breast cancer and recurrence. For this reason, it is thought that excess body fat in postmenopausal women may increase the risk of breast cancer.

AIs inhibit (block) the conversion of androgens to estrogens, thereby limiting the amount of estrogen that can reach cancer cells. This can lead to regression or stabilization of a tumor. However, AIs also act on other estrogen-sensitive tissues, which may account for some of the drugs’ side effects, such as muscle and joint pain and bone loss, which can increase fractures of the hip, spine, or wrist.

**Effectiveness**

While tamoxifen is still an option for adjuvant endocrine treatment in postmenopausal women, AIs have been found to be more effective in preventing cancer recurrence in the first two years following breast cancer surgery. Aromatase inhibitors are not associated with the thromboembolic events and uterine cancers that are seen with tamoxifen. While there have been several major trials comparing these drugs with tamoxifen, either separately or in combination (such as ATAC, BIG, and TEAM), it is still unclear whether
over time an AI alone is more effective than some sequential combination with tamoxifen.

How long women should continue taking AIs for optimal benefit is still being researched. Currently, it is recommended that women with ER/PR-positive breast cancer take an AI for at least five years. For those who do not tolerate or for other reasons do not want to take an AI, tamoxifen for five years is recommended (Kounalakis & Finlayson, 2016). A recent study announced at ASCO reported that women with hormone receptor–positive early-stage breast cancer who took an AI for 10 years had a 34% decreased risk of recurrence (Goss et al., 2016).

While recurrence-free survival, especially in the first two years after surgery, has been proven with AIs over tamoxifen, overall survival has not. Likely, the best strategy will prove to be some exposure to both to gain benefit while avoiding prolonged exposure to either to avoid harm (Kounalakis & Finlayson, 2016).

### Approved Therapies

Aromatase inhibitors are currently used to treat premenopausal women with hormone-responsive breast cancer, that is, cancer that is either ER-positive or PR-positive. Aromatase inhibitors should not be used for premenopausal women, as it is thought that blocking the conversion of androgens to estrogen reduces feedback of estrogen to the hypothalamus and pituitary glands, which would then trigger increased gonadotropin secretion leading to increased production of androgens, estrogen, and aromatase.

Three aromatase inhibitors have been approved by the FDA for use in advanced cancer: anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin). Anastrozole has also been approved as adjuvant therapy for postmenopausal women with hormone-responsive-positive breast cancer. Aromatase inhibitors can increase the risk of osteoporosis, therefore it is recommended that women have a dual energy X-ray absorptiometry (DEXA) scan when treatment is initiated and continuing every two years to evaluate bone density.

**Anastrozole (Arimidex)** was the first AI tested against tamoxifen in a major clinical trial, and it proved more effective than tamoxifen in protecting against recurrence of the cancer and against developing cancer in the other breast. However, like all drugs, anastrozole has side effects, which include increased risk of osteoporosis and fractures, memory problems and lack of concentration, muscle and joint pain, high cholesterol, and heart problems.

Although initially recommended as a first-line treatment only for women with advanced or metastatic breast cancer, later studies showed that anastrozole is appropriate as adjuvant treatment for some postmenopausal women with ER-positive breast cancer. Doctors may recommend anastrozole particularly for those at high risk for the type of side effects caused by tamoxifen (endometrial cancer, blood clots, stroke).
Like anastrozole, **letrozole (Femara)** has been shown to be more effective than tamoxifen in terms of recurrent-free survival and quality of life. Letrozole is indicated for treatment of postmenopausal women with hormone receptor–positive early breast cancer; extended adjuvant treatment of early breast cancer in hormone receptor–positive women after five years of adjuvant tamoxifen; first-line treatment of postmenopausal women with hormone receptor–positive or unknown, locally advanced, or metastatic breast cancer; and treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy (Wilkes & Barton-Burke, 2012).

Side effects of letrozole may include nausea and vomiting; muscle or bone pain; fatigue; headache; dizziness; muscle weakness; swelling of the hands, feet, or lower legs; loss of appetite; constipation; diarrhea; abdominal pain; hot flashes; and cough.

**Exemestane (Aromasin)** is used with postmenopausal women who have been previously treated with tamoxifen for 2 to 3 years. This medication may be indicated in women whose breast cancer has progressed while taking tamoxifen.

Side effects of exemestane may include hot flashes and sweating; muscle or bone pain; fatigue; headache; dizziness; nervousness; changes in vision; diarrhea; depression; sleep problems; hair loss; skin changes (redness and irritation); and changes in vision. Serious side effects include shortness of breath and chest pain.

Clinical trials of all hormonal therapies for breast cancer are underway in the United States and abroad. As new information becomes available, treatment recommendations may change, so it is always best to check the most current information available.

**Preventing and Treating AI-Induced Bone Loss**

Zolendronic acid (Zometa), a bisphosphonate, and denosumab (Xgeva, Prolia), a monoclonal antibody, are both approved drugs used to prevent and/or decrease AI-induced osteoporosis and risk for bone loss in breast cancer patients.

**Bisphosphonates** work by inhibiting resorption of bone by osteoclasts and have been studied extensively in breast cancer patients. These drugs have also been shown to decrease risk of bone metastasis and may increase overall survival. Bisphosphonates are generally administered every 6 months for 3 years for a total of six doses (Kounalakis & Finlayson, 2016).

**Denosumab** is a human monoclonal antibody that targets the RANK ligand (RANKL) protein, which acts as the primary signal promoting bone removal. By inhibiting the development and activity of osteoclasts, denosumab decreases bone resorption and increases bone density. Denosumab is also given every 6 months for 3 years (Tan, 2016).

**Vitamin D** supplementation may also be indicated in women treated for breast cancer to aid with bone mineral density.
Chemotherapy

Administration of cancer chemotherapy generally occurs after surgery for breast cancer; this is called adjuvant chemotherapy. However, women with large tumors may receive chemotherapy before surgery to shrink the tumor and perhaps avoid a mastectomy; this is called neoadjuvant chemotherapy. Neoadjuvant therapy also allows for an early evaluation of the effectiveness of systemic therapy. In addition, neoadjuvant therapy may provide the opportunity to obtain tumor specimens and blood samples prior to and during the preoperative treatment. This has enabled researchers to identify tumor- or patient-specific biomarkers in order to plan appropriate targeted therapies (ACS, 2014a).

EFFECTIVENESS

Statistically, chemotherapy treatment can reduce the relative risk of recurrence by about one fourth to one third. For example, a woman with a larger, more aggressive tumor and more lymph nodes involved might have a 75% chance of recurrence without chemotherapy. With chemotherapy, her statistical risk of recurrence might be reduced to around 50%. In contrast, a woman with a small tumor and negative lymph nodes might have her statistical risk of recurrence reduced from 12% to 8%. The higher the statistical risk of recurrence, the greater potential benefit from chemotherapy.

The medical oncologist generally determines a patient’s statistical risk of recurrence and the percentage of benefit she might expect from chemotherapy. This does not mean that the tumor will respond according to statistics, and chemotherapy may have a greater or lesser effect on the risk of recurrence than predicted.

TREATMENT REGIMENS

Chemotherapy treatment is generally given in cycles of either every 21 or 28 days over the course of 3 months, 6 months, or 1 year, depending on the individual patient situation. The time between treatments allows the bone marrow to recover. At times, two or three different chemotherapy drugs are given in combination in order to increase effectiveness in eradicating cancerous cells (Kounalakis & Finlayson, 2016; ACS, 2014a).

Oncologists have found that giving certain chemotherapy regimens closer together can lower recurrence rates and improve survival. Chemotherapy treatments are given as often as every 2 weeks with this regimen, called dose-dense chemotherapy. However, a dose-dense chemotherapy regimen can lead to more side effects and is difficult to tolerate. Growth factors to help the white blood cell count recover may be given as well (ACS, 2014a). Women who are HER2-positive receive trastuzumab (Herceptin) on a weekly schedule while receiving their chemotherapy every 21 days.

In most situations, chemotherapy is most effective when combinations of one or more drugs are used. Many combinations are currently being used, and it is not clear that any single combination is the best. Clinical studies continue to compare current treatments with new agents and combinations.
<table>
<thead>
<tr>
<th>Name</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>CMF</td>
<td>Cyclophosphamide (Cytoxan), methotrexate, and 5-fluorouracil</td>
</tr>
<tr>
<td>CAF (or FAC)</td>
<td>Cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), and 5-fluorouracil</td>
</tr>
<tr>
<td>AC</td>
<td>Doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan)</td>
</tr>
<tr>
<td>EC</td>
<td>Epirubicin (Ellence) and cyclophosphamide (Cytoxan)</td>
</tr>
<tr>
<td>TAC</td>
<td>Docetaxel (Taxotere), doxorubicin (Adriamycin), and cyclophosphamide (Cytoxan)</td>
</tr>
<tr>
<td>AC-T</td>
<td>Doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan) followed by paclitaxel (Taxol) or docetaxel (Taxotere); trastuzumab (Herceptin) may be given with the paclitaxel or docetaxel for HER2/neu-positive tumors</td>
</tr>
<tr>
<td>A-CMF</td>
<td>Doxorubicin (Adriamycin) followed by CMF</td>
</tr>
<tr>
<td>CEF (or FEC)</td>
<td>Cyclophosphamide (Cytoxan), epirubicin (Ellence), and 5-fluorouracil; may be followed by docetaxel (Taxotere)</td>
</tr>
<tr>
<td>TC</td>
<td>Docetaxel (Taxotere) and cyclophosphamide (Cytoxan)</td>
</tr>
<tr>
<td>TCH</td>
<td>Docetaxel (Taxotere), carboplatin, and trastuzumab (Herceptin) for HER2/neu-positive tumors.</td>
</tr>
</tbody>
</table>


Other chemotherapy drugs used to treat women with breast cancer include: cisplatin (Platinol), vinorelbine (Navelbine), capecitabine (Xeloda), liposomal doxorubicin (Doxil), gemcitabine (Gemzar), ixabepilone (Ixempra), mitoxantrone (Novantrone), albumin-bound paclitaxel (Abraxane), and eribulin (Halaven).

The targeted-therapy drug trastuzumab (Herceptin) may be used with HER2/neu-positive tumors, and lapatinib (Tykerb) may be combined with chemotherapy drugs for tumors that are HER1 and HER2/neu-positive (ACS, 2014a).

Different chemotherapy regimens are associated with particular risks, so it is important that each patient is informed and educated about the potential side effects of the regimen the oncologist recommends in order to make an informed decision about treatment. An instructional session that includes the significant other and/or caregiver by a knowledgeable, experienced oncology nurse or practitioner is crucial before chemotherapy commences. Other women who have been through chemotherapy can be helpful resources as well, together with local support groups or online blogs to help patients anticipate and cope with potential side effects.

**SIDE EFFECTS**

Most chemotherapy drugs used to treat breast cancer have toxic side effects. Nausea and vomiting, hair loss, and fatigue are the most common. Increased risk of infection and anemia due to bone marrow suppression are other commonly seen toxicities and can actually become dose-
limiting. Chemotherapy-induced menopausal symptoms, neuropathy, and cognitive changes are also frequent complaints. Common side effects of chemotherapy are described below.

**Nausea and Vomiting**

Despite advances in antiemetic therapies, chemotherapy-induced nausea and vomiting (CINV) remains one of the most feared and expected side effects of chemotherapy. Preventive use of antiemetic therapy is important because CINV may lead to reduced quality of life, an increased use of healthcare resources, and challenges to treatment adherence.

Fortunately for patients, the nausea and vomiting related to chemotherapy can be minimized or sometimes eliminated altogether by a number of medications such as palonosetron (Aloxi), aprepitant (Emend), and a newer form of delivery for granisetron (Kytril), in a transdermal patch. These medications have fewer side effects than previously used antinausea drugs and are dramatically more effective, making it possible for most chemotherapy to be given on an outpatient basis. The steroid dexamethasone is still widely used as an antiemetic and is considered very effective, especially for delayed nausea (Ng et al., 2015).

Healthcare providers can be proactive in teaching coping skills for CINV. It can be helpful for patients to eat small, frequent meals and avoid foods that are fried, high in fat, strong tasting, strong smelling, gas forming, spicy, or acidic.

It is vital that caregivers are aware of the risk factors for severe nausea (female gender, young age, and vomiting during previous chemotherapy treatment) and that the patient knows to contact the healthcare provider promptly if CINV is not well-controlled. Studies show CINV is most successfully treated with a preventive, proactive approach (Ng et al., 2015).

**Hair Loss**

Many breast cancer chemotherapy regimens cause hair loss, which can be traumatic for most cancer patients. Women cope with hair loss in different ways, and patients may need a reminder that cancer is nothing to be ashamed of. Exploring options such as hats, scarves, and wigs can be helpful during this time. Many women also discover a new sense of natural beauty and embrace the idea that “bald is beautiful.” Women have said, for instance: “I didn’t know how beautiful my face was until I lost my hair.”

Generally speaking, if hair loss occurs, it will begin about 10 to 20 days after chemotherapy treatment begins. It can affect not only scalp hair but also body and facial hair, although eyebrows and eyelashes can take much longer to fall out. It is important to explain that the scalp needs protection with either a hat or sunscreen when exposed to the sun and to minimize loss of body heat when it is cold.
Usually, about 3 to 6 weeks after chemotherapy is completed, hair regrowth begins. It is not uncommon for hair to grow back a different color or texture (known as “chemo-curl”), but typically, after about a year, it returns to its previous state. For older women, however, if their post-chemo hair growth is white or grey, it may stay that color indefinitely.

During this time, women may benefit from focused skin care and cosmetic programs designed to support cancer patients. The ACS’s “Look Good, Feel Better” program is designed to teach skin care, make-up application (i.e., for the loss of eyebrows), scarf tying, hats, and wig choices. This can help to boost self-esteem and increase quality of life for women dealing with the side effects of chemotherapy.

**Fatigue**

The most commonly reported side effect of chemotherapy is fatigue. It is also the most debilitating side effect, affecting all other areas of a patient’s life. This distressing symptom may or may not be associated with anemia; there is much research concentrated on the exact physiologic cause of cancer-related fatigue and ways to combat it (Berger et al., 2012).

It is important for healthcare providers to assess fatigue levels using a fatigue scale—much like a pain scale—in order to evaluate effectiveness of intervention and to be alerted to the potential of more serious problems (i.e., disease recurrence or progression) if the level is high.

Strategies to cope with cancer-related fatigue include:

- Prioritize tasks and activities in order of importance.
- Delegate errands and household chores to family and friends.
- Take short rest periods (20 to 30 minutes or less) during the day when needed.
- Plan activities that require higher energy during peak energy times.
- Incorporate moderate exercise (e.g., walking).
- Avoid caffeine, as it can interfere with sleep.
- Develop a bedtime routine to aid in sleep.
- Take in adequate fluids, as dehydration can contribute to fatigue.
- Eat a balanced diet; limit high-fat and high-sugar foods.

Patients should be encouraged to seek ways to decrease stress, which can contribute to fatigue, through relaxation techniques, quiet music, guided imagery, massage, meditation, etc.
Infection

Chemotherapy attacks rapidly dividing cancer cells. Unfortunately, it affects normal rapidly dividing cells as well. White blood cells, a vital part of the immune system, are some of the most frequently dividing cells in the body, so they can be profoundly impacted by chemotherapy (a state known as neutropenia).

Low white blood cell count can result in decreased resistance to infection in people who are receiving chemotherapy. For this reason, patients on chemotherapy treatments must be diligent in avoiding infection. The number-one preventive measure they and those in their households can take is frequent and thorough handwashing. A good reminder to give patients is to be sure hand hygiene is performed before eating, food preparation, and contact with eyes, nose, or mouth, and after using the toilet, contacting pets, and gardening.

Patients should also avoid crowds and people (especially children) with active colds or infections. Avoiding pet waste, such as changing cat litter boxes, is also recommended. Other precautions include prompt attention to cuts/injuries and to any signs of infection, wearing gloves while gardening, washing fruits and vegetables before consumption, and avoiding raw or undercooked animal products or seafood.

General signs and symptoms to watch for related to neutropenia include fever, chills, sweating, sore throat or sores in the mouth, abdominal pain, cough, and shortness of breath.

Frequent monitoring of blood work is standard for patients on chemotherapy treatment. The oncologist may prescribe colony-stimulating factors (CSF) such as filgrastim (Neupogen), pegfilgrastim (Neulasta), or sargramostim (Leukine) if needed to prevent neutropenic infection. CSF medications are given as a subcutaneous injection 24 hours after chemotherapy treatment and work by stimulating the bone marrow to produce more white blood cells, specifically neutrophils.

Anemia

Chemotherapy drugs can cause anemia because they can suppress the bone marrow’s production of red blood cells as well as decrease the normal lifespan of circulating red blood cells through cell lysis. Most people with cancer are at least mildly anemic, but chemotherapy and radiation therapy can exacerbate the problem. Anemia can result in fatigue, dizziness, shortness of breath, loss of stamina, and feeling cold, especially in the hands and feet.

Adding green leafy vegetables, lean red meat, and iron supplements to the diet can relieve some anemia if there is an iron-deficient component as well. Blood transfusions may also be necessary on rare occasion. Baseline iron studies should be done, followed by periodic checks during therapy, to determine the need for iron replacement.
Libido, Infertility, Early Menopause

Chemotherapy can affect sexuality, intimacy, and fertility. It can cause vaginal dryness, pain, and discomfort during sexual activity. Premenopausal women may experience infertility and early menopause induced by chemotherapy. The younger the patient, the more likely her periods will return when chemotherapy is finished. The closer she is to the age of natural menopause, the more likely chemotherapy will bring about menopause, with hot flashes, vaginal dryness, mood swings, and sleep disturbances. There may also be increased risk of osteoporosis.

Many of these factors, along with body image changes due to surgery and radiation, may impact a woman’s sexuality and intimacy. It is important to recognize and initiate a discussion about fertility and sexual changes as part of pretreatment education to address issues patients may face or are already experiencing. By normalizing the subject of intimacy and approaching it as a quality of life issue, healthcare providers may find patients become more comfortable in discussing their concerns.

Cognitive Effects

Many women who have received chemotherapy treatment notice cognitive changes, or “chemo brain”—the forgetfulness, loss of concentration, and decrease in mental functioning that often accompany chemotherapy. Consequences of cancer treatment, such as low blood counts, fatigue, infection, menopause, poor nutrition, and sleep issues, may also trigger cognitive symptoms. The medical community recognizes these symptoms as real. Cognitive changes that begin during cancer treatment that may last months and even years after treatment is complete (Reuter-Lorenz & Cimprich, 2013).

Strategies to cope with cognitive symptoms include:

- Exercise the brain by using crossword puzzles, number games, reading, etc.
- Maintain a regular daily routine.
- Reduce stress and anxiety with relaxation techniques.
- Stay organized by using calendars, lists, and planners.
- Incorporate moderate exercise, which can help with stress and fatigue.
- Maintain good nutrition.
- Take frequent breaks and divide tasks into manageable parts.

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Chemotherapy drugs used to treat breast cancer, including taxanes and platinum agents, can cause damage to the nerves, leading to peripheral neuropathy. The most common symptoms associated with CIPN are sensory neuropathies, including paresthesias (burning, tingling, and numbness) and pain starting in the fingers and toes, which can
spread proximally. CIPN can begin weeks to months after initial treatment and reach a peak at or after the end of treatment. In some cases, the pain and paresthesias completely resolve after treatment is stopped. However, in most cases, CIPN is only partially reversible and can be permanent (Hartmann & Loprinzi, 2012).

New research suggests that CIPN may be prevented with the use of frozen gloves/socks worn during drug infusion with weekly paclitaxel in women with breast cancer. However, additional phase III trials are needed to validate these results (Hanai et al., 2016).

**SCRAMBLER THERAPY FOR CIPN**

A new treatment device for CIPN called Calmare scrambler therapy has received FDA approval in the United States for use in patients experiencing pain from cancer and CIPN; pain occurring as a result of chronic diseases such as diabetes, multiple sclerosis, and arthritis; back and neck pain; and phantom limb pain.

Scrambler therapy is a transcutaneous electrical stimulation treatment. Scrambler therapy interrupts and confuses the electrical information via nerves that have been transmitting chronic pain information. Through a process termed plasticity, this therapy is able to retrain the brain so that it no longer recognizes pain to the area as chronic pain.

Scrambler therapy is administered using a device that resembles an electrocardiogram machine. Leads are placed on the patient in the areas of chronic pain. Scrambled electrical signals are then sent to the brain, which perceives them as normal, nonpain signals. With this process, the brain is retrained to perceive that there is no pain in the area that is being treated.

Scrambler therapy has been studied in numerous clinical trials in the United States and internationally since 2003.

Source: Majithia et al., 2016.

**Biological/Targeted Therapy (Immunotherapy)**

For most of the twentieth century, cancer drugs were cytotoxic (cell-killing) drugs. Aimed at killing any cancer cells that have escaped the primary site, chemotherapy also kills normal, healthy cells, especially those that grow and divide rapidly (such as hair and epithelial cells in the mouth, the lining of the digestive tract, and the reproductive tract). In many cases, cytotoxic drugs also suppress the bone marrow, where blood cells are produced, including the white blood cells, which are a major part of the immune system.

Researchers have long sought alternatives to cytotoxic drugs that do not have toxic side effects and that work with the body’s immune system instead of against it. Rather than destroying cancer cells (and other cells), these biological therapies (also called immunotherapies or targeted therapies) interrupt the tumor process through a variety of methods. In 1998, research
into biological therapies showed promising results, and the FDA approved the drug trastuzumab (Herceptin) for metastatic breast cancer.

**TRASTUZUMAB (HERCEPTIN)**

Twenty to thirty percent of newly diagnosed breast cancers have amplification or overexpression of the HER2 oncogene (ACS, 2014a). Trastuzumab was a major breakthrough in the treatment of this usually aggressive tumor type, improving progression-free, disease-free, and overall survival. (See also “Biomarker Tests” above.)

Trastuzumab is a targeted approach to treatment that is classified as a monoclonal antibody. Originally FDA-approved for use in metastatic breast cancer, trastuzumab is now also approved and used as standard treatment in the adjuvant setting in combination with chemotherapy. Women with HER2-positive breast cancer with nodal involvement and women with HER2-positive tumors >2 cm without nodal involvement are appropriate candidates for first-line adjuvant treatment with trastuzumab. Women with metastatic disease that is HER2-positive can also benefit from trastuzumab, sometimes as monotherapy, with very good results (NCI, 2016b).

There are several types of epidermal growth factor receptors, but HER2 overexpression is most highly associated with breast cancer growth. Trastuzumab interrupts this cancer cell division by deactivating the protein on the surface of the cell that fuels its growth, in essence acting as a “false key” in the lock that fits the receptor but does not turn. The attached monoclonal antibody now also signals for cell destruction by the patient’s own immune system.

**Side Effects and Contraindications**

Because trastuzumab works differently than cytotoxic chemotherapy, it is not associated with the same side effects. Instead, the most common side effect appears to be infusion reactions—including shaking, chills, fever, headache, abdominal pain, and dyspnea, especially with the first dose—which can appear during infusion and up to 24 hours after the infusion. Other possible but less common infusion reactions are vomiting, dizziness, rhinitis, hypotension, and rash.

Additional considerations are asthenia (loss of strength), left ventricular (LV) cardiac dysfunction, diarrhea, and increased incidence of leukopenia, anemia, neutropenia, and infection when used in combination with chemotherapy. Rarely, severe hypersensitivity reactions occur, in which case trastuzumab should be discontinued indefinitely. Also uncommon but documented are pulmonary toxicities such as interstitial pneumonia and acute respiratory distress syndrome (ARDS) in patients receiving trastuzumab (ACS, 2014a).

Because of the cardiac toxicity potential, patients who are to receive trastuzumab therapy are required to have either a multigated acquisition (MUGA) scan or a cardiac echocardiogram to determine baseline LV ejection fraction prior to start of therapy and at regular intervals throughout treatment. This monitoring is especially important for patients who also receive anthracyclines and/or chest irradiation. Patient education on the
signs and symptoms of heart failure to report urgently is a must (Wilkes & Barton-Burke, 2012).

Oncologists have specific guidelines for when to hold trastuzumab and when and how to restart therapy as testing shows improvement of LV function, although not standardized. Patients who have existing heart failure prior to treatment should not be started on trastuzumab, and those who show clinical signs of heart failure while on therapy should have therapy discontinued (Piotrowski et al., 2012).

Since anthracyclines can also have a cardiotoxic effect (albeit, potentially more permanent), they should not be given concurrently with trastuzumab. In the commonly used AC-T trastuzumab regimen, the four cycles of Adriamycin (an anthracycline) and cytoxan are given prior to the taxol and trastuzumab. Some regimens, such as TCH, leave out the anthracycline all together, thereby reducing cardiac toxicity risk while retaining similar recurrence risk-reduction as the anthracycline-containing regimen (Piotrowski et al., 2012).

Drug Resistance

While trastuzumab has successfully increased overall survival for many years now, tumor resistance to the drug develops in a large portion of HER2-positive breast cancers, ultimately causing recurrence and disease progression (Pritchard, 2013). Research is underway to counteract or overcome trastuzumab resistance.

OTHER TARGETED THERAPIES

Lapatinib (Tykerb) is another drug that targets the HER2 protein. When treatment with trastuzumab fails for patients with HER2-positive metastatic disease, lapatinib may improve progression-free survival. Lapatinib works by inhibiting intracellular cell signaling (ACS, 2014a).

Pertuzumab (Perjeta), like trastuzumab, is a monoclonal antibody that attaches to the HER2 protein. Pertuzumab targets a different part of the HER2 protein and can be used in combination with docetaxel and trastuzumab for first-line treatment in advanced breast cancer patients (ACS, 2014a).

Everolimus (Affinitor) is a newly approved targeted therapy (for advanced HER2-positive or -negative cancers) that blocks mTOR, a protein in cancer cells that promotes growth. By blocking this protein, everolimus can stop cancer tumors from developing blood vessels and limit growth. Everolimus is usually given along with exemestance (Aromasin) in women who have disease progression while on either letrozole or anastrazole (ACS, 2014a).

Another promising drug combination currently under trial is TDM-1 (trastuzumab emtansine), unofficially dubbed “Super Herceptin.” TDM-1, the monoclonal antibody trastuzumab bound to cytotoxic chemotherapy, retains the original action of the trastuzumab while also allowing
intracellular delivery of the chemotherapy specifically to HER2-positive cells. This results in targeted apoptosis (cell kill) with limited exposure of chemotherapy to healthy cells.

Targeted agents currently under investigation include gefitinib, erlotinib, and cetuximab, which target HER1 epidermal growth factor receptor (EGFR) positive tumors, as well as bevacizumab for vascular endothelial growth factor (VEGF) positive tumors. New research is also focusing on the PARP1/PARP2 (Poly ADP-ribose polymerases) targets with new PARP1 inhibitor agents (Ferri, 2016).

Treatment of breast cancer with targeted therapies and immunotherapies is an evolving field that continues to develop as the understanding of breast cancer cell mechanism and treatment grows.

**VACCINES**

Researchers think that cancer vaccines can help stimulate T cells to resist the growth and spread of cancer cells. Unlike traditional vaccines, cancer vaccines are designed to program the immune system to treat the disease and prevent recurrence. This approach has proved successful in treating multiple myeloma and metastatic melanoma, a deadly skin cancer. A number of vaccines for breast cancer and other cancers (multiple myeloma, prostate cancer, kidney cancer, and lymphoma) are currently being evaluated in clinical trials.

**Clinical Trials and New Cancer Therapies**

Patients with breast cancer may want to participate in a clinical trial. Most cancer treatment trials are randomized, which means that patients are assigned to receive either the new drug (or combination of drugs) being studied or standard treatment. Clinical trials are also usually double blind, which means that both the patient and the doctor are unaware of which drug the patient is getting. This avoids any bias on the part of the doctor or the patient.

There are both advantages and disadvantages to enrolling in a clinical trial. Advantages include the possibility of receiving cutting-edge breast cancer treatment. Disadvantages include potential insurance problems, unexpected side effects, and expense to the patient, such as travel costs as well as lab or test costs which may or may not be covered by their insurance or paid for by the trial sponsor (U.S. FDA, 2014).

It is important for patients to discuss the benefits and risks associated with participating in a clinical trial with their oncologist. The National Cancer Institute lists clinical trials and provides education for patients on their website (see “Resources” at the end of this course).

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**U.S. FDA APPROVAL PROCESS**

The U.S. FDA (Food and Drug Administration), within the Department of Health and Human Services, is in charge of making sure that new drugs, vaccines, gene therapies, and other biological treatments are safe and effective before they are released for standard treatment for cancer patients.
First, the new drug is studied in the laboratory and with animals. Next, clinical trials with people are needed to study the safety and best dose of the new treatment. This is done in Phase I clinical trials. After the first phase of study is complete, it moves on to Phase II to study how the new drug works against a specific cancer. Researchers continue to focus on safety and report the side effects, complications, and short-term safety.

If the early phases of the research are promising, the drug continues on to Phase III, which compares the new drug to standard treatment. This is typically done with hundreds of people across the country or around the world. Finally, if the new drug proves to be better than the standard treatment, the FDA reviews all of the research data, including the risks and benefits and any new side effects, and makes a decision regarding approval.

During the process of approval, the FDA can decide whether the new drug should have a priority classification (a faster approval), which is given when the new treatment shows major benefits over existing treatment. The FDA uses an independent advisory committee to review each new drug application. The committee is made up of experts in the field of medicine and research as well as consumers (patient advocates).

Sometimes post-marketing, or Phase IV, studies are completed on drugs that are already approved by the FDA and commercially available. The purpose of these trials is to expand the use of the drugs to a new indication that they were not originally approved for. Phase IV also further assesses toxicity data and long-term safety and effectiveness.


COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

It is estimated that up to 80% of patients with cancer and long-term survivors of cancer use CAM therapies during and after cancer treatment (Hartmann & Loprinzi, 2012). Many people with cancer choose one or more complementary therapies to reduce the side effects of chemotherapy and radiation, relieve pain, boost their immune system, improve quality of life, reduce stress, and promote healing. CAM treatments can also help patients in coping with their cancer, as it can increase their sense of empowerment and wellness.

**Complementary therapies** generally refer to strategies or treatments used in conjunction with conventional medicine as a complement to prescribed cancer treatment. The goal of these therapies is not to cure cancer but to work in concert with traditional cancer treatment to relieve symptoms and improve quality of life.

Complementary therapies may include nutritional supplements, dietary changes, herbal supplements, exercise, yoga, tai chi, guided imagery, mindfulness meditation, massage, or acupuncture used in addition to conventional medicine. Nutritional supplements are the most frequently chosen complementary therapies.
It is essential for healthcare providers to obtain a complete list of all complementary therapies a patient is utilizing to avoid possible interaction with or detrimental action against conventional cancer treatments. Assessment and monitoring throughout the illness trajectory is very important in protecting patient safety.

Complementary therapies differ from conventional medicine. Often, they are not covered by health insurance. While complementary therapies also have been studied for safety and efficacy, there may be limited scientific evidence about their effectiveness. Most complementary therapies are unregulated, which makes them difficult to study.

Unlike conventional medicine, which treats a specific problem by standard methods—such as surgery, radiation, or chemotherapy—complementary therapy views the patient as a whole entity and the body as more than the sum of its parts. More recently, this holistic approach has been referred to as mind-body medicine or integrative medicine (see also “Integrative Therapy” below).

**Alternative therapies** are unconventional treatments used in place of conventional, mainstream medicine. By definition, alternative therapies have not been scientifically proven, often have little or no scientific basis, and in some cases have even been disproved. Alternative therapies are too numerous and too controversial to address fully in this course. However, some common examples of alternative therapies for the treatment of cancer that patients may hear about include high-dose vitamin C, laetrile, and other herbal remedies.

Patients should be warned about the potential harm as well as the possible negative financial impact of using alternative therapy in place of evidence-based therapies exclusively for the treatment of cancer. The use of alternative therapies in place of conventional medicine may decrease the chance of remission or cancer cure. It is important to encourage a discussion of any and all treatment decisions in a nonjudgmental manner so as to keep the lines of communication open.

**Nutritional Approaches**

Most healthcare practitioners agree that eating a healthful diet makes sense for anyone, and especially for people with cancer. Eating healthy can speed recovery, strengthen the immune system, restore energy, and reduce risk of cancer recurrence.

**EATING HEALTHY**

Eating a low-fat diet such as the Mediterranean Diet may provide healthy benefits for cancer patients. The basic structure of the Mediterranean diet includes:

- Increased intake of fresh fruits and vegetables (7 to 10 servings a day)
- Use of whole grains (whole grain breads, cereals, and pasta)
- Use of olive oil instead of butter or margarine
• Adding herbs and spices instead of salt to enhance flavors
• Eating fresh fish and poultry instead of red meat
• Eating low-fat dairy products (e.g., Greek yogurt)

At times, nutritional drinks (e.g., Boost and Ensure) may be used to provide nutrients during acute cancer treatment when eating is difficult due to appetite changes, mucositis, and/or changes in taste. A referral to a registered dietitian can assist women who have nutritional concerns during and after the treatment period.

**VITAMINS AND MINERALS**

Food is the best source of vitamins and minerals, but sometimes food fails to provide enough of certain nutrients, especially during recovery from cancer and its treatments.

More than half of all cancer patients take one or more supplements, with or without their doctor’s approval. Common supplements used by cancer patients include vitamin C and E for antioxidant effects, St. John’s wort for depression, garlic extract for blood pressure, and echinacea to enhance the immune system. Taking these supplements during treatment may interfere with or decrease the effectiveness of chemotherapy or radiation (NCI, 2013c).

• Patients should be cautioned not to take **megadoses** of vitamins and minerals because some vitamins can be toxic in large doses.

• Patients should be advised to discuss taking **antioxidants** such as vitamins C and E with their oncologist and complementary health practitioner. Patients may believe that taking antioxidants will enhance and protect their body’s normal cells, however, use of antioxidants may also have a protective effect on tumor cells, thus making chemotherapy and radiation less effective. Radiation therapy and some types of chemotherapy work by generating free radicals to damage the DNA of tumor cells; taking antioxidants may block the therapeutic effect needed to kill tumor cells (NCI, 2013c).

Supplement use is controversial because of limited research. However, the Office of Dietary Supplements at the National Institutes of Health was established in 1995 to create scientific databases on vitamins, minerals, and herbs.

**Mind-Body Techniques**

Approaches within complementary therapy can include exercise, yoga, meditation, relaxation techniques, massage, and other integrative therapies.

**EXERCISE**

Exercise is essential for recovery and maintaining good health. Regular physical exercise after a cancer diagnosis can have a positive effect on quality of life, including physical (balance and
flexibility), functional (reducing fatigue, improving heart and bone health), psychological, and emotional well-being (boosting energy and mood) (Hartmann & Loprinzi, 2012). Patients who have specific concerns or chronic conditions may benefit from a consultation with a physical therapist who can tailor a therapeutic fitness program designed for their unique needs during the treatment, recovery, and survivorship period.

The benefits of exercise with breast cancer patients has been the topic of recent research. The effect of exercise on the risk for breast cancer recurrence is comparable to that seen with endocrine therapy. Tamoxifen can reduce the risk for breast cancer recurrence by about 40%, whereas regular physical activity at a level of 9 metabolic equivalents of task (METS)—considered to be vigorous activity such as jogging or biking—reduces the risk for recurrence by 50%. This has been observed in long-term studies that are 10 to 15 years in duration (Nelson, 2015).

A few points to consider when discussing exercise for breast cancer patients include the following:

- Encourage an initial discussion with their healthcare provider; focus on any long-term medical conditions.
- Plan a strategy; encourage patients to start slowly with 10-, 20-, and 30-minute sessions of some form of moderate activity each day. Encourage strength training as well as aerobic exercise.
- Choose activities patients enjoy; it is easier to stick with a plan when doing something enjoyable.
- Help patients explore new ways to exercise, including dancing, walking, climbing stairs, swimming, etc.
- Get the patient a pedometer; tracking progress can be a great way to see positive feedback.
- Encourage exercise as a daily habit.

YOGA

Yoga is a mind-body practice that involves moving the body through a series of postures while practicing controlled breathing. Yoga can be an excellent way to deal with stress and anxiety as well as improve posture, flexibility, strength, and range of motion. Recent evidence indicates that yoga may improve mood, combat fatigue, and improve survival in breast cancer survivors (Nelson, 2015; Hartmann & Loprinzi, 2012). Another study with breast cancer survivors compared yoga versus strengthening activities, reporting an increase in quality-of-life measures and decreased fatigue with both activities (Stan et al., 2016).
MEDITATION AND RELAXATION TECHNIQUES

Meditation is a simple form of relaxation that can be performed anywhere. Meditation and focused breathing can assist breast cancer patients during medical encounters such as procedures or chemotherapy administration. Meditation focuses on deep breathing with eyes closed for at least 5 to 10 minutes. Many patients find that adding soothing music or sounds can also help with relaxation.

Guided imagery is a form of meditation that includes forming a pleasant mental image to focus on while deep breathing. Tai chi, described as a form of “moving meditation,” may also be appropriate as both a form of meditation and as gentle exercise.

MASSAGE

The benefits of massage therapy may include relaxation and decreased muscle tension. Studies have shown that massage therapy can decrease anxiety, pain, fatigue, and distress (Hartmann & Loprinzi, 2012). Types of massage therapy common in cancer care include Swedish massage, aromatherapy massage, foot or hand massage (reflexology), and acupressure massage. A type of massage called manual lymph drainage, performed by a massage therapist trained to work with cancer patients, uses precise, light rhythmic motions to reduce swelling of the arm due to lymphedema after a mastectomy.

Acupuncture

Acupuncture is one of the most researched and accepted forms of alternative medicine. It involves inserting from 1 to 20 or more thin needles into the skin at specific points. The needles may be left in place for 15 to 30 minutes. Acupuncture causes physical responses in nerve cells, the pituitary gland, and parts of the brain. These responses allow the body to release proteins, hormones, and other chemicals that control a number of functions affecting blood pressure, body temperature, and the immune system. Acupuncture also releases endorphins, the body’s natural painkillers.

Research has shown that acupuncture is effective for relief of chronic pain associated with cancer or its treatment as well as reducing nausea and vomiting caused by chemotherapy (NCI, 2015b; Hartmann & Loprinzi, 2012).

CASE

Patti is a 46-year-old breast cancer patient with a busy family and career. She also has a diagnosis of systemic lupus erythematosus (SLE), which is well controlled but with flare-ups. She is now at the point of completing her initial chemotherapy treatment and has questions about dealing with fatigue, stress, and anxiety as a cancer survivor. During a clinic visit with her treatment nurse, Gwen, she states that she would like to incorporate new strategies to decrease fatigue and stress to stay healthy but is not sure where to start.
Gwen suggests that Patti start by testing a few strategies to see which technique works best for her. The discussion includes what has worked in the past and what her goals are for the present and future. Based on this discussion, Gwen refers her to resources and a class on mindfulness meditation, a local yoga class, an online support group for younger women with breast cancer, and a physical therapist who can tailor a specific exercise program keeping in mind her chronic SLE diagnosis and her individual goals.

As part of the discussion, Gwen reinforces that Patti may need to continue to ask for assistance with her younger children and may want to return to work at a reduced schedule at first. Gwen also stresses that fatigue can be a symptom that takes months or years to subside. Gwen plans to follow up with Patti after one month to see how she is doing and make adjustments if needed.

PSYCHOSOCIAL ISSUES

Few words strike greater fear than “you have cancer.” Even though many women survive breast cancer and go on to lead full lives, the diagnosis may at first seem like a death sentence. Add the word *breast* and nightmare images flash, not only of death but also of disfigurement. A host of emotions follow the fear and may include shock, disbelief, denial, anger, sadness, and depression. These are all normal reactions.

Support and Information Needs

Patients facing a diagnosis of breast cancer need support and information about treatment options and what to expect in the short term. Many find comfort in talking with survivors of breast cancer and joining a professionally facilitated support group of women who are currently in treatment. Healthcare providers can also provide essential information and support to women with breast cancer.

Providing written information to women newly diagnosed with breast cancer is important because stress and anxiety can lead to forgetfulness. (The National Cancer Institute, the American Cancer Society, and other organizations listed in the “Resources” section at the end of this course have many materials available for patients.)

WHAT WOMEN NEED TO KNOW ABOUT FACING BREAST CANCER

Healthcare providers can offer the following support to patients with a breast cancer diagnosis:

- **Take time to learn as much as you can about your breast cancer diagnosis.** You have time to learn about this disease and the options for treatment; indeed, it is essential to educate yourself about breast cancer. You have time for second opinions and even third opinions. You have time to talk with other women who have faced this diagnosis and survived. Learning all you can about breast cancer helps you regain a sense of
control and gives you a sound basis for making important decisions about your future. Ask questions and seek out information from reliable sources in order to understand your individual situation and choices for treatment.

- **You may have many choices about treatment for your breast cancer.** Treatment choices depend on many factors, including your age, personal risk factors, the size of your breast, and the size of your tumor. There are often other options than mastectomy. If your tumor is small, lumpectomy may be an alternative. It may not be necessary to remove your lymph nodes; however, it is important to know whether the cancer has spread to the nodes. Surgery, chemotherapy, hormone therapy, and/or radiation therapy are other choices that may be recommended. You may also want to consider adding integrative therapies to deal with stress and anxiety and help with the side effects of cancer treatment.

- **You are not alone.** There are millions of women living with breast cancer today. Many lead active, productive lives, much as they did before breast cancer. Most never forget what it felt like to hear the words of their diagnosis, so many are willing to reach out to others with breast cancer.

- **There is no one correct decision for everyone**—only the decision that is right for you.

- **Take someone with you to all appointments** if possible, someone who can act as your advocate and your recorder. The emotional impact of cancer can interfere with your ability to hear and remember what doctors say, so ask a friend or family member to go with you and record or take notes at each appointment.

- **Keep a complete record** of your breast cancer journey. Learning that you have breast cancer can be one of the most stressful times in your life. Stress can make you forgetful, so keep a written record of your breast cancer diagnosis and treatment, including test results, pathology reports, findings of the radiologist based on mammograms or other imaging studies, and any communication with hospitals and doctors. You will need these records to get second (and more) opinions, to deal with insurance companies, and to be sure the records are completely accurate.

  It may be helpful to keep a log of medical appointments from the initial visit throughout your follow-up care. Many people keep this information in a notebook, along with self-monitoring notes about pain, reactions to medications, fatigue, and other symptoms.

  Many women also keep a journal about their breast cancer experience. Writing about your feelings can aid in the healing process and help to integrate the cancer experience into the rest of your life.

- **It is your journey.** You decide how to take the journey and with whom to travel. Friends, family, and your healthcare team can help, but only you can decide what is best for you.
Concerns about Relationships

Many women fear that breast cancer will affect their relationships with others, particularly their sexual partners. It can. This is particularly true for women who choose mastectomy, and even some women who choose lumpectomy are surprised at the impact of the scar.

Concerns about relationships and sexuality are particularly important to young women with breast cancer. Many young women are single and seeking to establish relationships. Almost all young women are working and just beginning to build a career. Some have no health insurance. Some are just starting families, and others have very young children.

Young women also are likely to be diagnosed at a later stage and to have more aggressive tumors. Chemotherapy treatment may impair fertility and/or the ability to breastfeed if they do have children. These women can find information and peer support through groups such as the Young Survival Coalition (see “Resources” at the end of this course).

Understanding Feelings That May Arise

A diagnosis of breast cancer can create powerful feelings of loss: loss of control, loss of sense of oneself as a healthy woman, possible loss of a breast, and perhaps even loss of life. Grief is the normal response to that loss and can include feelings such as denial, anger, bargaining, and depression. Grieving can help the patient come to terms with the actual and potential losses and move toward healing.

Cancer is the ultimate loss of control. People often feel that the body they have lived in for so many years has betrayed them. Someone who has taken good care of herself, eaten right, exercised—in other words, followed all the “rules”—may ask, “Why me?” The question has no easy answer. Fortunately, a healthy lifestyle may have delayed the progression of breast cancer and may make the treatments ahead easier to tolerate.

The thought of losing one or both breasts to cancer threatens self-image and can lead to anger and/or depression. These are normal reactions. Given time, however, most women realize that they are more than just their breasts and that survival is more important.

Once breast cancer becomes a fact of life, women may feel guilty and blame themselves for something they did or failed to do. Not only is this not helpful, it is probably not true. The biggest risk factors for breast cancer are unchangeable: being female and getting older. Patients may find it useful to discuss their thoughts and feelings about what may have caused their breast cancer in a support group, with survivors, with a therapist/counselor, or with a supportive healthcare provider.

The feelings that surround breast cancer differ with each woman. Some women take longer than others to work through and resolve these feelings. It is normal and natural to become totally consumed by the process. Just as it takes time to recover from the loss of a friend or loved one, recovering from the losses that cancer represents also takes time.
Patients need time to heal emotionally as well as physically. Although breast surgery may be routine for the surgeon, it is highly unusual for the patient. Cancer changes a person forever, and it generally takes a while to understand what those changes will be. This can be difficult for patients who are still getting used to the idea of having a life-threatening illness and undergoing treatment. Treatment itself also requires rest and time for healing and recovery, as it can be an assault on the body’s defenses.

Support groups are helpful to many women with breast cancer. Being able to talk openly with friends and family can evoke an enormous outpouring of love and support. Accepting these offerings can comfort both the patient and the givers. People who care may need for the patient to tell them how best to help.

A cancer diagnosis also can cause people to distance themselves from the patient, at least initially, often out of fear of the disease or because they do not know how to react. Patients can prepare for this reaction and learn to focus on their immediate issues of treatment and recovery.

CASE

Brenda, a 42-year-old teacher who had a mastectomy for stage IIb ER+/PR-/HER2/neu breast cancer, comes in pretreatment for an instructional session by the oncology nurse, Teresa. Brenda has come alone for her visit and appears apprehensive. After speaking about the specifics of her chemotherapy regime, possible side effects, and ways to cope, Teresa asks Brenda about her support system. Brenda becomes teary-eyed, states she was divorced two years ago and recently moved into the area to get a “fresh start” for herself and her 12-year-old twin girls. Her mother has offered to come from out of state to “help out,” but her time would be limited and she is “getting on in years.”

Brenda expresses her fear and anxiety about being able to handle the cancer treatment and care for her young daughters at the same time. She also admits to feeling self-conscious about her body now and wonders if she will ever date again. Teresa acknowledges this is a stressful, life-changing time for Brenda, even without the diagnosis and treatment of breast cancer.

Teresa speaks to Brenda about the times she will most likely experience the greatest fatigue and other side effects, helping Brenda think through and plan the most helpful time for her mother’s visit. Teresa also refers Brenda to a local cancer support group and encourages her to seek support from the church she just joined. Teresa offers a referral to the social worker, which Brenda declines at this time. Teresa emphasizes the importance of positive coping through self-care, helping Brenda see this is not selfish but something that will enable her to be there in the future for her young daughters.

Brenda verbalizes her understanding and also thankfulness that she has “good insurance” and will be off work until the school year restarts in the fall.
Talking about Breast Cancer

The patient’s first decision is typically whom to tell, how to tell, and how to deal with the reactions they receive. Breaking the news that one has breast cancer is difficult and painful, particularly when the patient can scarcely believe it herself. But not telling family and others who care is difficult too. Keeping a secret takes time and energy that the patient will need for getting through the weeks and months ahead.

TELLING FAMILY AND FRIENDS

It is important to pick the right time and place to break the news: time enough for asking and answering questions and a place where it is okay to cry and hug and talk openly. Loved ones will be experiencing some of the same feelings as the patient—shock, fear, anger, denial—plus empathy for the situation and sorrow at the possible loss this disease might cause.

Family and friends may not know how to respond even though they may want to offer support. What they want most of all is for the patient to be okay again. Patients who explain their situation as they learn more about it help loved ones deal with the news and show them how they might help. Patients may keep a list of those who offer, “Let me know if there’s anything I can do.” These people can be called on for help as needed: for a ride to medical appointments, to run errands, to prepare food, to care for children or pets, or just to drop by for a visit. Family and friends are often delighted to be of help.

The patient is the only one who can decide whom to tell and how much to tell them. Some women may not want to “go public” about their breast cancer but instead confine the news to immediate family and friends. Some women cope by sharing their story openly with extended family and friends through social media such as Facebook or CaringBridge. The choice is very personal for each woman.

TELLING AN EMPLOYER

Breast cancer disrupts every part of life, and work is no exception. Diagnostic tests, medical appointments, surgery, and other treatments can mean weeks or months away from the job. Ideally, employee and employer work together to develop a plan for needed absences and a return to work. Some employers can be understanding about employee illness. For example, companies may offer a “sick pool” in which employees who use up their sick days can take additional time through other employees’ donations of sick days to the pool.

A few employers may prove difficult to deal with. Some women have experienced discrimination or even dismissal because of their cancer. Such a practice is now illegal, but it can happen anyway.

Those employed at the time of a cancer diagnosis may have the right to keep their job, and benefits may be protected by federal and state law, depending on the number of employees at a
company. The federal Family Medical Leave Act (FMLA) of 1993 applies to companies with 50 or more employees. FMLA specifies who is eligible, when leave can be taken and for how long, whether it will be paid or unpaid, how leave will affect benefits, returning to work, and other issues. State law may supersede FMLA if the state law provides better benefits for the employee.

Employees also have the right to privacy. Any information a patient communicates to an employer about illness or any other medical information must not be placed in personnel files but in confidential files with access restricted to only those with a legitimate need to know. Patients also have the right to examine their personnel files.

Employee rights for a person with cancer are protected by the Health Insurance Portability and Accountability Act (HIPAA). This law addresses preexisting conditions, forbids discrimination against employees based on health status, and guarantees availability and renewability of health insurance coverage to certain individuals.

SURVIVORSHIP AND FOLLOW-UP CARE

Cancer casts a long shadow. Anyone diagnosed with cancer lives with the possibility of recurrence. Although many women survive breast cancer and live out a normal lifespan, others do not. That is why each new pain or other symptom brings forth the fear of recurrence or metastasis until the symptom disappears or is found to be something other than cancer. Learning to live with uncertainty is part of recovery from cancer, and it is different for each individual. Healthcare providers can help reduce the fear and anxiety associated with cancer survivorship by providing practical information to patients.

Self-efficacy is the confidence to produce desired effects by one’s own actions. In one study on breast cancer survivors, self-efficacy is defined as one’s confidence in the ability to manage symptoms and emotions related to having breast cancer, including the ability to ask for help, knowing how and when to report symptoms, and doing what is important after breast cancer treatments are completed. Overall, the study found women ages 45 or younger had greater fear of recurrence than older survivors, especially if their self-efficacy was low. By providing education, encouragement, and referrals to both support groups and reputable websites, nurses can help increase self-efficacy, which may help decrease fear and anxiety associated with recurrence risk (Ziner et al., 2012).

Patients should be encouraged to focus on wellness—taking good care of body, mind, and spirit—by eating a healthy diet, getting enough sleep and exercise, paying attention to symptoms, and getting regular checkups. Wellness also includes grieving one’s losses, whether the loss of a breast, loss of a relationship, or loss of the sense of control. It means seeking support when one needs it. Many women continue with a support group after treatment has ended. Others seek individual counseling and psychological support. Many women find further healing by helping others who are just starting on their cancer journey. The best outcome in the “new normal” for patients is a lifestyle that has changed to a healthier one and an attitude that has changed to one of ongoing appreciation where each day is viewed as a gift.
Survivorship Care Plan

The Commission on Cancer has mandated that all cancer centers provide a survivorship care plan to all cancer patients. The American Cancer Society and American Society of Clinical Oncology both have published breast cancer survivorship care guidelines.

Breast cancer survivors may face significant short- and long-term effects of cancer and its treatment. To assist each survivor, an individualized care plan should be provided that includes a summary of all treatment as well as a follow-up care plan. This plan is created in partnership with the cancer survivor to identify and prioritize individual goals. The survivorship care plan should also include information about individual risks, recommended tests and procedures, supportive care, and wellness strategies (Runowicz et al., 2016). (See also “Resources” at the end of this course.)

Symptoms That Require Attention

When walking the tightrope between fear of recurrence and getting on with life, each new ache or pain can trigger anxiety. This is normal, but it can also be immobilizing. ASCO (2015) recommends that breast cancer patients see their doctor immediately if any of the following signs and symptoms occur and/or persist:

- Chronic bone pain or tenderness (persistent)
- Bone fractures
- Skin rashes, redness, or swelling in the breast or arm (persistent)
- New lumps in the breasts, under the arm or chest wall
- Changes in the shape or size of the breasts
- Chest pain and any shortness of breath (persistent)
- Pain that is constant, worsening and not relieved by OTC medication
- Changes in weight, especially weight loss when not intentional
- Seizures or headaches that are not relieved by OTC medication
- Chronic cough or problems breathing
- Abdominal pain
- Jaundice (yellowing of skin and eyes)
- Changes in vision
- Extreme fatigue
- Poor appetite
- Fevers, night sweats
These symptoms may or may not be a sign of recurrence, but they do call for prompt evaluation. If breast cancer recurs, it usually happens within the first five years after diagnosis and is most often suspected or discovered by women themselves.

**Routine Follow-Up Care**

Two major entities—ASCO (American Society of Clinical Oncology) and NCCN (National Comprehensive Cancer Network)—have issued guidelines for surveillance of breast cancer patients after curative-intent treatment.

**ASCO guidelines** (2015) include:

- History and physical exam every 3 to 6 months for 3 years, then every 6 to 12 months for 2 years, then annually thereafter
- Annual mammogram starting no sooner than 6 months after radiation therapy is completed
- Regular bone mineral–density testing for patients taking AIs
- Breast self-exam every month
- Endocrine therapy, continued as directed by oncologist

**NCCN guidelines** mirror ASCO’s, except they recommend a history and physical exam every 4 to 6 months for 5 years, then annually thereafter.

Both guidelines recommend referral for genetic counseling for familial cancers. Both guidelines do not recommend any other routine laboratory tests or imaging unless abnormalities are detected with history and physical or mammogram because more intense surveillance has not been shown to improve overall survival.

These guidelines do not take into account a patient’s hormone receptor status. This is significant because hormone receptor–positive cancers are slower growing and may take longer to recur. As the population of cancer survivors grows, additional research may lead to more accurate and specific guidelines (Margethaler et al., 2012).

**Health and Wellness Recommendations**

Women recovering from breast cancer are encouraged to follow established wellness guidelines. These include maintaining a healthy weight, exercising, not smoking, and eating a balanced diet.

The following guidelines are encouraged:

- Eat a plant-based diet focused on fruits and vegetables, whole grains, and legumes; exclude high-calorie foods and beverages and consume less saturated fat.
• Include moderate physical activity for at least 150 minutes or vigorous activity for 75 minutes each week.
• Participate in strength training exercises at least two days per week.
• Limit alcohol consumption to no more than one drink per day.
• Quit smoking or using other types of tobacco.
• Follow recommendations for general cancer screening (see below).
  (ASCO, 2015)

Other Cancer Screenings

Breast cancer patients also need to stay current with screenings for other types of cancer, which may include colorectal, cervical (if cervix is present), endometrial (if uterus is present), and skin cancer, among others. Depending on age and family history, patients should also have a colonoscopy to screen for colon cancer. If detected early, colorectal cancer can be completely cured by surgery to remove polyps. Women should have a Pap smear for detection of cervical cancer every 3 years, especially in younger women (ages 21 to 29). Women ages 30 to 65 should have Pap with HPV testing every 5 years (ACS, 2016f). This is also a highly curable cancer when caught early, but it can be very deadly if not.

RECURRENT BREAST CANCER

Breast cancer that recurs may be local, regional, or metastatic. Treatment may be local/regional or systemic and can range from surgery alone to high-dose chemotherapy. The choice depends on several factors, including but not limited to:

• Location and size of the new tumor(s)
• Length of time since the initial cancer diagnosis
• Degree of lymph node involvement
• Whether distant organs are involved

Cancer that recurs within two years after the initial treatment tends to be more aggressive than cancer that recurs later.

Local Recurrence

Breast cancer most commonly recurs locally—in or near the site of the original tumor, for example in or around the scar. When recurrent cancer is confirmed, the physician orders blood tests and a bone scan to determine whether the cancer has spread beyond the breast. Any cancer that recurs locally is regarded as aggressive and resistant to treatment. When cancer recurs locally after lumpectomy, mastectomy is the preferred treatment.
Regional Recurrence

When breast cancer cells have spread to the adjacent lymph nodes (usually in the axilla) or to the chest wall, it is termed a regional recurrence. This may require surgical treatment and/or localized radiation therapy as well as systemic treatment.

Cancer in a different part of the breast or in the contralateral (opposite) breast may be a new cancer, which is called a second primary cancer. This cancer may be an entirely different cell type and may be treated successfully with surgery alone, depending on the stage and tumor type. The biopsy may or may not be able to determine whether the new tumor is recurrent disease or a second primary, but it will help determine the treatment.

Metastatic Disease (Distant Metastasis)

Once breast cancer has spread to distant organs (stage IV), cure is no longer possible. However, palliative care measures—including radiation, chemotherapy, endocrine therapies, targeted therapies, and bisphosphonates—can significantly improve survival length and quality of life. The most common sites of metastasis for breast cancer are the bone, brain, lungs, and liver.

Breast cancer that metastasizes to the bone can be treated with targeted radiation therapy, either stereotactic external beam or with radiopharmaceuticals. Therapies such as zoledronic acid (Zometa) and denosumab (Zgeva, Prolia) can help reduce the pain of bone metastases, strengthen bones, and decrease morbidity due to skeletal-related events (SREs) (Hartmann & Loprinzi, 2012). There may be the need for surgical intervention, in some cases for rod placement, to either treat or prevent fracture in large, weight-bearing bones that are affected by disease. Patients with cancer in the bone should be cautioned about the increased risk of fracture.

Metastatic cancer that develops in the brain or around the spinal cord can also be treated to improve quality of life. Steroid medications can be given to decrease pain, swelling, and neurological symptoms. Whole brain radiation or localized brain radiation (Gamma Knife treatment) can be used to treat women whose cancer has spread to the brain.

Palliative Care

Palliative care can be offered during this time. Palliative care specialists work together with the healthcare team, such as nurses, nutritionists, social workers, chaplains, pharmacists, and others, to focus on creating an individual plan to address any lasting treatment side effects, pain, emotional aspects, and other concerns of the cancer patient. The idea is to treat the whole person—including the physical, emotional, social, and spiritual aspects.

Palliative care is often confused with hospice care, which is provided for people who have a terminal diagnosis. Palliative care can be provided at any time during a cancer diagnosis, not just at the end of life.
The inclusion of palliative care may include positive benefits such as:

- The ability to fully complete treatment
- Improved quality of life during treatment
- Increased ability to perform daily activities
- Living longer
- Improved ability to deal with the emotions
- Increased connection to social support
- Fewer hospitalizations

**WHEN CURE IS NO LONGER POSSIBLE**

When efforts to slow cancer growth are no longer effective, emphasis shifts from cure or control of the cancer to providing comfort and symptom management with a goal of providing the best quality of life possible during the time remaining for the patient. For many women, making the decision to stop cancer treatment that is no longer working can be a powerful step to be free of the side effects of treatment and take control of their lives.

Patients with recurrent or metastatic breast cancer need support and understanding more than ever, not only from family and friends but from health professionals as well. They need to be able to talk openly about their cancer, their feeling and concerns, their care preferences, and their decisions about ending treatment. Helping patients and their family members change their focus from seeking cure to seeking the best comfort and quality-of-life measures with end-of-life care is paramount. Because this can be very stressful for some people, they may require support from various resources, such as social work, certified counseling/psychotherapy, peer support groups, and chaplains.

Cancer reminds us to take care of unfinished business, not only in personal relationships but also in practical matters, sometimes referred to as “getting one’s affairs in order.” Although family and friends may be uncomfortable with these discussions, they can be reassuring to the patient.

**WAYS TO MAINTAIN HOPE AND CONNECTION TO OTHERS**

- Encourage quality time with family (plan a trip or outing that they have always wanted to take together)
- Focus on pain and symptom management
- Encourage expression of feelings (communicating their love for others, forgiveness, and/or gratitude)
- Create a living legacy to leave for family members (writing letters or recording family stories or videotaped messages)
- Encourage time with friends who are supportive
ELEMENTS OF PRACTICAL END-OF-LIFE PLANNING

- Advance medical directives
- Do-not-resuscitate (DNR) or allow natural death (AND) orders
- Legal issues such as wills and estate planning
- Hospice care
- Organ donation
- Legacy building
- Funerals and memorials

Hospice Care

Hospice care is provided for people once they receive a terminal diagnosis. The hospice team usually includes doctors, nurses, pharmacists, social workers, therapists, chaplains, and others. The goal of hospice is to provide the best quality of life during the time remaining and to allow the patient and family to have a peaceful and natural death experience.

People may mistakenly think that hospice refers to a place. Although there are some residential hospice facilities, most hospice care takes place in the client’s home or the home of a loved one, with family members participating in care if they choose. However, hospice care also occurs in hospitals and nursing home settings.

Often, when patients have reached a place of acceptance about nearing the end of life, they can be very peaceful about it but still fearful of the death itself being painful. At this stage in the patient’s care, it is important to ensure the level of pain control is satisfactory for the patient. Hospice nurses especially are trained in this area and work closely with the patient and physician in utilizing medications and strategies available to attain the best pain control possible while minimizing unwanted side effects.

Nurses and other health professionals can provide information and resources to help friends and family members understand why implementing hospice care doesn’t mean that the patient is “giving up” and may actually be comforting to the patient. For example, some people think calling in hospice will shorten the patient’s survival. However, patients who receive hospice care many times live longer than those who do not have hospice care.

No matter where women are in their breast cancer journey, nurses and other healthcare professionals can empower them to cope in the best manner possible through individualized education, skilled care, encouragement, and support.

CASE

Today in the clinic, the clinical nurse educator, Susan, is meeting with a patient to discuss end-of-life planning. Constance was diagnosed with advanced breast cancer that had spread beyond
the breast at the time of her diagnosis. She has been treated with surgery, radiation, chemotherapy, and hormonal therapy for the past three years. She and her family have been actively involved in her treatment decisions. Two weeks ago, she decided to stop active treatment since she was no longer responding to the therapy. When Susan meets with her today, Constance states that she would like to consider writing a living legacy and plan for hospice care when the time is appropriate.

Susan provides resources and ideas to encourage writing her personal messages and family stories. She also stresses the importance of taking time to communicate her feelings in person. They discuss hospice care, and Constance mentions that she would like to have hospice resources provided in her own home so that she can have family present with her during her final days and weeks. Goals for care, comfort, and support are part of this conversation. Susan refers her to a hospice nurse to plan goals for her care as well as to a social worker to fill out advanced directives and address any other needs she may have related to end-of-life planning.

Constance thanks Susan for the visit together, and they agree to a follow-up call in two weeks to check in on any unmet needs she may have identified during this time.

CONCLUSION

Breast cancer is a common malignancy among women, representing 4 in 10 female cancer survivors in the United States. Long-term survival is common after breast cancer treatment, with a 5-year survival rate of almost 90% (Runowicz et al., 2016).

Diagnosis and treatment for breast cancer may vary based on many factors, including type, stage, and other individual differences. Women may be presented with various treatment options and need expert guidance to assist in decision making, weighing short- and long-term effects of each treatment choice. For most, treatment does not end with the initial surgery, radiation, and/or chemotherapy but may also include long-term surgeries for reconstruction as well as endocrine therapy for a period of 5 to 10 years to prevent recurrence.

Survivorship for women with a history of breast cancer may include monitoring and surveillance of short- and long-term effects of treatment as well as screening for other secondary cancers. Women who are actively involved in their care with a focus on wellness goals—including nutrition, mind-body strategies, and exercise—may experience a better quality of life and have a decreased chance of cancer recurrence (Runowicz et al., 2016).

As women live longer with breast cancer and the associated long-term treatments, care has shifted to a chronic care model. Women with a history of breast cancer will benefit from the initiation of standards and expectations to provide patients with an individualized survivor care plan to assist them in being as informed as possible about their future.
RESOURCES

American Cancer Society
http://www.cancer.org/cancer/breastcancer/

Breastcancer.org
http://www.breastcancer.org

Breast cancer survivorship
http://www.cancer.net/cancer-types/breast-cancer/survivorship

CancerCare (Emotional, practical, financial issues)
http://www.cancercare.org

ClinicalTrials.gov (National Institutes of Health)
http://clinicaltrials.gov

Living Beyond Breast Cancer
http://www.lbbc.org

Mammography facilities (U.S. FDA)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMQSA/mqsa.cfm

National Cancer Institute (National Institutes of Health)
http://www.cancer.gov

NCCN guidelines (National Comprehensive Cancer Network)

Office of Dietary Supplements (National Institutes of Health)
http://ods.od.nih.gov

Oncology Nursing Society
http://www.ons.org

Society for Integrative Oncology
http://integrativeonc.org

Young Survival Coalition
http://www.youngsurvival.org

REFERENCES


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1. Breast cancer typically originates in the:
   a. Stromal tissue.
   b. Epithelial cells.
   c. Nipple fluid.
   d. Lymph nodes.

2. The most common sign of breast cancer is:
   a. Pain in the breast or underarm.
   b. Pitting of the breast.
   c. A painless, irregular lump.
   d. A retracted nipple.

3. The two racial/ethnic groups with the highest incidence of breast cancer in the United States are:
   a. Non-Hispanic black and Asian/Pacific Islander women.
   b. Non-Hispanic white and black women.
   c. Asian/Pacific Islander and Non-Hispanic white women.
   d. American Indian/Alaska Native and Non-Hispanic black women.

4. Which is a modifiable risk for breast cancer?
   a. Long-term, heavy smoking
   b. A history of dense breast tissue
   c. Early menarche or late menopause
   d. Genetic mutations associated with breast cancer

5. As a genetic risk factor for breast cancer, the BRCA2 gene mutation is:
   a. Common, accounting for the majority of breast cancer cases diagnosed each year.
   b. Uncommon, but associated with an increased risk for breast cancer.
   c. Not a risk factor with known association to breast cancer.
   d. Associated with breast cancer only in women of Ashkenazi Jewish heritage.
6. There is a well-established link between an increased risk of breast cancer and:
   a. Prior radiation treatment to the chest area.
   b. Exposure to PCB and DDT.
   c. Exposure to hair dyes and electromagnetic fields.
   d. Repeat mammography screening.

7. Mammography screening is most effective in reducing the risk of breast cancer death among women:
   a. Under 50 years of age.
   b. Aged 50 to 74 years.
   c. With dense breast tissue.
   d. Aged 75 years or older.

8. The current debate surrounding the recommendations for mammography screening includes:
   a. Whether MRI should replace mammography as the gold standard.
   b. The age at which routine mammography screening for average-risk women should begin.
   c. Whether women at high risk should participate in mammography screening.
   d. The best way to ensure women have access to mammography screening.

9. After her mammography screening detects an unusual finding, a female patient returns for ultrasound testing, which is most useful in:
   a. Distinguishing between fluid-filled cysts and solid tumors.
   b. Diagnosing breast cancer in premenopausal women.
   c. Pinpointing the location of a tumor.
   d. Identifying ductal carcinoma in situ.

10. The most definitive test for diagnosing breast cancer is:
    a. A mammographic evaluation.
    b. A breast biopsy.
    c. An ultrasound.
    d. An estrogen receptor test.
11. As part of a comprehensive evaluation for establishing a diagnosis of breast cancer, a primary care provider may test for possible metastasis by ordering blood tests such as:
   a. A thyroid function test and a lipid profile.
   b. A glucose tolerance test, a glutamine level, and a folic acid level.
   c. A serum alkaline phosphatase level and a calcium level.
   d. A cortisol level and a chromosomal analysis.

12. The standard of care in biomarker testing of breast tumors includes ER, PR, and:
   a. G-protein coupled (GPC) receptors.
   b. Human epidermal growth factor receptor 2 (HER2/neu) oncogene.
   c. Carcinoembryonic antigen (CEA).
   d. Interleukin-6 (IL6) receptors.

13. The TNM staging system for breast cancer describes whether the cancer has metastasized, the size of the tumor, and:
   a. The number of lymph nodes removed.
   b. The location of lymph nodes removed.
   c. The number of lymph nodes involved.
   d. The assessment of lymphatic transplantation.

14. Which TNM classification describes stage IIIa breast cancer?
   a. T1 N0 M0
   b. T1 N2 M0
   c. T0 N1 M0
   d. T3 N0 M0

15. Invasive lobular carcinoma commonly presents as:
   a. A hard lump in the breast.
   b. A thickened area of the breast.
   c. Mammary skin warmth and redness.
   d. Nipple drainage in a nonlactating woman.

16. Breast tumor cells described by a pathologist as “low histologic grade”:
   a. Closely resemble their cells of origin.
   b. Are irregular and unlike normal cells.
   c. Grow at a rapid rate.
   d. Are more likely than high-grade cells to become invasive over time.
17. In a high–nuclear grade breast tumor, the cancer cells are:
   a. Readily identified by their morphologic shape.
   b. Unlikely to become invasive.
   c. Undergoing cell death.
   d. Proliferating rapidly.

18. Triple-negative breast cancer is more common among:
   a. Postmenopausal white women.
   b. Young Asian American and young Native American women.
   c. Postmenopausal Native American women.
   d. Young and African American and Hispanic women.

19. Unlike other forms of breast cancer, inflammatory breast cancer is initially treated with:
   a. Surgery.
   b. Radiation therapy.
   c. Neoadjuvant chemotherapy.
   d. Hormone therapy.

20. In a female patient with a large breast tumor, neoadjuvant treatment is typically administered:
   a. During surgery to remove the tumor.
   b. Prior to definitive surgery to remove the tumor.
   c. To reduce the risk of lymphedema.
   d. After surgery to remove the tumor.

21. When a patient with early-stage breast cancer chooses to have a lumpectomy (breast-conserving surgery), which follow-up treatment is generally recommended?
   a. Chemotherapy
   b. Radiation therapy
   c. Hormone therapy
   d. Targeted therapy

22. Which term refers to the surgical procedure that involves removal of the entire breast and axillary lymph nodes but leaves the chest wall muscles intact?
   a. Modified radical mastectomy
   b. Simple or total mastectomy
   c. Radical mastectomy
   d. Prophylactic mastectomy
23. In a patient with breast cancer, a lymph node assessment is performed to:
   a. Determine the type of breast cancer.
   b. Show the grade of the tumor.
   c. Determine whether the cancer has spread.
   d. Predict the cure rate of the cancer.

24. One year after breast cancer treatment, including axillary lymph node dissection, a female patient reports that her arm on the affected side has now begun feeling heavy and is painful. The patient’s symptoms are most likely related to:
   a. The normal recovery process after surgery.
   b. Overuse of the arm after surgery.
   c. The development of lymphedema after surgery.
   d. Lymph node recovery after surgery.

25. A female patient who recently had breast cancer surgery, including lymph node dissection, can reduce her risk of developing lymphedema by:
   a. Limiting driving, swimming, and resistance exercise training.
   b. Restricting her intake of fluids.
   c. Avoiding arm constriction and needle puncture on the surgical side.
   d. Taking vitamins B, C, and D.

26. In patients who have had breast reconstruction surgery, chemotherapy treatments normally begin:
   a. Immediately after surgical breast reconstruction.
   b. Prior to surgical breast reconstruction.
   c. Six months after reconstructive surgery.
   d. Two to three weeks after reconstructive surgery.

27. A female patient is meeting with the surgeon to discuss breast reconstruction options. Her treatment plan includes surgery followed by radiation therapy. The surgeon explains that the best option for the patient is delayed autologous tissue reconstruction instead of implant-based reconstruction due to the higher risk of:
   b. Capsular contraction.
   c. Surgical site infection.
   d. Lymphedema.
28. Which is a description of the typical dosage for hypofractionated radiation therapy as given after breast cancer surgery?
   a. Larger-dose radiation therapy given over 2 to 3 months
   b. Lower-dose radiation therapy given over 2 to 3 months
   c. Larger-dose radiation therapy given over 3 weeks
   d. Lower-dose radiation therapy given over 3 weeks

29. Which are two common short-term side effects associated with radiation therapy for breast cancer?
   a. Fatigue and skin irritation
   b. Constipation and nausea
   c. Nausea and dyspnea
   d. Depression and diarrhea

30. Female patients who are treated with tamoxifen (Nolvadex) are at risk for which life-threatening side effects?
   a. Heart failure and cardiac toxicities
   b. Stroke and endometrial cancer
   c. Lymphoma and other blood cancers
   d. Decreased pulmonary function and cervical cancer

31. Which medications are successful in controlling or eliminating chemotherapy-associated nausea and vomiting?
   a. Clonidine (Catapres) and meperidine (Demerol)
   b. Palonosetron (Aloxi) and aprepitant (Emend)
   c. Oxybutynin (Ditropan) and azithromycin (Zithromax)
   d. Ofloxacin (Floxin) and doxorubicin (Adriamycin)

32. Recommended strategies to help with fatigue due to cancer and its treatment include:
   a. Eating foods higher in sugar for energy.
   b. Incorporating moderate regular exercise.
   c. Drinking more caffeine for energy.
   d. Taking long (over 60 minutes) rest periods during the day.
33. In patients treated with trastuzumab (Herceptin), it is important to monitor for which major side effect?
   a. Electrolyte imbalance
   b. Cardiac toxicity
   c. Severe mucositis
   d. Neurocognitive changes

34. It is important to educate a patient who is using vitamins and supplements during cancer treatment that some antioxidant supplements may:
   a. Enhance the effectiveness of the treatment.
   b. Be taken in higher doses during treatment.
   c. Be taken in lower doses during treatment.
   d. Decrease the effectiveness of the treatment.

35. Which alternative therapy has been shown to reduce the chemotherapy side effects of nausea/vomiting?
   a. Acupuncture
   b. Yoga
   c. Meditation
   d. Exercise

36. Which law protects a patient who is recovering from breast cancer from insurance discrimination because of her cancer diagnosis?
   a. Healthcare Quality Improvement Act (HQIA).
   b. Health Insurance Portability and Accountability Act (HIPAA).
   c. Consolidated Omnibus Budget Reconciliation Act (COBRA).

37. Which symptom in a breast cancer survivor should be evaluated further as a sign of cancer recurrence?
   a. Chronic bone pain
   b. Low blood pressure
   c. Elevated blood pressure
   d. New onset of type 2 diabetes
38. Six months after completion of radiation therapy for breast cancer treatment, routine follow-up care recommendations for a normal-risk female patient who is without symptoms include:
   a. An endometrial biopsy.
   b. A mammogram.
   c. An MRI scan.
   d. A PET scan.

39. Cancer that recurs within the first two years following diagnosis and adjuvant treatment tends to be:
   a. More aggressive than cancer that recurs later.
   b. Localized.
   c. Less aggressive than the original cancer.
   d. Untreatable.

40. For a patient who has advanced breast cancer that is no longer responding to treatment, hospice care is provided:
   a. For comfort and improved quality of life for patients who are terminal.
   b. When a patient has exhausted all other treatment options available.
   c. In a hospital setting because of the medications prescribed.
   d. When a patient no longer wishes to live.