

the outer surface of the cervix are squamous (flat and scaly), whereas the cells lining the endocervical canal are columnar (columnlike).

Greater understanding of the behavioral and biologic mechanisms accounting for early age of first sexual intercourse and subsequent HPV infection in adolescents may help direct primary prevention of HPV infection and HPV-related disease. In addition to the risky behaviors discussed previously, it is now known that the cervix is particularly vulnerable to HPV during adolescence and especially early puberty.¹⁵¹ There are a number of potential reasons for increased vulnerability of the cervix. Cervical immaturity in the young girl and adolescent female is marked by inadequate cervical mucus, which acts as a protective barrier against infectious agents. Two other examples include cervical ectopy, which is characterized by rapid physiologic changes in the cervical epithelium, or immature immune response to HPV infection.¹⁵¹

Cervical ectopy refers to the condition in which a small ring of cells extend beyond the normal border of the endometrium (the inner wall of the uterus) to the cervical os (the neck of the uterus). Cervical ectopy is a normal physiologic phenomenon in women under hormonal influence, such as during puberty, but may increase cervical susceptibility to infection with STIs, including HPV.

The development of a protective cervical mucus is progressive through adolescence to full maturity. Until cervical maturity is reached, the woman remains at increased risk for HPV infection (and other STIs). Cervical immaturity is a risk factor for women who engage in sexual intercourse at a young age, including those who are sexually abused.¹⁵¹

Clinical Manifestations

Most people never know they have had HPV because there are no symptoms and a healthy immune system clears the body of infection. When it persists, HPV can cause lesions in the cervix, vagina, or vulva. Left untreated, these lesions can progress to cancer. Early-stage cervical cancer, especially in the preinvasive stage, is usually asymptomatic. Often women have advanced disease before abnormal bleeding occurs. This can present as spotting between menstrual periods, longer and heavier periods, bleeding after menopause, or bleeding after sexual intercourse. Pelvic or low back pain can occur, but this is uncommon.

More advanced stages of cervical cancer may cause bowel and bladder problems because of pressure on the rectum or bladder or sexual difficulties because of the growth in the upper vagina, causing discomfort. Ureter blockage can lead to death because of uremia (the inability of the body to excrete waste), which causes uremic poisoning. The progression to this type of advanced cancer is relatively rare in developed countries.

The physical effects of cervical cancer after treatment are actually more significant. Women who have the conization procedure or loop electrosurgical excision procedure (LEEP) may experience cramping, bleeding, or a watery discharge. Hysterectomy, radiation therapy, surgery alone or combined with radiation, and/or chemotherapy may all cause significant side effects, which should improve over time with proper intervention.

The emotional effects of cervical cancer are often significant as well. Women treated with radiation almost always lose the benefits of estrogen because the ovaries are extremely sensitive to radiation. HRT is usually prescribed, and without this intervention, the emotional effects of cervical cancer can be compounded by hypoestrogenism and its emotional side effects.

Sexuality after hysterectomy or other interventions for this cancer can be impaired; women may experience depression from no longer being able to have children; and some women may feel guilt and shame associated with feeling "unclean" because of genital tract disease.

MEDICAL MANAGEMENT

PREVENTION. Risk of HPV and HPV-related cases of cervical cancer can be reduced and/or prevented using barrier contraceptives, engaging in monogamous sex with a likewise monogamous partner, or practicing sexual abstinence (see the section on Sexually Transmitted Disease in Chapter 8).¹⁵²

Although not preventive, studies show that consistent condom use can speed the regression of the HPV-related lesions on the cervix and on the penis and shorten the time it takes to clear HPV infections.^{153,154} Women with five or fewer lifetime sexual partners have higher regression rates compared with women who have had more than five partners.¹⁵⁵

The possibility of HPV infection among women who have sex with women (WSW) has been reported based on limited data.^{156,157} STDs can be spread between female sex partners, probably through the exchange of cervico-vaginal fluid and direct mucosal contact.¹⁵⁸

EARLY DETECTION AND SCREENING. Early detection is the key to a 100% cure rate for cervical cancer. Routine cervical screening is recommended for all women regardless of sexual orientation or practices beginning approximately 3 years after the onset of vaginal intercourse but no later than age 21 years (Table 20-2).

WSW should receive Pap smear screening according to the current guidelines. It should not be assumed that testing is not needed for those who use condoms consistently or for women who have not been in a sexual relationship with men.^{159,160} WSW should be educated about preventive measures including washing hands, using rubber gloves, and cleaning sex toys or using a protective barrier, such as a condom, especially when partners share such devices.¹⁶¹

Until age 30 years, annual screening is recommended with conventional cervical cytology. For women who have had three consecutive normal or negative cytology results, screening may be reduced to every 2 or 3 years. Average risk women aged 70 and older with an intact cervix may choose to stop cervical cancer screening if they have had no abnormal or positive cytology tests within the 10 years before age 70 years.¹⁶²

Some experts advise that Pap screening can be discontinued in women who have had the cervix removed (e.g., in conjunction with hysterectomy). Others support annual testing for most women regardless of age and to detect vaginal cancer in women who have had the cervix removed.

Table 20-2 Cervical Cancer Screening Guidelines*

	American Cancer Society†	American College of Obstetricians and Gynecologists‡
When to start cervical screening	Approximately 3 years after beginning sexual intercourse, but no later than 21 years of age	Same
Frequency of Screening		
Conventional Pap test	Annually; every 2-3 years for women older than 30 years with 3 negative cytology tests	Same
If liquid-based cytology	Every 2 years; every 2-3 years for women older than 30 years with 3 negative cytology tests	Annually; every 2-3 years for women older than 30 years with 3 negative cytology tests
If HPV testing used§	Every 3 years if HPV is negative, cytology negative	Every 3 years if HPV negative, cytology negative
When to stop screening	Women older than 70 years with more than 3 recent, consecutive negative tests and no abnormal test in prior 10 years	Inconclusive evidence to establish upper age limit

HPV, Human papilloma virus.

*Exceptions exist for women who are immunocompromised, have human immunodeficiency virus (HIV), or were exposed prenatally to DES.

†Data from Saslow D, Runowicz CD, Solomon D, et al: American Cancer Society Guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 52:342-362, 2002.

‡Data from Cervical Cytology Screening: AGOG Practice Bulletin No. 45, *Obstet Gynecol* 102:417-427, 2003.

§Wright TC, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol* 103(2):304-309, 2004.

Women with known HIV infection, HPV, or other STDs must especially be screened for cervical cancer.⁵⁰ Women who have a history of cervical cancer or in utero exposure to DES should continue screening after age 30 years using the same protocol as for women before age 30 years.²⁸⁵

VACCINE. The first cervical cancer vaccine (Gardasil) is now available; other HPV vaccines may be on the market soon (e.g., Cervarix). Gardasil blocks viruses that cause cervical cancer and protects against two strains of HPV believed responsible for 70% of cervical cancer cases and 2 viruses that cause 90% of genital wart cases.³¹⁷ Ongoing studies are investigating the effectiveness of Gardasil in boys and men ages 16 to 26 years and in mid-adult women ages 24 to 45 years.

Currently, the vaccine is administered intramuscularly in a series over 6 months and costs between \$300 and \$400, which may make its use prohibitive as a routine vaccination. The vaccination is advised for females before becoming sexually active, but sexually active females can also benefit. Even if the woman is already infected with one or more of the four HPV strains covered by the vaccine, the vaccine will help protect her from the remaining strains.^{121a} The vaccine can be given to females between ages 9 and 26.

The Advisory Committee on Immunization Practices (ACIP), which is part of the Centers for Disease Control and Prevention (CDC), has issued its first summary statement about recommendations for HPV vaccination.²¹³ The interested reader can read the full summary at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr56e312a1.htm?s_cid=rr56e312a1_e. The ACIP recommends routine

immunization of girls aged 11 to 12. This is a controversial social issue because safe sex practices can prevent HPV and its associated complications, making universal vaccination unnecessary. Both the ACIP and the National Women's Health Network advise that the vaccine should not replace routine cervical screening or education regarding sexual practices.⁷ Guidelines from the American Cancer Society (ACS) suggest routine vaccination for females aged 11 to 12 years, although girls as young as 9 years of age may receive the HPV vaccination. Universal vaccination for females aged 19 to 26 years is not advised.²⁶⁸

Each woman should make an individual decision regarding HPV vaccination based on her own risk and the potential benefit from the vaccination. Ideally, the vaccine should be administered before exposure to genital HPV through sexual intercourse because the potential benefit is likely to diminish with an increasing number of sexual partners.²⁶⁸

Vaccination is more imperative for women who do not have access to cervical cancer screening services. The protective effect of vaccination that is successfully provided to adolescent and young women who are unlikely to undergo regular Pap screening will yield greater positive outcomes than vaccination provided to women who will seek regular screening regardless.²⁶⁸

Vaccine trials in males are ongoing with results expected about the time this text is published. If efficacy is found among males, then vaccination may be recommended for males. It is not clear yet that vaccinating both males and females will provide any additional benefit in reducing HPV-cervical disease, and it may not be cost-effective.²⁶⁸

DIAGNOSIS. Information is gathered from examinations and diagnostic tests to determine the size of the tumor, how deeply the tumor has invaded tissues within and around the cervix, and the metastases to lymph nodes or distant organs. Staging to find out how far the cancer has spread is an important process and the key factor in selecting the right treatment plan.

Cervical cancer is detected using a Pap test, and the Pap test is credited with reducing the incidence of this cancer in the United States by 75% over the past 50 years. This test is used to detect changes in the cells of the cervix that may indicate a precancerous or cancerous condition. However, Pap tests have a 15% to 25% false-negative rate for detecting cervical dysplasia²⁷⁹ and can be inconclusive, requiring further testing, including HPV testing, colposcopy, conization (cone-shaped biopsy), or LEEP.

New automated screening systems (PAPNET or AutoNet) have been approved by the U.S. Food and Drug Administration (FDA) for computer review of negative Pap smears and for primary screening. These systems have the ability to reduce human error, but their cost-effectiveness is under intense scrutiny. Numerous other cervical biomarkers are under investigation for possible diagnostic use.¹⁴⁷

A new laparoscopic assessment of the sentinel lymph node in early-stage cervical cancer is under investigation with excellent preliminary results.^{66,187} Computed tomography (CT) scanning may be used in women who are not candidates for surgical.

STAGING. There are four stages of cervical cancer with intermediate steps within each stage (Box 20-3). Staging of cervical cancer is based on clinical staging rather than surgical staging. This means that the extent of disease is evaluated by the physician's physical examination and in some cases, a few other tests that are done such as cystoscopy and proctoscopy. Surgery may determine that the cancer has spread more than initially assessed. This new information may change the treatment plan, but it does not change the woman's FIGO stage.

Stage 0 is the precancerous stage, and there are no gross lesions; carcinoma is limited to the mucosa and is referred to as carcinoma in situ (CIS) or cervical intraepithelial neoplasia (CIN) grade 1, grade 2, or grade 3. For premalignant dysplastic changes, the CIN grading is used for Stage 0. Grade 1 is most likely to regress naturally and does not require treatment; grade 3 is most likely to advance to cancer. Grades 2 and 3 both require treatment.

Stage I is strictly confined to the cervix, and lesions are measured as less than or greater than 4 cm in size. In stage II, the cancer extends beyond the cervix but has not extended to the pelvic wall. The vagina is minimally involved, and there may or may not be parametrial involvement.

In *stage III* the carcinoma has extended to the pelvic wall and involves the lower one-third of the vagina and there may be kidney involvement (spread via the ureters). *Stage IV* is characterized by carcinoma that has extended beyond the true pelvis or has infiltrated adjacent organs (e.g., mucosa of the bladder or rectum). There may be metastatic spread of the growth to distant organs.¹⁴⁸

Box 20-3

STAGING FOR CERVICAL CANCER

Cervical cancer is staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system, based on clinical examination rather than surgical findings. The TNM staging system for cervical cancer is analogous to the FIGO stage. For premalignant dysplastic changes, CIN grading is used.

Stage 0: Full-thickness involvement of the epithelium (surface) without invasion into the stroma (support structure); carcinoma in situ (CIN grades 1, 2, or 3 are assigned)

Stage I: Invaded the cervix but has not spread any further

- IA: Small enough it can only be diagnosed by microscopy; there are no visible lesions
- IA1: Area of invasion is less than 3 mm ($\frac{1}{8}$ -inch) deep and less than 7 mm ($\frac{1}{4}$ -inch) wide
- IA2: Area of invasion is between 3 and 5 mm (about $\frac{1}{3}$ -inch) with horizontal spread of 7 mm or less
- IB: Visible lesion or a microscopic lesion with more than 5 mm of depth or horizontal spread of more than 7 mm; has spread into connective tissue of the cervix
- IB1: Visible lesion 4 cm or less in greatest dimension
- IB2: Visible lesion more than 4 cm

Stage II: Invades beyond cervix to upper $\frac{1}{3}$ of the vagina only

- IIA: Without parametrial (tissue next to the cervix) invasion
- IIB: With parametrial invasion

Stage III: Extends to pelvic wall or lower $\frac{1}{3}$ of the vagina

- IIIA: Involves lower $\frac{1}{3}$ of vagina but not the pelvic wall
- IIIB: Extends to pelvic wall and/or blocks urine flow to the bladder; may have spread to pelvic lymph nodes

Stage IV: Extends beyond the true pelvis

- IVA: Invades mucosa of bladder or rectum and/or extends beyond true pelvis
- IVB: Distant metastasis to other organ (beyond the pelvis) such as lungs

If the woman is treated surgically, the pathology report can be used to provide a separate pathologic stage; this does not replace the original clinical stage.

CIN, Cervical intraepithelial neoplasia.

TREATMENT. There is a concern that precancerous stages (CIN 2 or 3) may progress to invasive cancer so these are treated with cryotherapy, laser vaporization, excision (e.g., LEEP), cone biopsies, and possibly indoles (phytochemicals found in cruciferous vegetables, such as broccoli, cauliflower, and cabbage, when taken as a supplement).^{22,337}

Some of these treatment methods can interfere with a woman's ability to have children because weakening of the cervix makes carrying the child to full-term difficult. New findings suggest that some women with CIN 2 or 3 may not need treatment right away as the abnormality may go away on its own. The best candidates are women who have had five or fewer lifetime sexual partners who do not have HPV infection. Regression rates for CIN 2 and 3 in this group are over 60%.⁵⁰

Concurrent cisplatin-based chemotherapy and radiation have shown significant survival improvement for women with locally advanced cervical cancer. The use of hypoxic cell radiosensitizers and monoclonal antibodies that inhibit cell growth increase numbers of malignant cells killed.²⁵⁹ More advanced cases are managed by

surgery (i.e., hysterectomy) followed by radiation or chemoradiation therapy for high-risk or advanced stages.¹⁴⁷ In addition to a vaccine and chemopreventive agents, biologic response modifiers are under investigation for future treatment options.

PROGNOSIS. Cervical cancer is a slow-growing neoplasm with a good response rate to intervention. Almost all women with preinvasive cancer are cured. Reconstructive surgery and ovary preservation may be able to preserve childbearing status in younger women. The majority of treated women who develop recurrences do so in the first 2 years after primary therapy. Women with more advanced-stage disease or with lymph node involvement have a significantly less favorable prognosis.

SPECIAL IMPLICATIONS FOR THE THERAPIST 20-5

Cervical Cancer

PREFERRED PRACTICE PATTERNS

4B: Impaired Posture

4C: Impaired Muscle Performance

6H: Impaired Circulation and Anthropometric Dimensions Associated with Lymphatic System Disorders

The physical therapist can continue to function in the role of educator and prevention specialist when conducting a personal/family history that includes questions about the consistency of Pap testing and presence of STDs (e.g., HPV or genital warts), since these relate to cervical cancer for women of all ages.

Although new, more sensitive testing is available, the majority of medical specialists agree that being screened for cervical cancer on a regular basis is more important than the availability of the latest technology. Any woman with a previous history of cervical cancer who presents with suspicious supraclavicular (or other) unusual lymph node presentation must be referred to her physician for medical evaluation. Reported symptoms of vaginal bleeding and GI or genitourinary dysfunction must also be promptly investigated before initiating pelvic rehabilitation.

Ectopic Pregnancy

Overview

Ectopic pregnancy, also known as *tubal pregnancy*, is marked by the implantation of a fertilized ovum outside the uterine cavity (Fig. 20-5). The fallopian tube is the most common site of ectopic pregnancy, with approximately 95% implanting there, but extrauterine pregnancies can occur anywhere outside the uterus (e.g., ovary, abdomen, or pelvic peritoneum). Ectopic pregnancy is a true gynecologic emergency, since accompanying complications are one of two primary causes of maternal death in the United States.

Incidence and Risk Factors

The incidence of ectopic pregnancy is increasing in the United States and worldwide with approximately 20 per

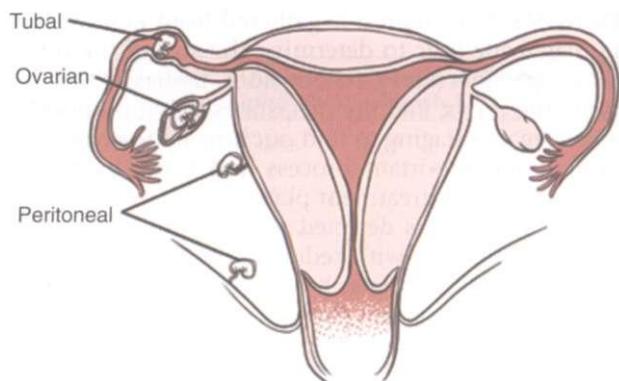


Figure 20-5

Ectopic pregnancy (outside the uterus) with implantation inside the fallopian tube (tubal pregnancy), abdomen (peritoneal or abdominal), or ovary. The majority of ectopic pregnancies (98%) are implanted inside the fallopian tube. (From Goodman CC, Snyder TE: *Differential diagnosis for the physical therapist: screening for referral*, ed 4, Philadelphia, 2007, WB Saunders.)

1000 ectopic pregnancies each year. This represents a fourfold increase globally over the last 20 years.¹⁷¹ The reasons for this rise are unclear, although several risk factors have been identified such as any condition that causes damage to the fallopian tubes that could impair transport of the ovum or impede the migration of the fertilized ovum to the uterus.

Three risk factors that have been traditionally associated with an increased risk of ectopic pregnancy are STDs (especially chlamydia and gonorrhea), prior tubal surgery, and current intrauterine contraceptive device (IUD, or IUCD). Other risk factors include ruptured appendix, endometriosis, pelvic inflammatory disease, douching,¹⁶⁰ and previous ectopic pregnancy. In addition, a history of infertility and the use of clomiphene citrate to induce ovulation are associated with an increased risk of this condition.

Etiologic Factors and Pathogenesis

Ectopic pregnancy is caused by delayed ovum transport secondary to decreased fallopian tube motility or distorted tubule anatomy. Advancements in diagnostic technology have revealed a number of etiologic factors, the most common being salpingitis. Salpingitis is an infection and inflammation of the fallopian tubes.

Three to four days are typically required for the ovum to travel through the fallopian tube to the uterus. The ovum is rapidly dividing and growing throughout the journey. During ectopic pregnancy, fertilization does not occur in the uterus. The sperm fertilizes the ovum soon after the ovum enters the ampulla of the fallopian tube. If the journey is slowed sufficiently (tubule motility), the ovum becomes too large to complete the passage through the tubule. If the tubule anatomy has been affected by recurrent infection or endometriosis, the same problem occurs. The trophoblasts that cover the surface of the ovum easily penetrate the mucosa and wall of the tubule, and implantation occurs.

Bleeding occurs during implantation with leakage into the pelvis and abdominal cavity. Vaginal bleeding that

may be perceived as menstruation may occur. The pregnancy will typically outgrow its blood supply, terminating the pregnancy. If the pregnancy does not terminate, the thin-walled tubule will no longer support the growing fetus, and rupture can occur by the twelfth week of gestation. Tubal rupture is life threatening because rapid intraabdominal hemorrhage can occur.

Clinical Manifestations

The classic presentation of ectopic pregnancy is marked by amenorrhea or irregular bleeding and spotting, non-specific lower abdominal quadrant or back pain, and a pelvic mass. The woman may believe she had a menstrual period but when questioned will report the period was atypical for her.

The pain reported can be diffuse and aching or localized and will progress to a sharper, lancinating acute type of pain. The pain can be sudden in onset and intermittent and may be accompanied by hemorrhage. The pain is thought to be primarily a result of the leakage of blood into the pelvic and abdominal cavity. Pain referred to the shoulder area can occur if the blood comes in contact with the kidney or diaphragm.

Since the woman is pregnant, signs and symptoms associated with normal pregnancy may also be present. These findings include fatigue, nausea, breast tenderness, and urinary frequency.

MEDICAL MANAGEMENT

DIAGNOSIS. Physical examination reveals a pelvic mass in approximately 50% of the cases. Pelvic ultrasound studies can reliably reveal a gestational sac by 5 to 6 weeks into the pregnancy. An empty uterine cavity with elevated (slight) human chorionic gonadotropin-beta subunit (hCG- β) and symptoms strongly implies an extrauterine pregnancy. Blood studies may show anemia, and serum pregnancy tests (hCG-(3 hormonal levels) will be positive but show levels lower than expected in the presence of a normal pregnancy (lack of doubling over 2 days). Definitive diagnosis requires laparoscopy.

TREATMENT. Surgical intervention consisting of a noninvasive laparoscopic salpingostomy to remove the ectopic pregnancy is performed if the fallopian tube has not ruptured. Laparotomy is indicated if there is internal bleeding or if the ectopic site cannot be adequately visualized with the laparoscope.

A chemotherapeutic agent, methotrexate, can be administered to remove residual ectopic tissue after laparoscopy. This drug is also used when the pregnancy is intact and surgery is contraindicated or the diagnosis is made early enough that the condition is not life threatening and preserving fertility is desirable.

SPECIAL IMPLICATIONS FOR THE THERAPIST 20-6

Ectopic Pregnancy

An awareness of this potentially life-threatening condition is important for the therapist. This awareness should include knowledge of the preexisting conditions that increase the risk of ectopic pregnancy and

of the symptoms associated with pregnancy. If a woman of childbearing age complains of an onset of lower abdominal, ipsilateral shoulder, or back pain, the therapist should ask questions regarding her menstrual cycle and if any of the symptoms of pregnancy are present.

Anytime a sexually active woman of childbearing age presents with shoulder, back, pelvic, and/or abdominal pain with vaginal bleeding, medical referral is required. In general, if the therapist suspects ectopic pregnancy, an immediate telephone call to the physician or medical referral is warranted.

If follow-up care occurs, the therapist should be aware that perinatal loss can be a profound experience for the woman (and her family). A sensitive presence and validation of the loss may be helpful. Cultural responses to perinatal loss vary; the therapist should remain alert to any intervention needed.³⁸

DISORDERS OF THE OVARIES

Ovarian Cystic Disease

Overview

Ovarian cysts, most of which are benign, are the most common form of ovarian tumor. The different types of cysts include functional cysts (follicular cysts and luteal cysts), endometrial cysts, neoplastic cysts, and cysts that result from PCOS.

The follicle and corpus luteum are the source of most symptomatic ovarian cysts in premenopausal women. These cysts are called *functional cysts* and rarely produce symptoms (unless they rupture or hemorrhage) because they develop in the course of normal ovarian activity. A *follicular cyst* develops when an egg matures but does not erupt from the follicle but rather continues to swell as it fills with fluid. A *luteal cyst* develops from a corpus luteum when the tissue that is left after the egg has been expelled fills with blood or other fluid.

Endometrial cysts develop when endometrial tissue migrates to the ovaries, forming blood-filled cysts called *endometriomas*, or *chocolate cysts*, because of the dark-brown color of the contents. Endometrial cysts can grow large enough to impair ovulation and cause pain and cramping during menstrual periods.

Neoplastic cysts are "new growths" considered benign in the majority of cases; only a small percentage of neoplastic cysts are cancerous or have the capacity to invade neighboring tissues and metastasize to distant sites. Cystadenomas are the most common type of neoplastic cyst.

A disorder marked by the presence of multiple cysts is called *polycystic ovary syndrome* (PCOS). This polycystic disorder is a hormonal disorder affecting premenopausal women and one of the most common causes of infertility. The disease gets its name from the many small cysts that build up inside the ovaries.

Incidence and Etiologic and Risk Factors

Ovarian cysts are one of the most common endocrine disorders in women, affecting 3% to 7% of women of childbearing age. The exact etiology of ovarian cysts remains unknown, but intrinsic ovarian defect combined with factors outside the ovaries is suspected.

In the case of PCOS, a series of central and peripheral mechanisms related to insulin resistance occurs that is determined genetically and inherited; PCOS is now considered a systemic metabolic disease.^{77,169} About 20% of women in the United States have this disorder, and more than one-half are obese. Among those women who seek treatment for infertility, more than 75% have some degree of PCOS.

Pathogenesis

Two types of ovarian cysts (the follicle and corpus luteum) are a normal part of the reproductive cycle. At least one follicle (a sac containing an egg and fluid) matures in an ovary during each cycle. During ovulation, the follicle ruptures to release the egg. The follicular remnant, or corpus luteum, is a smaller sac containing a viscous yellow liquid. The corpus luteum releases progesterone, which promotes the development of the uterine lining in preparation for the implantation of a fertilized egg.

Ovarian cysts develop when excess circulating androgens are converted to estrone in the peripheral adipose tissue. The elevated levels of circulating estrogens stimulate the release of Gn-RH by the hypothalamus and inhibit the secretion of FSH by the pituitary. Gn-RH stimulates the pituitary, which produces LH. The increased secretion of LH stimulates the ovary to produce and secrete more androgens. This self-perpetuating cycle results in abnormal maturation of the ovarian follicles, the development of multiple follicular cysts, and a persistent anovulatory state.

Several genes have been implicated in the pathogenesis of PCOS. Researchers have discovered that many women are resistant to their own insulin. To counter this resistance, the pancreas makes extra insulin; over many years this may exhaust the pancreas' ability to make insulin and thus lead to diabetes and subsequent cardiovascular complications. In addition, high insulin levels boost the production of androgens that may induce muscular changes, leading to reduced insulin-mediated glucose uptake creating a repeated cycle and worsening condition.¹³⁵

Clinical Manifestations

The likelihood of symptoms developing often has more to do with the size and location than the type of ovarian cyst. As cysts grow, their weight often pulls the ovary out of its customary position, sometimes cutting off the blood supply to the ovary. Pressure from the ovary in its new position against the uterus, bladder, intestine, or vagina may result in a variety of symptoms such as abdominal pressure; pain; abdominal bloating; or discomfort during urination, bowel movements, or sexual intercourse. Large cysts can impair ovarian function reducing ovulation and causing irregular periods or infertility in premenopausal women.

Depending on the type of cyst, if a cyst ruptures, the contents of the sac are usually absorbed by the body. When endometriomas rupture, the contents may be distributed on the uterus, bladder, and intestines. As the immune system moves in to clean up the debris, scar tissue develops, forming adhesions with resultant chronic pelvic pain. In the case of neoplastic cyst rupture, the more toxic contents can result in peritonitis.

Pain can be a manifestation of cysts. A dull, aching sensation experienced in the lower abdominal, groin, low back, or buttock areas can occur. The sensation may also be described as a heaviness. This pain is associated with bleeding into the cyst or with quick enlargement of the cyst. Sudden or sharp pain can indicate a cyst rupturing or hemorrhaging or a torsion occurring.

PCOS is characterized by physical and metabolic changes such as obesity, prominent facial or body hair, severe acne, thinning hair, infertility, and menstrual problems. Fifty percent of these women have amenorrhea, and another 30% have abnormal uterine bleeding. PCOS is associated with endometrial cancer because high levels of androgen interfere with ovulation so women with PCOS do not regularly shed the endometrium. Impaired glucose tolerance, a major risk factor for type 2 diabetes present in 40% of women with PCOS, and the subsequent risk for heart disease have been documented.¹⁹⁴ Other symptoms or conditions associated with PCOS include obstructive sleep apnea and daytime sleepiness³¹⁶ and benign breast disease (formerly fibro-cystic breast disease).⁶²

MEDICAL MANAGEMENT

DIAGNOSIS AND TREATMENT. The history and pelvic examination lead to suspicion of cystic disease. Confirmation is made by ultrasonography or laparoscopy. Ultrasound may be transvaginal (inserting a tampon-sized transducer into the vagina) or abdominal (moving a transducer across the lower abdomen) and can help identify the type of cyst and whether a cyst contains solid or liquid material. Laboratory tests include a complete blood count to identify infection or anemia (heavy bleeding) and a carcinoembryonic antigen-125 (CA-125) test for ovarian cancer. All women with PCOS should be screened for glucose intolerance.¹⁷⁷

The treatment of ovarian cysts depends on the results of the diagnostic tests and the age of the woman (preserving childbearing status). In premenopausal women, the decision whether to drain or remove the cyst depends on the problems the cyst is causing (e.g., follicular or luteal cysts resolve without treatment, and endometriomas and neoplastic cysts may be removed surgically).

The treatment of PCOS is primarily hormonal with the goal being an interruption of the persistent elevated levels of androgens. Clomiphene citrate (Clomid) is often administered to induce ovulation. If medication is not effective, laser surgery can be instituted to puncture the multiple follicles.

It is now known that the application of diabetes management techniques aimed at reducing insulin resistance and hyperinsulinemia (e.g., weight reduction, oral hypoglycemic agents, and exercise) can reverse testosterone

and LH abnormalities and infertility, as well as improve glucose, insulin, and lipid profiles.

SPECIAL IMPLICATIONS FOR THE THERAPIST 20-7

Ovarian Cystic Disease

Depending on the clinical presentation, therapists may ask women if menstrual dysfunction is present. A history of ovarian cystic disease could account for a woman's low back or sacral pain, but usually there is some indication in the menstrual history to suggest a gynecologic link.

In women with known PCOS, impaired glucose tolerance, or insulin resistance, elevated androgens with the associated muscular changes that further reduce glucose uptake and elevated cholesterol warrant the use of exercise and increased physical activity before the onset of macrovascular and microvascular symptoms.^{135,169} See also the section on Diabetes Mellitus in Chapter 11.

Considering how common PCOS is, therapists need to be aware of the potential side effects of clomiphene citrate. These include insomnia, blurred vision, nausea, vomiting, urinary frequency, and polyuria. The onset of any of these symptoms warrants communication with the physician.

Box 20-4

RISK FACTORS FOR OVARIAN CANCER

- Family history (mother's or father's side) of breast, ovarian, or colon cancer
- Personal history of endometrial or breast cancer
- Increasing age (>40 years, most occur in women 55 to 75 years)
- Nulliparity (never pregnant, giving birth for the first time after age 35 years)
- Never breast fed
- Presence of *BRCA1* or *BRCA2* mutation
- White race
- Exposure to talc or asbestos
- Living in an industrialized Western nation
- Obesity
- High dietary fat intake
- Prolonged exposure to estrogen (early onset of menarche/before age 12 years, menopause after age 50 years, postmenopausal estrogen replacement therapy)
- Infertility
- Fertility drugs (under investigation, not yet confirmed)
- Never used oral contraceptives
- Tobacco and alcohol use (mucinous ovarian cancer)

epithelial tumors peaks in women during their fifties and sixties; it is rare before puberty.

In the United States, white and Hawaiian women have the highest incidence of ovarian cancer, whereas Native American and black women have the lowest incidence.

Etiologic and Risk Factors

The etiology of ovarian cancer is not well understood. No single cause of ovarian cancer has been discovered, but hormonal, environmental, and genetic factors appear to influence the development of the disease (Box 20-4). None is as important as a family history of ovarian or breast cancer.

The average woman has less than a 2% chance of developing ovarian cancer in her lifetime (1 in 57 versus 1 in 8 for breast cancer), whereas a woman with first-degree relatives with ovarian cancer or who has the *BRCA1* (*BRCA* stands for breast cancer) mutation has about a 45% lifetime chance, and for *BRCA2*, the risk is approximately 25%.²⁵³

Loss of two tumor suppressor genes (*p53* and *BRCA1*) has been shown to occur early in ovarian carcinogenesis in women who are *BRCA1* mutation carriers.³²⁶ Overall, more than 90% of all cases occur sporadically; only 10% of all women with ovarian cancer have a hereditary predisposition.

Nulliparous women are at increased risk of developing ovarian cancer. This factor may be related to the repeated epithelial surface disruption that occurs with cyclic ovulation. Since epithelial tumors make up approximately 90% of ovarian cancers, many of the risk factors described relate to this entity.

A history of breast feeding also is important, since women who breast feed are at decreased risk of developing this condition compared to nulliparous women and parous women who have not breast fed.

Ovarian Cancer

Overview

Ovarian cancer is estimated to be the second most common female urogenital cancer and the most lethal of these cancers. The term *extraovarian primary peritoneal carcinoma* (EOPPC) is sometimes used interchangeably with the term *ovarian cancer*. This has been identified as a relatively newly defined disease that develops only in women, accounting for approximately 10% of cases with a presumed diagnosis of ovarian cancer. Characterized by abdominal carcinomatosis, uninvolving or minimally involved ovaries, and no identifiable primary form of cancer, EOPPC has been reported after bilateral oophorectomy performed for benign disease or prophylactically for ovarian cancer.⁸²

The occurrence of EOPPC may be explained by the common origin of the peritoneum and the ovaries from the coelomic epithelium. The various histologic differences of ovarian and peritoneal lesions are under investigation.

Incidence

An estimated 23,300 women in the United States developed ovarian cancer in 2007 with 15,280 deaths from ovarian cancer.¹⁴⁸ The poor outcome is based on the difficulty of diagnosing the disease, which results in 60% to 70% of the women having metastatic disease at the time of diagnosis. Although there are a number of types of ovarian cancers, epithelial tumors make up approximately 90% of the cases and are the leading cause of death from gynecologic cancer in the United States. The incidence of

At the present time, there are no established nutritional risk factors for ovarian cancer. The association of milk/dairy products or calcium consumption with ovarian cancer has not been proved. Moderate alcohol consumption may reduce the risk; the role of obesity and physical activity in this cancer is unclear.¹⁷³

Pathogenesis

The development of ovarian cancer seems to correlate with the number of times a woman ovulates during her lifetime. Every time an egg is released, it ruptures the surface of one of the ovaries. Cells have to replicate to repair the damage, and the more times they do this, the greater the chances that a cancer-causing mutation will occur. This is why anything that interferes with ovulation (e.g., pregnancy, breast feeding, or hormonal contraceptives) diminishes the risk of developing ovarian cancer.

The classification of ovarian tumors is based on the tissue of origin. The most common tumors arise from the surface epithelium or serosa of the ovary. As the ovary develops, the epithelium extends into the stroma of the ovary, forming glands and cysts. In certain cases, these inclusions become neoplastic. Other categories of tumor include germ cell tumors, sex cord and stromal tumors, and steroid cell tumors. Once present, ovarian cancer spreads to the pelvis, abdominal cavity, and bladder, whereas lymphatic metastasis carries the disease to the paraaortic lymph nodes and to a lesser extent the inguinal or external iliac lymph nodes. Hematogenous spread of the cancer can result in liver and lung involvement.

Clinical Manifestations

Most ovarian cancers are asymptomatic or present with symptoms so vague that the disease is advanced in many cases by the time the woman seeks care. The vague complaints include abdominal bloating, flatulence, fatigue and malaise, gastritis, or general abdominal discomfort. Abnormal vaginal bleeding, leg pain, pelvic mass, and low back pain are less common symptoms. Local pelvic pain also occurs late in the disease.

Symptoms associated with metastatic spread of the disease include unexplained weight loss, weakness, pleurisy, ascites, and cachexia (general feebleness and wasting). Ascites is an accumulation of fluid within the peritoneal cavity. This can occur when there is marked increased pressure within the liver sinusoids or portal hypertension that results in serum exuding through the superficial capillaries into the peritoneal cavity (see Fig. 16-4).

Paraneoplastic cerebellar degeneration (PCD) is a type of paraneoplastic syndrome that primarily affects women with gynecologic cancers. Symptoms typically include ataxic gait, truncal and appendicular ataxia, nystagmus, and speech impairment (dysarthria).¹⁸¹

MEDICAL MANAGEMENT

PREVENTION. Women at high risk for ovarian cancer (e.g., those with a family history of ovarian cancer in a mother, sister, or daughter) and any woman with a personal history of breast, colon, or uterine cancer should receive annual screening with a combination of the CA-125 blood test, physical examination, and vaginal sonography.

There is no reliable screening test to detect ovarian cancer in its early, most curable stages. Two diagnostic tests are used but both lack sensitivity and specificity. The CA-125 blood test (carcinoembryonic antigen, a biologic marker produced by ovarian cancer cells) is elevated in about half the women with early-stage disease and about 80% of those with advanced disease (normal range is between 0 and 35). This test is not adequate as a screening tool because it does not detect the disease early in women who are asymptomatic and it can be elevated in other conditions, such as pelvic infections, fibroids, or endometriosis, and even during ovulation.

Researchers are continuing to evaluate CA-125 as a screening tool (e.g., rapidly rising CA-125 may be more predictive than elevation on a single test) and also investigating other substances, such as lysophosphatidic acid (LPA), a growth factor for ovarian cancer cells measured in the blood.²⁵⁴

Researchers at the University of Washington School of Medicine in Seattle have been able to accurately predict ovarian cancer based on the duration and frequency of key signs and symptoms, including pelvic/abdominal pain, urinary urgency or frequency, increased abdominal size and bloating, and difficulty eating/feeling full (early satiety). This symptom index is considered positive for ovarian cancer if any of these signs and symptoms occur more than 12 times a month for less than 12 months.

Routine ultrasound imaging is also under investigation as an effective screening tool when used to identify enlarged ovaries.²⁷⁰ Transvaginal ultrasonography helps determine whether an existing ovarian growth is benign or cancerous. Because the early-stage symptoms are quite nonspecific, most women do not seek medical attention until the disease is advanced.

Some women with a positive immediate family history of ovarian cancer choose to have prophylactic oophorectomies after completing childbearing to prevent the development of this disease. This intervention is not 100% protective because the lining of the peritoneal cavity comprises the same cells as the lining of the ovaries and development of primary peritoneal cancer after prophylactic oophorectomy can occur.²⁶³

A history of one or more full-term pregnancies, a history of breast feeding, and the use of hormonal contraceptives reduce the risk of ovarian cancer. Hormonal contraceptives (whether in pill form, injectable, or patch form) are recommended as chemoprevention for women with a family history of ovarian cancer, especially if the *BRCA* mutation is present. The mechanism of protection is unclear, but it is probably a result of the inhibition of ovulation; there is a potential increased risk of cervical cancer with this treatment.^{219,263}

As a result of analgesics reducing the risk for colorectal cancer, studies of the effect of similar pharmacologic effects on ovarian cancer have been conducted. Regular use of acetaminophen (but not aspirin) may be associated with lower risk of ovarian cancer.²¹⁷

DIAGNOSIS AND STAGING. Despite ovarian cancer's reputation as a silent killer, more than 90% of women with ovarian cancer (whether early or advanced) reported experiencing symptoms long before diagnosis.¹²⁶ However,

these are often nonspecific and vague and frequently are misdiagnosed as irritable bowel syndrome or some other nongynecologic condition. A pelvic mass with ascites is usually indicative of ovarian cancer that is then confirmed by ultrasonography. A cervical smear may reveal malignant cells, and a biopsy will reveal whether the mass is benign or cancerous.

Staging of the disease is as follows: stage I—disease limited to the ovaries; stage II—extension to other pelvic organs; stage III—intraperitoneal metastasis (spread to other abdominal organs but not the liver); and stage IV—distant metastasis (spread to the liver or organs outside the abdominal cavity). The cancer is considered advanced at stages II to IV.

For a more comprehensive breakdown of the American Joint Committee on Cancer (AJCC) TNM and FIGO staging systems for ovarian cancer, see the NCCN Clinical Practice Guidelines.²²⁶

TREATMENT. Treatment of ovarian cancer depends on the specific tumor type but usually consists of cytoreductive surgery that includes total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy (removal of supportive tissue attached to organs in the abdominal cavity), and lymphadenectomy followed by adjuvant combination chemotherapy.²²⁷

Fertility-sparing surgery and comprehensive staging is done for any woman who desires to maintain her fertility.²²⁶ Anyone (men and women) interested in more information about preserving fertility after cancer should talk to their physicians about future fertility. The ACS offers an excellent review of this topic.²⁸¹

Giving intraperitoneal (IP) chemotherapy along with intravenous (IV) chemotherapy may improve survival of women with Stage III ovarian cancer. IP chemotherapy allows higher doses and more frequent administration of drugs and appears more effective at killing cancer cells in the peritoneal cavity where ovarian cancer is likely to spread or recur first. Successful surgery to remove the bulk of the tumor is required first.^{14,325}

New cancer drugs are being developed to treat resistant or recurrent disease. Ovarian growth is angiogenesis dependent, causing researchers to investigate the use of antiangiogenic treatment (e.g., angiostatin or endostatin) to inhibit tumor growth in this type of cancer.³³⁶ Other new interventions and approaches under investigation include the use of monoclonal antibodies (laboratory-produced substances that find and bind to cancer cells, delivering tumor-killing agents without harming normal cells), genetic techniques (e.g., gene therapy to supply a working copy of the tumor-suppressing gene *p53*), vaccines to boost a woman's immune response to ovarian tumor cells that emerge after treatment, and new combinations and sequences of currently used drug interventions.

PROGNOSIS. Ovarian cancer has a very poor prognosis because it is difficult to detect early and usually presents with advanced metastases (70% present in an advanced stage). The cancer is generally responsive to treatment if found early, with a 90% 5-year survival rate. In most cases, clinical response to treatment is approximately

80%, but tumor recurrence within 3 years after treatment occurs in most women.²²² Return of the tumor within 6 months of therapy is a poor prognosticator because the cancer cells are often resistant to drug treatment. Five-year survival without recurrence is a good prognostic indicator.

SPECIAL IMPLICATIONS FOR THE THERAPIST

20-8

Ovarian Cancer

PREFERRED PRACTICE PATTERNS

4B: Impaired Posture

4C: Impaired Muscle Performance

6H: Impaired Circulation and Anthropometric Dimensions Associated with Lymphatic System Disorders

Therapists treating women with a history of ovarian cancer need to be cognizant of the moderate-to-high risk of recurrence of the disease. Gait disturbance may be the first sign of a paraneoplastic syndrome associated with gynecologic cancer. Other symptoms associated with metastases may include thoracic or shoulder girdle pain secondary to lymphadenopathy, symptoms associated with lung (dyspnea, see Chapter 15) or liver (see Chapter 17) disease, and weight loss and fatigue. Onset of any of these complaints warrants communication with the physician.

Oophorectomy induces menopause in women. Therefore an onset of the symptoms described in the beginning of this chapter may occur in addition to headaches, depression, and insomnia. Side effects from cancer treatment are often present. Chemotherapy-induced peripheral neuropathy is a common problem after treatment with Taxol. Symptoms may or may not resolve.

Ovarian Varices

Incompetent and dilated ovarian veins (as well as other uterine and pelvic veins) are a known cause of abdominal and pelvic pain and contribute to pelvic congestion syndrome (Fig. 20-6). This is only one of many possible causes of chronic pelvic pain and pelvic congestion syndrome (see the section on Pelvic Floor Disorders in this chapter). Ovarian varices may occur unilaterally or bilaterally, most often in women who have had children but occasionally in nonparous women.²⁶²

Reported symptoms include pain that worsens toward the end of the day or after standing for a long time, pain that occurs premenstrually and after intercourse, sensations of heaviness in the pelvis, and prominent varicose veins elsewhere on the body. This type of pelvic pain arises when blood pools in a distended ovarian vein rather than flowing back toward the heart and is more common among women with low blood pressure. This distention and pooling form a varicocele, a term traditionally applied to men to describe varicose veins in the testicles, but varicoceles can also occur in the female counterparts of those organs. In fact, 10% of men experience pelvic varices of the gonadal veins presenting as

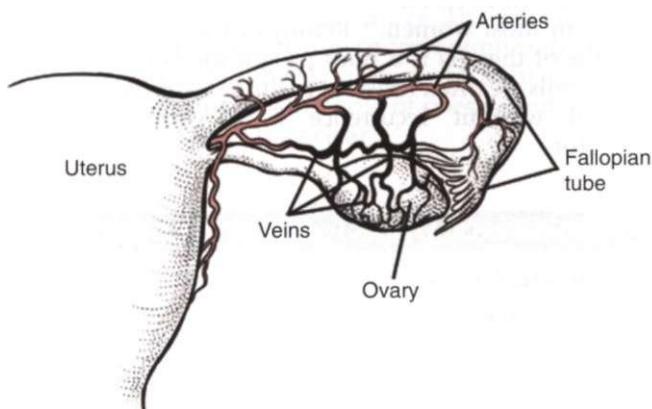


Figure 20-6

Varicose veins (varicosities) of the ovary. Ovarian varicosities associated with pelvic congestion syndrome are the cause of chronic pelvic pain for women. This form of venous insufficiency is often accompanied by prominent varicose veins elsewhere in the lower quadrant (buttocks, thighs, calves). Men may have similar varicosities of the scrotum (not shown). (From Goodman CC, Snyder TE: *Differential diagnosis for the physical therapist: screening for referral*, ed 4, Philadelphia, 2007, WB Saunders.)

varicoceles similar to uteroovarian varices seen in women.⁴⁰

Ovarian vein incompetence may be suspected from the presence of vulvar varicosities and can be diagnostically visualized with CT scanning, venogram, or transvaginal ultrasound. If observed during pregnancy, these may disappear after delivery but become more prominent with subsequent pregnancies.

Treatment with embolization of the ovarian veins (see discussion of this technique in the section on Uterine Fibroids in this chapter) is relatively new but reportedly safe and effective in alleviating pain and symptoms, improving sexual functioning, and reducing anxiety and depression with subsequent improved quality of life reported.¹⁸⁵

PELVIC FLOOR DISORDERS

Pelvic Inflammatory Disease

Overview and Incidence

Pelvic inflammatory disease (PID), the infection and inflammation of the female upper genital tract, is made up of a variety of conditions (i.e., it is not a single entity), including endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. Any inflammatory condition affecting the female reproductive organs (uterus, fallopian tubes, ovaries, and cervix) may come under the diagnostic label of PID. It is a common cause of infertility, chronic pain, and ectopic pregnancy.¹¹⁹ Approximately 1 million women are affected each year; 75% occur in women under the age of 25 years and 100,000 become infertile.

Etiology and Risk Factors

PID occurs as a result of multimicrobial bacteria, such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and anaero-

bic and mycoplasmal bacteria. Either gonorrhea or chlamydia (two common STIs) acquired through vaginal, oral, or anal intercourse is the most likely cause. Infection can occur when the uterus is traumatized. Infection can be introduced from the skin, vagina, or GI tract. It can be an acute, one-time episode or chronic with multiple recurrences.

PID is often associated with STIs/STDs or develops after birth or after a surgical procedure involving the reproductive tract such as an abortion or a dilatation and curettage (D&C). D&C is a procedure to scrape and collect the tissue (endometrium) from inside the uterus. Dilatation (*D*) is a widening of the cervix to allow instruments into the uterus. Curettage (*C*) is the scraping of the contents of the uterus.

Early age at first vaginal intercourse (higher prevalence for age less than 15 years) and number of male sex partners are two major risk factors for PID.⁵¹ The more partners the woman has, the greater the risk of PID. PID occurs if chlamydia is not treated and even if treated, damage to the pelvic cavity cannot be reversed. Other risk factors include sexual activity without a condom, a sexual partner who reports symptoms or has a known history of chlamydia or gonorrhea, and previous pelvic infection(s).

Clinical Manifestations

Signs and symptoms of PID vary widely, making the medical diagnosis difficult. It is often asymptomatic but can present with vaginal bleeding and discharge and burning during urination. Constitutional symptoms associated with infection, such as fever or chills, and sometimes nausea and vomiting may be reported.

Painful intercourse (dyspareunia), painful menstruation, and back or pelvic pain are commonly reported. Pelvic pain does not occur until chlamydia leads to PID. Moderate (dull aching) to severe back, abdominal, and/or pelvic pain are possible. If the condition progresses to PID, scarring in the pelvic organs, including the ovaries, fallopian tubes, bowel and bladder, can cause chronic pain. The women can be left infertile because of damage and scarring to the fallopian tubes.

After one episode of PID, a woman's risk of ectopic pregnancy increases sevenfold compared with the risk for women who have no history of PID.^{48,49} Ectopic pregnancy can occur when a partially blocked or slightly damaged fallopian tube causes an egg to get stuck in the fallopian tube where it is then fertilized.

MEDICAL MANAGEMENT

PREVENTION. PID can be prevented by making safer choices to avoid STDs (e.g., always using barrier methods during intercourse, limiting number of sexual partners and with frequent testing for treatment of STDs, choosing a partner who does not have a current or previous history of STD, and abstaining from sexual activity until infected partner has completed treatment). All medication prescribed must be taken to prevent reinfection.

DIAGNOSIS, TREATMENT, AND PROGNOSIS. PID is diagnosed on the basis of clinical presentation, a physical and pelvic examination, and laboratory tests. A vaginal swab

or urine sample will be taken and sent to the laboratory. Ultrasound may be used to visualize the fallopian tubes or screen for pelvic abscess. Laparoscopic examination (thin, flexible tube with a light at the end is inserted through a small incision in the lower abdomen) allows the surgeon to view the internal organs and take tissue samples for diagnostic purposes.

PID is curable with antibiotics; prompt treatment does not reverse any damage already done. PID may require hospitalization and can be life threatening. Complications of PID include chronic pelvic pain, infertility (inability or difficulty getting pregnant), and ectopic or tubal pregnancy.

The CDC recommends that all sexually active teens and young adult women be screened annually for STIs. Any woman who has had a new sexual partner (male or female) and those with multiple sexual partners should be screened regularly. Signs of infection or recurrence of infection should be investigated immediately and treated appropriately.^{48,49}

Pelvic Floor Dysfunction

Overview and Etiologic Factors

Many diagnoses and symptoms that result in dysfunction of the pelvic floor musculature or chronic pelvic pain are included under the heading of pelvic floor disorders (Box 20-5). Although men and women can both be affected by pelvic floor dysfunction, women are more often treated in a physical therapy practice. Only general concepts related to the multitude of causes and symptoms can be covered in this text. For more specific information related to each of these conditions, the reader is referred elsewhere.^{289,329}

Chronic pelvic pain (continuous or intermittent pelvic pain lasting for 6 months or more) is a significant part of pelvic floor disorders. Any of the conditions listed in Box 20-5 can result in chronic pelvic pain, and in turn, chronic pelvic pain can contribute to or result from hypertonus dysfunction of the pelvic floor muscles.

Many of these conditions fall into several categories and are not strictly classified as one entity. For example, vulvodynia and vulvar vestibulitis are both hypertonus dysfunctions, as well as neuropathic pain syndromes resulting in chronic pelvic pain (a third classification). Overall, there is considerable overlap of conditions in the categories listed.

Incidence

The prevalence of pelvic floor dysfunction remains unknown, but it is considered a common problem among women of reproductive age, many of whom have never been diagnosed. The lack of a consensus on the definition of chronic pelvic pain and lack of a classification scheme hinder epidemiologic studies. Although the majority of these conditions affect women, men can also be affected.

Pathogenesis

The pelvic floor muscles are a band of muscles sometimes referred to as the pubococcygeal (PC) muscles. These are actually made up of several muscle groups stretching like

Box 20-5

CAUSES OF PELVIC FLOOR DISORDERS

- Pregnancy alone and/or birth-related trauma
- Rectocele, cystocele, prolapsed uterus
- Anorectal tumors or neoplasm anywhere in the pelvic cavity
- Hypertonus dysfunctions
 - Levator ani syndrome
 - Tension myalgia
 - Coccygodynia
 - Dyspareunia
 - Vaginismus
 - Anismus
 - Vulvodynia
 - Vulvar vestibulitis
 - Pudendal neuralgia
- Ovarian varices, pelvic vein varicosities, congestion syndrome
- Other vascular disorders (e.g., aortiliac occlusion, claudication, arteriovenous malformations)
- Dysmenorrhea, premenstrual syndrome (PMS)
- Endometriosis
- Uterine fibroids
- Congenital malformation(s), uterine malposition
- Musculoskeletal injury or trauma (back, sacrum, sacroiliac area, hip, pelvis)
- Fibromyalgia, chronic fatigue syndrome
- Nerve entrapment or injury, nerve root irritation
- Spinal cord injury or other neurologic condition (e.g., stroke, Parkinson's disease, multiple sclerosis)
- Myofascial pain syndrome, trigger points
- Abdominal or pelvic surgery
- Psychogenic origin
- Sexual assault, sexual abuse, or negative sexual experiences
- Sexually transmitted diseases
- Pelvic inflammatory disease (PID), infection, postabortion syndrome (more common with multiple induced abortions)
- Interstitial cystitis
- Gastrointestinal disorders
 - Diverticulitis
 - Constipation
 - Rectal hemorrhoids, rectal fissures
 - Irritable bowel syndrome
 - Regional enteritis (Crohn's disease)
 - Appendicitis, peritonitis
- Hernia (inguinal or femoral)
- Unknown cause ("gynecalgia")

a sling from the pubic bone to the coccyx at the base of the spine that work together as a whole to support the internal and pelvic organs (Fig. 20-7). The pelvic floor muscles are voluntary, internal muscles surrounding the vagina, urethra, and rectum and also function to help close off the urethra and rectum to maintain continence (Fig. 20-8).

Weakness or laxity in the endopelvic fascia or other structures of the pelvic floor results in partial or total prolapse of the organs it supports as described in the next section. Hypertonus dysfunction comprises a large portion of pelvic floor dysfunctions and is characterized by an increase in pelvic floor muscle tension or active spasm causing musculoskeletal pain or dysfunction of the urogenital and/or colorectal system.³²⁰ The pathogenesis of chronic pelvic pain remains poorly understood,

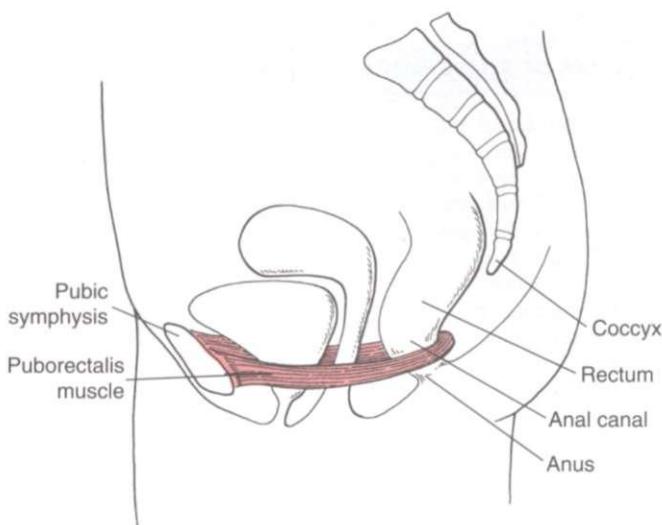


Figure 20-7

Pelvic floor sling. The first layer of the pelvic floor is made up of the endopelvic fascia, one continuous body of connective tissue surrounding and supporting the pelvic organs (not pictured). The levator ani muscles (pelvic floor muscles) make up the second layer, forming a sling across the pelvic cavity from the pubis to the coccyx with openings to allow passage of the urethra, lower vagina, and anus. The puborectalis muscle (part of the levator ani muscle) works together with the pubococcygeus muscle (not shown, also part of the levator ani muscle) to support the pelvic viscera in both the male and female. (From Myers RS: *Saunders manual of physical therapy*, Philadelphia, 1995, Saunders.)

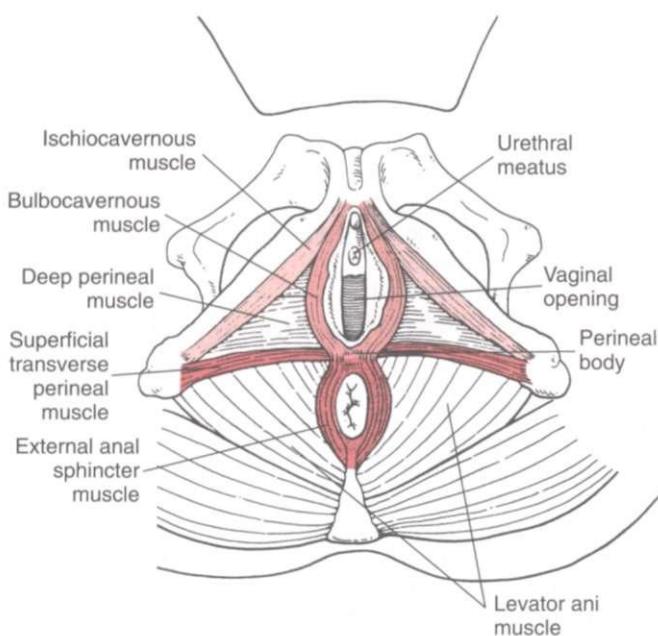


Figure 20-8

Pelvic floor muscles. Third layer of the pelvic floor, sometimes referred to as the urogenital diaphragm or deep perineum. The deep transverse perineal muscle, external urethral sphincter, and enveloping fascia of the third layer are overlaid by the fourth (superficial) layer (perineum), including the bulbocavernous, ischiocavernous, superficial transverse perineal muscles and the external anal sphincter and muscle. (From Myers RS: *Saunders manual of physical therapy*, Philadelphia, 1995, Saunders.)

and often, laparoscopic investigation reveals no obvious cause for pain.

Clinical Manifestations

Clinical manifestations of pelvic floor disorders are determined by the underlying etiologic factors and pathologic findings. For example, the primary presentation of someone with hypertonus is a pain, pressure, or ache, usually poorly localized in the perivaginal, perirectal, and lower abdominal quadrants and pelvis (suprapubic or coccyx regions) and sometimes radiating down the posterior aspect of the thigh. Symptoms are often reproduced by manual palpation and examination of the pelvic floor muscles.

Vulvar vestibulitis is characterized by a telltale patch of skin at the vaginal opening that is extremely sensitive to the gentlest tap with a cotton swab; and vulvodynia is marked by persistent pain and burning in the external genitalia, making it impossible for a woman to wear closely fitting pants or jeans, engage in sexual intercourse comfortably, or even sit comfortably.

Signs and symptoms associated with prolapsed structures, ovarian or pelvic vein varices, and endometriosis are presented elsewhere in this chapter. STDs, hernia, and GI disorders, including hemorrhoids, are presented in other chapters in this text. Other symptoms of pelvic floor dysfunction may include low back pain that is intermittent and unpredictable, changing locations often and difficult to reproduce; groin pain with hip and knee flexion; sharp rectal pain; painful intercourse with penetration or inability to penetrate; extreme rectal pressure during intercourse; urinary or bowel incontinence; abnormal vaginal discharge; and pubic bone pain or tenderness.

MEDICAL MANAGEMENT

Diagnosis and diagnostic testing depend on history and clinical presentation. Ultrasonography is being used more often now that the technology has advanced. Previously, laparoscopic examination was used with poor results in more than one half of all cases. Specific medical intervention can be employed in cases of known and treatable causes, but more often, medical management has been limited to palliative use of pharmacologic and hormonal agents and surgical intervention with variable results.

Physical therapy intervention is quickly becoming the first-line therapy of choice for many causes of pelvic floor dysfunction. Working with a counselor or other skilled professional is recommended when treating someone with a past (or current) history of abuse.

SPECIAL IMPLICATIONS FOR THE THERAPIST 20-9

Pelvic Floor Dysfunction

PREFERRED PRACTICE PATTERNS

4B: Impaired Posture

4C: Impaired Muscle Performance

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction

It is imperative that women (including adolescent females) receive education about the functions and

dysfunctions of the pelvic floor complex to promote preventive rather than restorative benefits of pelvic floor exercise. Exercises for the pelvic floor should be part of every woman's fitness regimen, either as prevention or specific to the type of pelvic floor muscle dysfunction and its causes.³¹⁹

Therapists need to routinely ask women questions about pelvic floor function (e.g., presence of urinary incontinence, pain with sexual intercourse or other sexual dysfunction, presence of known reproductive organ or pelvic floor dysfunction, and past history) and provide education and exercise programs for these muscles, making a medical referral when appropriate. Review of the normal pelvic floor function and the type of evaluation and intervention programs necessary for anyone with pelvic floor dysfunction is available.³¹⁹

Intervention must be determined based on examination, including external assessment and, in the case of those therapists with additional training, internal examination. Special considerations include cultural differences in modesty, the possibility of current substance use or abuse, and past (or present) sexual abuse or sexual dysfunction. Behavioral intervention options focus on physical therapy education, therapeutic exercise, physiologic quieting (e.g., relaxation exercises, hand or foot warming, and diaphragmatic breathing), and the use of physical modalities that aid in pain relief and the restoration of muscle function.³¹⁹

Intervention may also focus on postural education to place the pelvic floor in the most optimal position for relaxation and function and aerobic exercise to mobilize the pelvis; motor learning techniques (e.g., use of a Swiss ball); behavioral training; joint alignment (including craniosacral); soft tissue, scar, and/or visceral mobilization; trigger point therapy; strain-counterstrain; and stretching for the adductors, iliopsoas, piriformis, internal obturator, abdominals, and other muscles as determined by the assessment. Principles of motor learning guide the therapist in incorporating pelvic muscle function with breathing (work of the diaphragm), the abdominals, and low back muscles. This is an important step in creating sensory awareness of the pelvic floor that takes time and repetition.

Other types of pelvic floor prolapse may include cystocele (bladder and urethra prolapse into the vagina), rectocele (rectum prolapses into the vagina), enterocoele (part of the intestine and peritoneum prolapses into the vagina), and vaginal vault prolapse (the apex of the vagina prolapses, occurring sometimes after a hysterectomy).

Etiologic and Risk Factors

Cystocele, rectocele, and uterine prolapse are a result of pelvic floor relaxation or structural overstretching of the pelvic musculature or ligamentous structures. Multiple pregnancies and deliveries combined with obesity increase the risk of these disorders developing. Prolonged labor, bearing down before full dilation, and forceful delivery of the placenta are possible causes of prolapse. Trauma to the pudendal or sacral nerves during birth and delivery is an additional risk factor.

Decreased muscle tone because of aging, complications of pelvic surgery, or excessive straining during bowel movements may also result in prolapse of some or all of these structures. Pelvic tumors and neurologic conditions, such as spina bifida and diabetic neuropathy, which interrupt the innervation of pelvic muscles, can also increase the risk.

Pathogenesis

The uterus and other pelvic structures are maintained in their proper position by the uterosacral, round, broad, and cardinal ligaments. The pelvic floor musculature forms a slinglike structure that supports the uterus, vagina, urinary bladder, and rectum (see Fig. 20-7). Multiple pregnancies and deliveries progressively stretch and potentially weaken or damage these important structures.

Cystocele occurs when the muscle support for the bladder is impaired. This allows the bladder to drop below the uterus. Over a period of time the vaginal wall will stretch and bulge downward. Eventually the bladder can herniate through the anterior vaginal wall and form a cystocele. A rectocele occurs when the posterior vaginal wall and underlying rectum bulge forward. Eventually protrusion occurs through the introitus as the supporting structures continue to weaken. Uterine prolapse occurs when the supporting ligaments become overstretched.

Clinical Manifestations

The symptoms associated with a cystocele include urinary frequency and urgency, difficulty in emptying the bladder, cystitis, and a painful bearing-down sensation in the perineal area. Urinary stress incontinence may also be associated with the presence of a cystocele. The symptoms associated with a rectocele include perineal pain and difficulty with defecation. There may be a feeling of incomplete rectal emptying, constipation, painful intercourse, and aching or pressure after a bowel movement. If the rectocele becomes large enough to trap feces, manual pressure applied to the vaginal wall may be necessary in order to complete a bowel movement without excessive straining (a practice called *splinting*, or *stenting*, which is usually an indication of the need for corrective surgery).

Cystocele, Rectocele, and Uterine Prolapse

Overview

The three types of pelvic floor disorders discussed here are cystocele, rectocele, and uterine prolapse. A *cystocele* is a herniation of the urinary bladder into the vagina (Fig. 20-9, A and B). A *rectocele* is a herniation of the rectum into the vagina (Fig. 20-9, C and D) in which part of the rectum protrudes into the posterior wall of the vagina, forming a pouch in the intestine. A *uterine prolapse* is the bulging of the uterus into the vagina (Fig. 20-10).

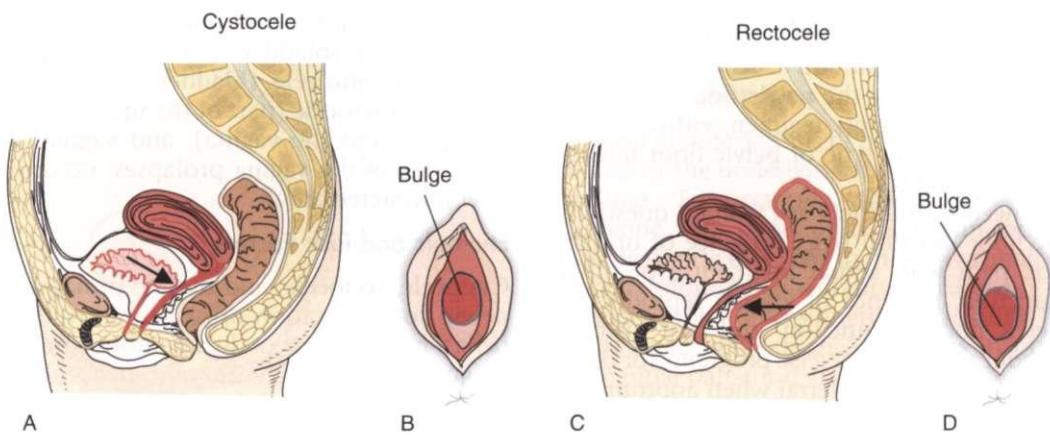


Figure 20-9

A, Cystocele (sagittal view). Note the bulging of the anterior vaginal wall. The urinary bladder is displaced downward. **B**, Lithotomy view: the bladder pushes the anterior vaginal wall downward into the vagina. **C**, Rectocele (sagittal view). **D**, Note the bulging of the posterior vaginal wall associated with rectocele (lithotomy view).

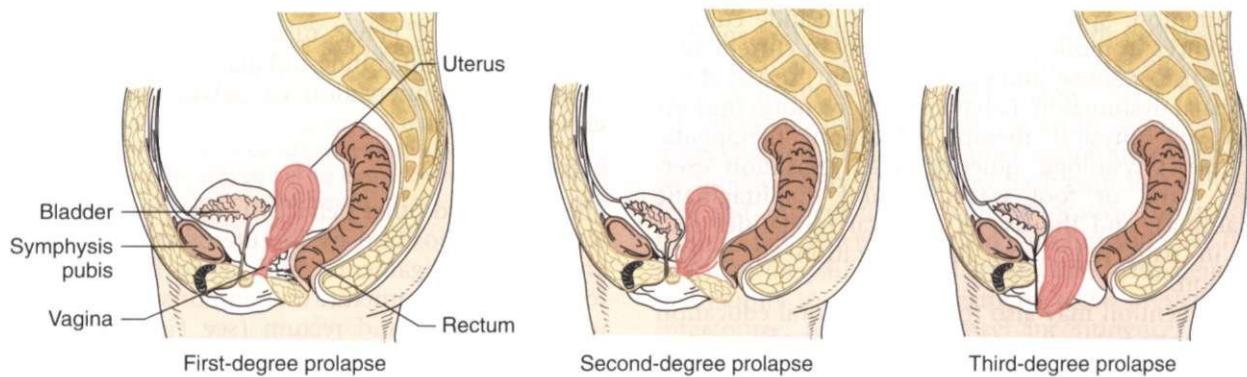


Figure 20-10

Stages of uterine prolapse. Herniation of the uterus through the pelvic floor resulting in protrusion into the vagina. *First-degree*: the cervix remains in the vagina. *Second-degree*: the cervix appears at the perineum or protrudes on straining. *Third-degree*: the entire uterus protrudes outside the body, and there is total inversion of the vagina.

Primary symptoms resulting from uterine prolapse are backache, perineal pain, a sense of "heaviness" in the vaginal area, a perceived "lump" at the vaginal opening (third-degree prolapse), and irritation and excoriation of the exposed mucous membranes of the cervix and vagina, especially from sexual intercourse and from wiping after toileting. Symptoms may be relieved by lying down and are aggravated by prolonged standing, walking, coughing, or straining. Urinary incontinence is also a common problem as a result of uterine prolapse.

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of these disorders is primarily derived from observation and the pelvic examination. A uterine prolapse is graded as first, second, or third degree, depending on how far the uterus protrudes through the introitus. A first-degree prolapse is marked by some descent, but the cervix has not reached the introitus. A second-degree prolapse is marked by the cervix as part of the uterus having descended through the introitus. A third-degree prolapse is manifested

by the entire uterus protruding through the vaginal opening.

TREATMENT. At one time, corrective surgery was the first treatment option, but pelvic floor rehabilitation has become the standard treatment of choice. Rehabilitation includes pelvic floor strengthening exercises and muscle reeducation, postural education, biofeedback, and electrical stimulation. Surgery remains a management tool for these disorders and may be required, especially with second- and third-degree uterine prolapse. Vaginal hysterectomy, vesicourethral suspension, and abdominal hysterectomy are possible surgical approaches, depending on the diagnosis. Strengthening of the pelvic floor should be incorporated into the postoperative rehabilitation program as well.

Lifestyle changes, such as adequate hydration, fiber intake, developing regular bowel habits, and regular exercise, for constipation are often effective for rectocele. HRT may be used to help maintain the elasticity of the pelvic floor muscles.

SPECIAL IMPLICATIONS FOR THE THERAPIST 20-10**Cystocele, Rectocele, and Uterine Prolapse****PREFERRED PRACTICE PATTERNS****4B: Impaired Posture****4C: Impaired Muscle Performance**

As with urinary incontinence, physical therapists have a primary role in the treatment of pelvic floor disorders (see the section on Urinary Incontinence in Chapter 18). Therapists will also see people with pelvic floor disorders as a comorbidity. In these cases, therapists must be vigilant that the woman does not hold her breath or perform a Valsalva maneuver because these could exacerbate the pelvic floor condition.

In addition, a woman with a second- or third-degree uterine prolapse will have difficulty tolerating extended periods of weight-bearing activities. Alternative positions for sexual intercourse should be discussed (e.g., pillow under the hips or avoiding being above the partner), and alternative positions for exercise will need to be incorporated into the rehabilitation program.

Dabbing the vaginal/perineal area with soft toilet paper rather than wiping can help in reducing friction-related tissue injury. Women who leak urine when dabbing (applying pressure to the prolapsed bladder causes urine leakage) may be helped by a series of specific exercises to modulate the reflex responses of the urinary system. Sometimes, just rolling the legs in and out a series of four times before dabbing while sitting on the toilet is sufficient to prevent this from happening. Pelvic floor rehabilitation is recommended for eliminating this problem.¹³³

BREAST DISEASE

Most breast lumps are benign or noncancerous and include fluid-filled cysts, fibrous tumors called *fibroadenomas*, fatty tumors called *lipomas*, and benign breast disease (formerly called *fibrocystic breast disease*) characterized by lumpy, tender breasts. Cancerous tumors of the breast cannot be distinguished from benign lesions so that all lumps of any kind must be medically evaluated.

Benign Breast Disease and Fibroadenoma**Overview**

Benign breast disease or *mammary dysplasia* (formerly *fibrocystic breast disease*) is a term used to describe a number of benign breast irregularities. The preferred clinical term for fibrocystic breasts is *tissue nodularity*, which is felt on palpation. Only the pathologist can confirm whether the tissue has fibrocystic characteristics.¹⁹⁹

The constellation of morphologic changes can include cystic dilation of terminal ducts, a relative increase in the

fibrous stroma, and proliferation of the terminal duct epithelial elements. Fibroadenoma is the most common benign neoplasm of the breast. Epithelial and stromal elements that arise from the terminal duct lobular unit make up the tumor.

The following six diagnostic categories of benign breast disease are based on symptoms and physical findings^{182a}:

- Cyclical swelling, discomfort, tenderness
- Mastalgia (severe breast pain, may or may not be cyclical)
- Nodularity (significant lumpiness, may or may not be cyclical)
- Nipple discharge
- Infections and inflammations (e.g., mastitis, Mondor's disease, abscess)

Incidence and Risk Factors

Benign breast disease and fibroadenomas make up the majority of benign breast neoplasms. Benign breast disease is the single most common breast disorder occurring in about half of all women and peaking between ages 40 and 44 years. This condition accounts for more than one-half of all surgical procedures on the female breast.

The risk factors for developing breast cancer (see next section) also apply to the development of this condition. Fibroadenomas occur most commonly in premenopausal women (33/100,000 woman-years), with peak incidence between 20 to 29 years. Noncalcified fibroadenomas of the breast are not unusual in postmenopausal women and may simulate a carcinoma.¹⁴¹

Etiologic Factors and Pathogenesis

The cause of benign breast disease and fibroadenoma is unknown. Fibroadenomas appear to be estrogen-induced or estrogen-sensitive, stimulated by pregnancy and lactation, and usually regressing after menopause. The changes typically involve the terminal ducts and surrounding stroma and can be proliferative or nonproliferative. Nonproliferative tissue nodularity is generalized, occurring in multiple areas of both breasts. A majority of the time these cystic changes are minimal and do not result in a discrete mass, although cysts up to 5 cm can develop.

Clinical Manifestations

Nodularity occurs bilaterally and presents as regular, firm, mobile nodules that feel rubbery, like small water balloons. Pain, tenderness, or discomfort may be described in a cyclical fashion or just before menses as the breast tissue responds to hormonal changes and the nodules enlarge.

Fibroadenomas are typically solitary lesions and are 2 to 4 cm in size when first detected. A typical fibroadenoma is a nontender, round, firm, and discrete mass. This round and rubbery lesion is sharply demarcated from surrounding breast tissue and as a result moves freely within the surrounding tissue. These cysts can fluctuate in size with rapid appearance or disappearance. Masses associated with breast nodularity may or may not be painful. The tenderness may become evident during the

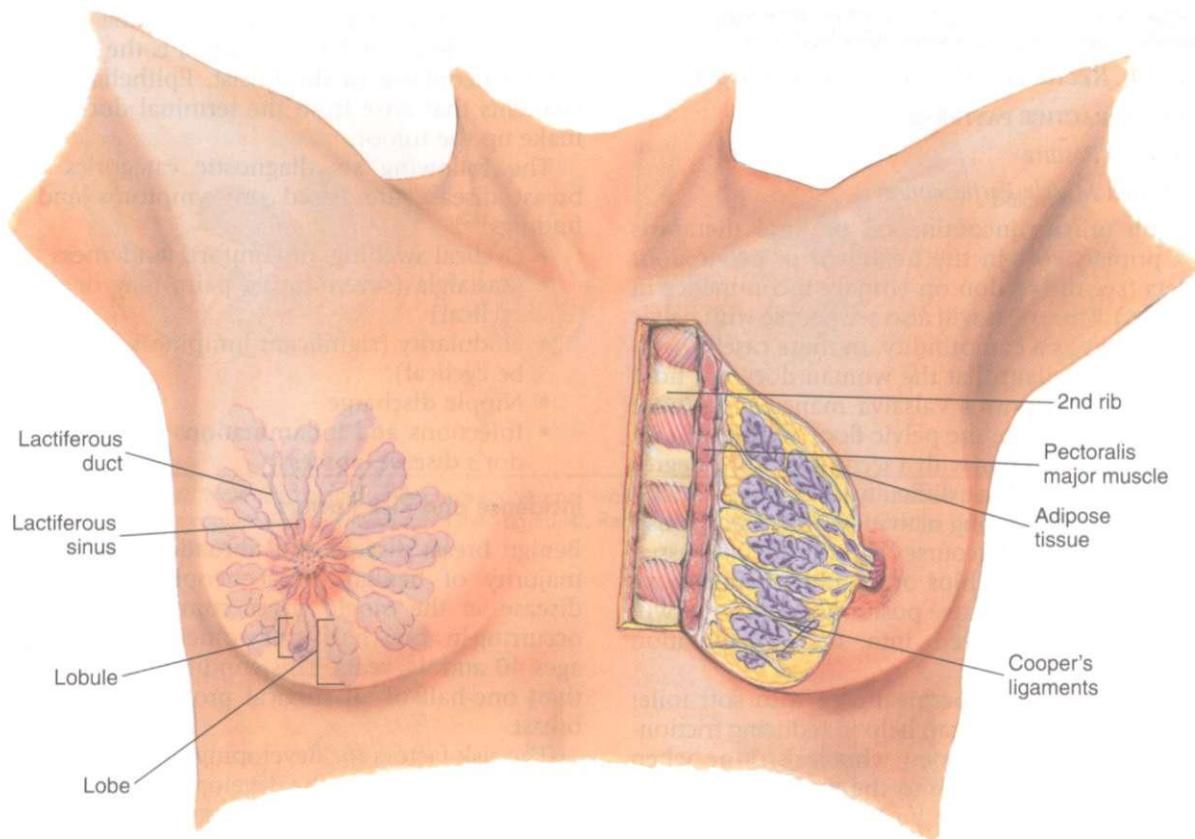


Figure 20-11

Breast anatomy. The breast is composed of glandular tissue; fibrous tissue, including suspensory ligaments; and adipose tissue. Glandular tissue contains 15 to 20 lobes radiating from the nipple and composed of lobules. Within each lobe are clusters of alveoli that produce milk. Each lobe is embedded in adipose tissue and empties into a lactiferous duct. There are 15 to 20 lactiferous ducts that form a collecting duct system converging toward the nipple. These ducts form ampullae or lactiferous sinuses behind the nipple, which are reservoirs for storing milk. The lobules and ducts are surrounded by fatty and connective tissue, nerves, blood vessels, and lymphatic vessels. The suspensory ligaments (Cooper's ligaments) are fibrous bands extending vertically from the surface attaching to the chest wall muscle. These support the breast tissue and become contracted in cancer of the breast, producing pits or dimples in the overlying skin. (From Jarvis C: *Physical examination and health assessment*, ed 4, Philadelphia, 2004, WB Saunders.)

premenstrual phase of the cycle when the cysts tend to enlarge.

MEDICAL MANAGEMENT

DIAGNOSIS AND TREATMENT. Diagnosis of these benign lesions is based on physical examination, mammography, and biopsy. Because benign disease and fibroadenoma are often indistinguishable from carcinomas, biopsy is often used to confirm the diagnosis. More advanced ultrasonography now allows for the differentiation of cystic (fluid-filled) masses from solid masses. The presence of nodularities does not predispose a woman to cancer but may make diagnosis of cancerous lumps more difficult.

Treatment for these conditions is often palliative and includes aspirin, mild analgesics, and local heat or cold. Dietary changes are often recommended such as avoiding coffee, colas, chocolate, and tea (foods and drinks that contain xanthines). Women are encouraged to wear a brassiere that provides adequate support. For women in severe pain, danazol may be given. Surgery is performed

if a suspicious mass that is deemed not to be malignant on cytologic examination does not resolve over several months.

Breast Cancer

Overview

Breast cancer is the most common malignancy of females in the United States and accounts for one-third of all cancers diagnosed in American women. Breast cancer begins in the lobules (20%), which are the milk-producing glands of the breast, or in the ducts (80%), which bring the milk to the nipple (Fig. 20-11). Most breast carcinomas are adenocarcinomas originating in the single layer of epithelial cells that line the ductal and lobular systems of all milk ducts.

Not all breast cancers are the same; different characteristics in gene expression profiles result in differential clinical behavior. Gene profiling assays aid in documenting different subtypes of breast cancer.¹⁵³ For now, clinical practice recognizes six types of breast cancer:

(1) ductal CIS (DCIS); (2) invasive (infiltrating) ductal carcinoma (IDC); (3) invasive (infiltrating) lobular carcinoma; (4) medullary, tubular, and mucinous carcinoma; (5) inflammatory breast cancer (IBC); and (6) Paget's disease of the breast.

DCIS (sometimes called *intraductal cancer*), the most common type of *in situ* cancer, occurs in 20% to 30% of newly diagnosed breast cancer cases and develops at several points along a duct, appearing as a cluster of calcifications or white flecks on a mammogram. DCIS accounts for about 10% of breast cancers in men. This is a precancerous change in breast tissue (abnormal but not malignant cells and highly curable) with a broad continuum from slow-growing cells with little potential to be transformed into cancer to life-threatening aggressive types of cancer that will invade the duct wall and grow beyond it.

IDC is the most common of the invasive breast cancers, beginning in a duct, breaking through the duct wall, and invading fatty tissue of the breast with further metastasis possible via lymphatic invasion. IDC is usually detected as a mass on a mammogram or as a palpable lump during a breast examination. From 80% to 90% of breast cancer cases in men are caused by IDC.

Invasive lobular carcinoma makes up 10% to 15% of invasive cancers. This type grows through the wall of the lobule and spreads via the lymphatic or circulatory system.

Medullary, tubular, and mucinous carcinomas are less common types of ductal carcinoma, together accounting for less than 10% of breast cancers. Medullary carcinoma and tubular carcinoma are both invasive but have better outcomes than invasive ductal or invasive lobular carcinomas.

IBC, a less common form of invasive ductal cancer, is a rare and very aggressive form of breast cancer that presents much like an infection with warmth, redness of the skin, and lymphatic blockage. It is often missed or misdiagnosed as a breast infection because of its appearance and because there may not be a distinct lump or tumor; it is not usually detected by ultrasound or mammography. Although most common in young women, it has been reported in men as well. When the symptoms last longer than a week after starting antibiotics for a breast "infection," then a biopsy is strongly recommended.

Paget's disease of the breast is a rare form of ductal carcinoma arising in the ducts near the nipple, with itching, redness and flaking of the nipple, and occasionally bleeding (Fig. 20-12).¹²⁵ This condition occurs in conjunction with a ductal adenocarcinoma of the breast, which has frequently metastasized to the axillary lymph nodes.

Breast cancer appears biologically similar in both genders, although it is often diagnosed at later stages in older men. Men and women develop the same types of breast cancer, although lobular carcinoma is rare in men because of the absence of lobules in the male breast. Most breast cancers in men are carcinomas, most commonly IDC.

Incidence

In recent years the statistical picture of breast cancer has brightened, thanks to early detection and advances in

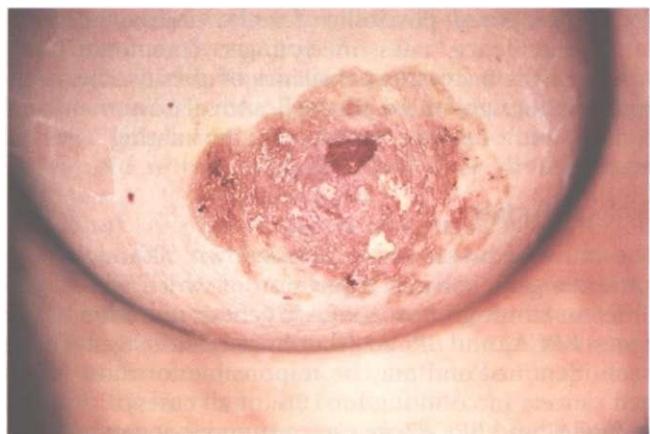


Figure 20-12

Paget's disease of the breast. An erythematous plaque surrounds the nipple. (From Bologna JL: Dermatology, St. Louis, 2003, Mosby.)

treatment. More tumors are found at an earlier stage. This fact, combined with a slowing in the rise in incidence, has dropped the death rate. Even so, breast carcinomas still account for approximately 30% of all the female cancers in the United States. In addition, breast cancer is the number two cause of female cancer deaths in the United States, second only to lung cancer.

Estimated new breast cancer cases in 2007 were 2030 (up from 1500 in the year 2002) for men and 178,480 for women (down from 203,500 in 2002). Approximately 450 men and 40,460 women died as a result of breast cancer in 2007.¹⁴⁸ This is up from 400 for men and 39,600 for women in 2002.

The cumulative lifetime risk of developing breast cancer for white women in the United States is 1 in 8 based on a woman living 95+ years, but it should be kept in mind that a woman's risk at age 25 years is 1 in 21,441, with increasing risk as she ages.⁹¹

Approximately 70% of all breast cancer occurs in women over age 50 years. Demographics suggest that in the next 2 decades, women over the age of 65 years will become the most prevalent patient cohort in the breast cancer population. The number of complicating comorbidities will likely be a complicating factor in the diagnosis and treatment in this age group.¹³³

Female breast cancer incidence rates vary by race and ethnicity. Cases remain highest in white women followed by African Americans. Incidence of breast cancer in African Americans has stabilized for women age 50 years and older and decreasing for women younger than 50 years. Death rates in African-American women remain 37% higher than in whites, despite lower incidence rates.²⁸⁴

According to a new analysis of breast cancer rates, overall breast cancer rates may be decreasing, possibly as a result of the decline in use of HRT. For women of all ages and all breast cancer types, the incidence of breast cancer dropped by 7% in 2003. This is the first reported decrease in incidence since 1980, possibly reflecting the saturation of mammography utilization and reduction in the use of HRT.¹⁴⁸

One proposed possibility for the decline in breast cancer incidence rates in younger (premenopausal) women is the increasing prevalence of obesity. The mechanism is thought to be through anovulatory menstrual cycles and lower levels of circulating steroid hormones.²⁸⁴

Etiologic Factors

The cause of breast cancer is unknown, although there are some genetic bases, expression of which will vary in different ethnic groups. A known genetic mutation in two genes, *BRCA1* and *BRCA2* (the "breast cancer" genes), has been identified and may be responsible for most inherited cancers (accounting for 10% of all cases).

BRCA1 and *BRCA2* are tumor suppressor genes. Everyone has two copies of each gene, and when working properly, they produce proteins that keep cell growth in check. Mutations can render these genes inactive, increasing the risk for developing breast, ovarian, and certain other cancers.

Risk Factors

Female gender, age, ethnicity, family history, medical history, menstrual history (early onset of menstruation with greater exposure to estrogen), nulliparity or infertility (greater number of menstrual cycles with hormonal exposures), and geography are all factors linked to breast cancer (Box 20-6).

Gender and Hormone Exposure. Gender (female) is the most significant risk factor associated with this disease. Although women have many more breast cells than men, the primary reason they develop breast cancer more often is because breast cells are constantly exposed to the growth-promoting effects of the female hormones estrogen and progesterone. New evidence indicates that estrogen exposures throughout life including in utero may have an effect on breast cancer risk. Over half of all women diagnosed with breast cancer will have estrogen receptor-positive (ER-positive), lymph node-negative breast cancer.²²⁹ Tumors that are ER-positive have estrogen receptors and are stimulated to grow by estrogen. Tumors that do not have estrogen receptors are called *ER-negative* and are not influenced by the hormone.

Previous history of first-generation hormonal contraceptive use (higher dose formulations before 1975) and recent (last 5 years) prolonged use of combined HRT have been linked with increased risk of breast cancer, often found at a more advanced stage.

The established role of estrogen in the development and progression of breast cancer raises questions concerning a potential contribution from the many chemicals in the environment with estrogenic activity that can enter the human breast. A range of organochlorine pesticides and polychlorinated biphenyls possess estrogen-mimicking properties that have been measured in human breast adipose tissue and in human milk. These may enter the breast from contamination of food, water, and air.⁶⁵

Fewer than 1% of breast cancers occur in males. In men, age (>60 years) and heredity are the most common risk factors, but more than one-half have no known risk factors. Other factors associated with an increased risk of

Box 20-6

RISK FACTORS FOR BREAST CANCER IN WOMEN

Key Risk Factors

- Gender (female)
- Age 60 years or older
- Age at menarche (first menstruation <12 years = greater risk), especially when combined with late menopause (>55 years)
- Age at first live birth (>35 years = greater risk)
- Two or more first-degree relatives (mother, sisters, or daughters) with breast or ovarian cancer
- Male relative with breast cancer
- Number of previous breast biopsies (whether positive or negative)
- At least one biopsy with atypical (ductal or lobular) hyperplasia or radial scars
- Previous personal history of breast cancer

Additional Risk Factors*

- History of benign breast disease
- Ethnicity (whites: greater incidence; blacks: more deaths)
- Late menopause (>50 years)
- Nulliparity, infertility; first child born after age 30 years
- DES exposure
- Alcohol (≥ 2 drinks/day of beer, wine, hard liquor)
- Postmenopausal weight gain (20 to 30 lb or more since age 18 years); obesity
- High doses of chest radiation before age 30 years (e.g., Hodgkin's disease)
- Environmental exposures (under investigation)
- High-fat diet
- Long-term use of first-generation oral contraceptives before 1975 (high doses, e.g., EstrAval) or recent (last 5 years) combined HRT
- High bone density (postmenopausal women); circulating estrogen promotes bone formation

DES, Diethylstilbestrol; HRT, hormone replacement therapy.

*These risk factors are not included in the National Cancer Institute's *Breast Cancer Risk Assessment* tool for two reasons: either (1) evidence is not conclusive or (2) researchers cannot accurately determine how much these factors contribute to the calculation of risk for an individual. Nevertheless, these additional risk factors are known to contribute to the increased risk of breast cancer. For more information about risk assessment, see <http://www.yourcancerrisk.harvard.edu> or visit the National Cancer Institute's Breast Cancer Risk Assessment tool at <http://www.cancer.gov/bcrisktool/>

breast cancer in men include chest radiation exposure, liver disease, treatment with estrogen, treatment with immunosuppressants after organ transplantation, *BRCA2* gene mutations, Klinefelter's syndrome, history of benign breast disease or gynecomastia, and history of testicular pathology.

Weight Gain and Obesity. Many studies show that weight gain is a risk factor for breast cancer, especially for women after menopause. The ACS reports that women who gain 20 to 30 lb (or more) during adulthood (after age 18) are 40% more likely to develop breast cancer after menopause compared with women who gain no more than 5 lb and compared to women who have been overweight since childhood.^{9,79}

Estrogen stored in fat keeps the hormone circulating even when ovarian production stops at menopause. There

is evidence to suggest that fat cells in different parts of the body metabolize differently. For example, excess fat in the waist area may affect risk more than the same amount of fat in the hips and thighs. Obesity at the time of diagnosis is also thought to be significant as a poor prognostic factor.⁴³

Age. Age is the second most significant risk factor; the incidence of breast cancer increases with advancing age. For example, the 10-year risk of developing breast cancer jumps from 1 in 48 at age 40 years to 1 in 26 at age 60 years. The median and mean ages of women with breast cancer are between 60 and 61 years. Women with a personal or family history (personal history of breast, ovarian, or uterine cancer or family history of breast cancer among first-degree relatives) have a significantly increased risk of developing breast cancer.

Personal or Family History and Heredity. A personal history of breast cancer in one breast increases a woman's risk of developing a new cancer in the other breast or in another part of the same breast threefold to fourfold. This is not the same as a cancer recurrence of the first cancer. About 5% to 10% of breast cancer cases are hereditary as a result of gene mutations, most commonly affecting the *BRCA1* and *BRCA2* genes. Normally, these genes help prevent cancer by making proteins that keep cells from growing abnormally. Inheriting either mutated gene from a parent increases the risk of breast cancer.⁵²

Women with an inherited *BRCA1* or *BRCA2* mutation have up to an 80% chance of developing breast cancer during their lifetime and at a younger age than women who do not have these gene mutations. Women with these inherited mutations are also at increased risk for developing ovarian cancer. Other genes that might also lead to inherited breast cancer (e.g., ataxia-telangiectasia mutation [ATM] and *CHEK2* gene) are under investigation.⁹

Although only a small percentage of breast cancer cases are hereditary, about 20% to 30% of women with breast cancer have a family member with this disease. Having one first-degree relative with breast cancer doubles a woman's risk; breast cancer in two or more first-degree relatives (mother, sister, daughter) increases the risk fivefold.⁹

Breast cancer before age 50 years in a relative on either side of the family also increases the risk; the risk is higher if the mother or sister has a history of breast cancer. Although the exact risk is not known, women with a family history of breast cancer in a father or brother also have an increased risk of breast cancer.⁹

In addition, a history of benign breast disease, when accompanied by proliferative changes, papillomatosis, or atypical epithelial hyperplasia, increases the risk of cancer. Even with all these potential risk factors, the majority of women with breast cancer do not have any apparent risk factors.

Race/Ethnicity. White women are slightly more likely to develop breast cancer than are African-American women but African-American women are more likely to die of this cancer, possibly because of more aggressive tumors in African-American women. Black men are at almost twice the risk of white men. Asian, Hispanic, and

Native American women have a lower risk of developing and dying from breast cancer.⁹

Ashkenazi Jews who have a mutation in either *BRCA* gene have an 80% risk of developing breast cancer by age 80 years. This is compared to a 13% risk for the average 80-year old woman who does not have an Ashkenazi heritage.

Alcohol. Alcohol intake is also associated with an increase in risk, particularly for women whose intake of folate is low.¹⁷ Folate is a vitamin that helps prevent birth defects and has been linked to cancer prevention. The exact mechanism between alcohol consumption and breast cancer remains unknown, but alcohol may interfere with the body's ability to use folate.^{17,66}

It is also possible some individuals are more susceptible to the harmful effects of alcohol intake because of differences in alcohol metabolism. How much daily alcohol makes the difference remains under investigation; for now, research overwhelmingly agrees that risk increases with the amount of alcohol consumed and that even moderate alcohol consumption (two drinks or 20 g/day) increases breast cancer risk by at least 1.5 times.^{301,339}

Factors in Question. Scientists thus far have been unable to establish a direct link between breast cancer and tobacco smoke; electromagnetic fields; silicone breast implants; abortion or miscarriage^{23,32,299}; work at night; or the chemicals used in pesticides, plastics, herbicides, or hair colorings.^{9,125,230} The role of estrogenic chemicals applied as antiperspirants, deodorants, or cosmetics to the underarm and breast areas remains hotly debated. Evidence in support of a functional role for the combined interactions of cosmetic chemicals with environmental estrogens, pharmacologic estrogens, phytoestrogens, and physiologic estrogens has been presented^{53,65} along with evidence to refute the role of antiperspirants in breast cancer.²⁰⁸

Although scientists have found chemicals from antiperspirants and deodorants in breast tumors, the concentrations were far lower than the amount of estrogen naturally circulating in the body. The chemicals may be present in normal breast tissue, too, but this has not been studied yet.⁶⁴

Breast cancer is the most common solid tumor among women treated for Hodgkin's disease. Radiotherapy of the mediastinum has been implicated. The secondary cancer risk to females seems to increase 10 years after the initial diagnosis and treatment of Hodgkin's disease. Whereas there is a fifteenfold increase in risk for a second malignancy, the risk of breast cancer for females who had childhood Hodgkin's disease is 45 times greater than for those who did not have childhood Hodgkin's.^{266,300}

Pathogenesis

The pathogenesis of breast cancer is unknown, but estrogen is believed to be a key factor in promoting (rather than initiating) breast cancer. It may not trigger the series of genetic changes that are required to transform normal breast cells into malignant ones, but it may spur the proliferation of transformed cells, increasing the likelihood that they will develop into cancer. The development of invasive breast cancer involves epithelial hyperplasia,

premalignant change, *in situ* carcinoma, and invasive carcinoma.

These progressive alterations in the structure of the mammary epithelium are accompanied by a reorganization in the composition of the epithelial, periductal, and stromal extracellular matrix (ECM). This observation is important because ECM proteins (elastin, collagens, proteoglycans, and glycoproteins) not only provide a physical support for cells within developing and mature tissues but also act as an informational system.

These proteins detect and coordinate signals originating from the tissue microenvironment and adjacent cells. Networks of ECM interact with transmembrane receptors called *integrins* to transmit signals from the ECM to the cell interior. It is hypothesized that modifications in the mammary ECM that occur during tumor formation or a failure to respond appropriately to the preexisting ECM may result in aberrant cell behavior. Studies show that changes in cell adhesion play a major part in the development and progression of breast cancer.¹⁵⁰

Biologists collecting and recording salivary estrogen levels have recognized patterns of low feminine fertility correlated with famine. Estrogen samples from the mouths of hungry women are found to be about one-half of estrogen levels in the saliva of well-nourished women, a difference that can account for the drop in pregnancy rate in lean women.

Improved nutrition in developed countries, such as the United States, has led to increased exposure to estrogen over a lifetime. This variable combined with the resulting earlier age of menarche, delayed and decreased childbearing, increased prevalence of obesity, and the increase in exposure to environmental toxins all may contribute to more and prolonged estrogen exposure, possibly resulting in genetic mutations, loss of suppressor genes, and cell proliferation or cell growth.

An older but still unproved theory is the environmental exposure hypothesis that prolonged and cumulative exposure to hormonally active synthetic chemicals contributes to the rising incidence of breast cancer. Synthetic chemicals may do this directly by acting as estrogen, altering the way the body produces or metabolizes estrogen; they can work bifunctionally, through genetic or hormonal paths, depending on the periods and extent of exposure.⁶⁹

Prenatal exposure to estrogens may predispose a woman to breast cancer later in life through an "imprinting" process that sensitizes her to estrogen exposure. One way that synthetic chemicals may increase breast cancer risk is to alter the way the body processes its own estrogen. This theory is the basis for the use of indoles (phytochemicals found in vegetables) shown to reduce cancer risk.

Most carcinomas develop in the glandular epithelium of the terminal duct lobular unit. In the normal breast, the milk ducts and lobules are neatly lined with epithelial cells. Over time, some extra (noncancerous) cells may grow within the duct (hyperplasia) and begin to look odd (atypia); this condition is atypical ductal hyperplasia.

When cancer cells multiply but remain contained within the duct, the condition is called DCIS. A stromal invasion by malignant cells usually results in fibroblastic

proliferation. A palpable mass within the breast tissue will typically develop. IDC occurs when cancer cells break through the duct wall and enter other tissues.

Breast cancer has a propensity for metastases to the bone, possibly related to a small protein found in the bone marrow (osteonectin) that both attracts breast (and prostate) cancer cells to bone and once attracted, stimulates the cells to invade the bone. Researchers suggest that metastasis of breast cancer cells to the bone is mediated by the ability of osteonectin to promote migration, protease activity, and invasion.¹⁴⁶

Clinical Manifestations

The most common initial presenting sign of breast cancer is a palpable lump or nodule. Approximately 90% of breast masses are discovered by the woman herself; for men, the lump is usually in the center behind the areola and for women, either centrally behind the areola or in the upper, outer quadrant, although neoplasm can occur anywhere in the breast tissue (Fig. 20-13).

The mass tends to be firm and irregular if it is a carcinoma versus smooth and rubbery if it is benign. The mass is typically not painful if it is cancer. Fixation of the breast to the underlying pectoral muscles and chest wall can cause significant asymmetry (Fig. 20-14).

Other manifestations include a change in breast contour or texture, nipple discharge and retraction or inversion, local skin dimpling (Fig. 20-15), erythema, and a local rash or ulceration. Lymphadenopathy may also be the initial presentation of this disease. Most local breast cancer recurrence occurs along the incision line.

IBC is characterized by one breast becoming larger than the other. Warmth, redness, swelling, itching, pain, skin dimpling called *peau d'orange*, and nipple changes (e.g., retraction or flattening) are just some of the many symptoms of IBC. Some women report it looks like a bug bite on their breast. They may also report a bruise on the breast that does not go away.

Metastases

Local metastases by direct extension of the primary disease site may involve the chest wall, ribs, pleura, pulmonary parenchyma, or bronchi and may erode the first and second ribs and associated vertebrae.²⁰⁰ Symptoms associated with metastases can include upper extremity edema, bone pain, jaundice, or weight loss. These findings are rarely the initial complaint.

If not diagnosed and treated early, the cancer can spread to the regional lymph nodes, including the axillary, internal mammary, and supraclavicular nodes. As the disease progresses, the cancer commonly spreads to the lungs, liver, bone, adrenals, skin, and brain.

Signs and symptoms of the affected system may be the first clinical indication of a problem. For example, lung lesions may present as vague, aching chest pain, hemoptysis, or unexplained dyspnea. Metastases to the liver may present as fatigue, jaundice, CTS, or skin changes.

Bone metastases is especially common affecting the vertebrae, pelvis, ribs, hip, femur, and humerus (see Table 9-2); metastatic spread from breast cancer rarely presents in locations below the elbows and knees. Bone pain and

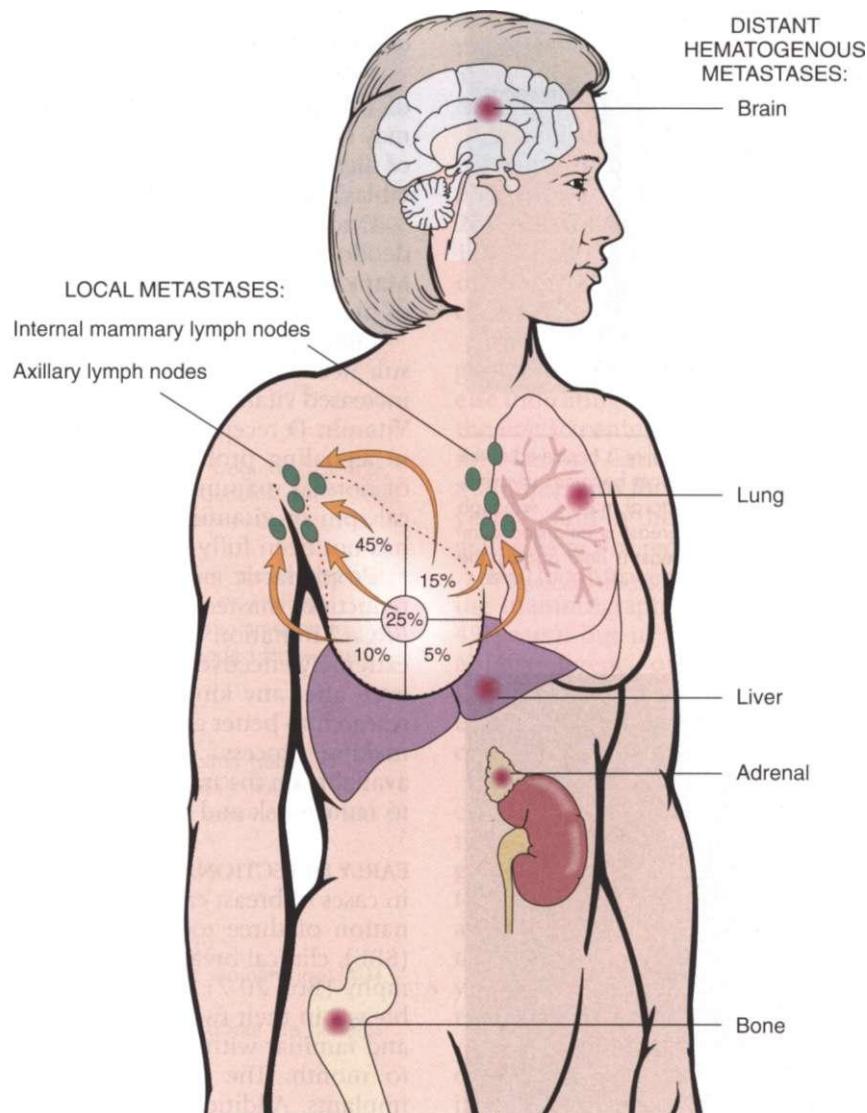


Figure 20-13

The distribution of breast carcinoma and the pathway of lymphatic metastases. Most tumors in women are found in the upper lateral quadrant and behind the nipple (areola) and for men, behind the nipple. (From Damjanov I: *Pathology for the health-related professions*, ed 3, Philadelphia, 2006, Saunders.)

fracture are the most common symptoms of bone metastases.

Paraneoplastic Syndrome

A rare neurologic paraneoplastic syndrome associated with breast cancer in women called *stiff-man syndrome* has been reported with increasing frequency.^{145,232,245} Paraneoplastic stiff-person syndrome is characterized by progressive symptoms of neuropathy or myelopathy with increased muscle tone and rigidity in the spine and lower extremities, especially the ankle dorsiflexors with loss of ankle motion. See further discussion on Paraneoplastic Syndrome in Chapter 9.²¹⁸

MEDICAL MANAGEMENT

PREVENTION. *Healthy People 2010* has identified the reduction of the breast cancer death rate by 20% as its primary objective related to breast cancer. The ACS's 2015

Challenge Goals and Nationwide Objectives include a reduction of 15% in the age-adjusted incidence rate of the disease and a 45% reduction in the age-adjusted mortality rate. By the year 2008, the ACS hopes that 90% of women 40 years of age or older will undergo breast cancer screening that is consistent with their guidelines.^{36,334} Additionally, by 2008, the ACS's goal is to increase to 90% the portion of breast cancers diagnosed at a local stage or earlier.

Risk factor modification is advocated, including moderate-to-vigorous physical activity (45 to 60 minutes on 5 or more days per week), weight control and minimal lifetime weight gain, alcohol restriction (avoid alcohol if at high risk for breast cancer), and chemopreventive agents to reduce exposure to estrogen.

Controlling weight, anytime after age 18 but especially in middle age, may help in preventing breast cancer, the recurrence of breast cancer, and death from breast

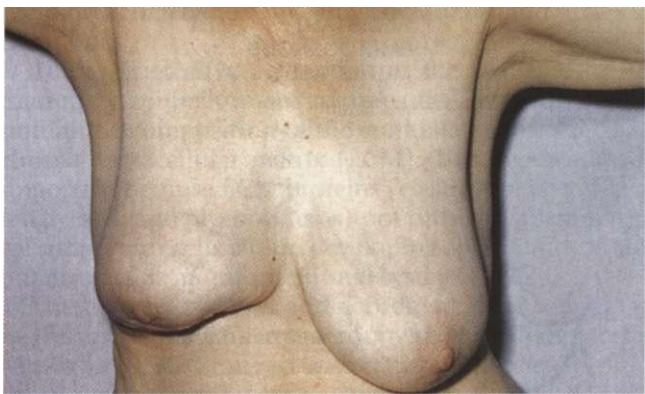


Figure 20-14

Fixation. Asymmetry, distortion, or decreased motility is observed in the woman's right breast as she lifts her arms. As cancer becomes invasive, fibrosis can fix the breast to the underlying pectoral muscle. Although at first glance, it looks as if the woman's left breast is enlarged compared to the right, in fact, the woman's right breast is held against the chest wall. (From Mansel R: *Color atlas of breast diseases*, London, 1995, Mosby.)

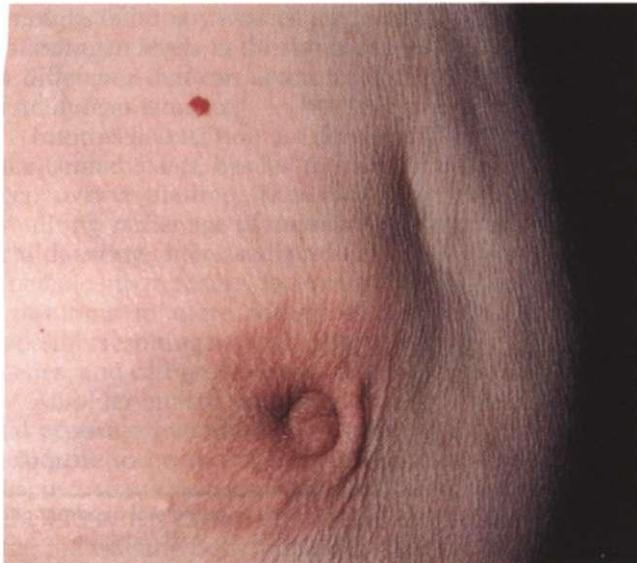


Figure 20-15

Dimpling. The shallow dimple above and slightly to the right of the nipple as viewed in this photograph shows signs of skin retraction or skin tethering. Cancer causes fibrosis, which contracts the suspensory ligaments of the breast, resulting in this clinical change in the breast tissue. The dimpling may be visible at rest, with compression, or with lifting of the arms. The fibrosis can also pull the nipple as seen by the distortion of the areola here. (From Evans AJ: *Atlas of breast disease management: 50 illustrative cases*, Philadelphia, 1998, WB Saunders.)

cancer.⁴³ Fat tissue contains an enzyme that converts adrenal gland hormones to estrogen. The extra estrogen in overweight women acts as a nutrient and aids the growth of precancerous or abnormal cancerous cells in the breast.

Data from the Nurses' Health Study show a clear benefit for postmenopausal women from engaging in some form of exercise. Postmenopausal women who get at least 1 hour of physical activity per day are 15% to

20% less likely to develop breast cancer than sedentary women.²⁵⁸

Restricting alcohol is a proven risk reducer. Excess risk of breast cancer associated with alcohol consumption may be reduced by adequate folate intake.^{17,340} The effects of diet and nutrition (low fat and rich in fruits and vegetables) remain under investigation.

Evidence to support a link between antiperspirants or deodorants and breast cancer remains controversial. Many women choose to avoid these products as a means of preventing breast cancer until proved otherwise.

Other preventive steps may include exposure to the sun needed by the skin to manufacture vitamin D and increased vitamin D intake (food or supplementation).¹⁴⁹ Vitamin D receptor (VDR) in mammary cells has a role in signaling proliferation, differentiation, and survival of normal mammary epithelial cells. However, whether calcium or vitamin D intake modifies risk by genotype has not been fully investigated.³⁷¹⁹⁷

Prophylactic mastectomy (also referred to as risk-reduction mastectomy) for women with a *BRCA1* or *BRCA2* mutation and positive family history has proved extremely effective, but there is still a risk of breast cancer even after any kind of mastectomy. There is a need for **research to better guide high-risk women in the decision-making process.**^{179,290} Numerous reputable books are available on the trade market specifically addressing ways to reduce risk and prevent breast cancer.

EARLY DETECTION. The hallmark of effective intervention in cases of breast cancer is early detection using a combination of three tools: monthly self-breast examination (SBE), clinical breast examination (CBE), and mammography (Box 20-7). Women should start examining their breasts in their twenties so they are comfortable doing it and familiar with the way their breasts feel from month to month. The same is true for women with breast implants. Additional mammogram screening, called an *implant displacement view*, may be requested.

Clinical Breast Examination (CBE). The ACS makes the following screening recommendations for asymptomatic women at average risk: beginning at age 20, CBE and counseling to raise awareness of breast symptoms; for women ages 20 to 39 years, a CBE every 3 years and annual mammogram after age 40 years.

Self-Breast Examination (SBE). The ACS no longer recommends that all women conduct regular SBE, but women should be informed about the potential benefits and limitations associated with SBE.²⁸⁵ This change in the recommendation came about as a result of a large study of female factory workers in China (referred to as the Shanghai Study). The women were taught how to do SBE with follow-up to see if the number of deaths from breast cancer was reduced. Although the rate of breast cancer was not reduced, the authors of the study clearly note that the women were not asked if or how often they performed the SBE. Without the availability of mammography, when women did find a cancerous lump, the cancer was more advanced with a much worse prognosis.³⁰⁴

There is still much controversy over the methodology and results of this study. Many experts still advocate monthly SBE performed 1 week after the cessation of

Box 20-7**AMERICAN CANCER SOCIETY RECOMMENDATIONS FOR BREAST CANCER SCREENING**

The American Cancer Society (ACS) recommendations for breast cancer screening are presented below in abbreviated form. Readers should refer to the original full text guideline document to see the complete recommendations, along with the rationale and summary of the evidence.

Clinical breast examination (CBE) should be part of periodic health examinations, at least every 3 years for women in their 20s and 30s; asymptomatic women age 40 and older should have an annual CBE by a qualified health care professional.

Mammography should be done annually beginning at age 40. Women should be educated about the benefits, limitations, and potential harms associated with regular mammography.

Additional screening (e.g., starting annual mammography at a younger age and/or at closer intervals, or adding magnetic resonance imaging or ultrasound examination to mammography screening) may be recommended for women with any of the following:

- Previous personal history of breast cancer
- History of chest wall radiation
- Documented genetic mutation (BRCA or other genes)
- Strong positive family history without genetic mutation
- High-risk benign pathology (e.g., lobular carcinoma *in situ* or atypical hyperplasia)
- Very dense breast tissue on mammography

Summary of New ACS Guidelines

- CBE every 3 years for women ages 20-39
- Annual CBE every year for asymptomatic women ages 40+
- SBE occasionally or not at all
 - Women ages 20+ should be educated about the benefits and limitations of the SBE
- Mammogram annually from age 40

Data from American Cancer Society (ACS); ACS News Center: Updated breast cancer screening guidelines http://www.cancer.org/docroot/NWS/content/NWS_1_1x_Updated_Breast_Cancer_Screening_Guidelines_Released.asp, May 2003. Accessed January 24, 2007.

bleeding from the menstrual cycle or in the postmenopausal woman consistently perhaps on the same day each month. The American College of Obstetricians and Gynecologists (ACOG) advocates performing BSE as one way to increase a woman's breast cancer awareness. If a woman chooses to perform BSE, she should learn the correct procedure from a qualified health care professional (including physical therapists)^{106,107} who can evaluate her technique.

One of the striking changes in the presentation of breast cancer in the United States over the past 25 years is the reduction in the size of lumps discovered by women themselves.¹²³ There is also case-control evidence that excellent BSE may reduce mortality.¹²⁷ For a discussion of the relative merits and disadvantages of the study, see the American Cancer Center News Center: *Do breast self-exams make a difference?* available at http://www.cancer.org/docroot/nws/content/nws_1_1x_do_breast_self-exams_make_a_difference.asp.

The Susan G. Komen Foundation also offers step-by-step BSE instructions in English and Spanish (see www.komen.org/bse).

Mammography. Screening mammography can reduce mortality from breast cancer by approximately 20% to 35% in women aged 50 to 69 years and approximately 20% in women aged 40 to 49 years.^{81,92} Approximately 11% of all mammography studies are abnormal and 3% of those "abnormals" are actually diagnosed as breast cancer.¹⁶²

The term *screening mammography* implies the mammogram is done when there is no palpable lump or anything else indicating cancer. Until 1997 the ACS recommended the first screening mammogram by age 40 years, whereas the National Cancer Institute stopped advocating routine mammograms for women between the ages of 40 and 50 years²²⁷; and in the rest of the world, screening mammograms were not recommended until age 50 years.

Much controversy and debate centered around screening mammography for this particular age group (40 to 49 years); but in 1997, based on data presented at the NIH conference on breast cancer screening establishing the effectiveness of mammography in women younger than 50 years, the NIH began recommending breast cancer screening to women in their forties.^{227,286}

Organizations, including the American Medical Association (AMA), ACOG, and the ACS, support mammography screening beginning at age 40 years, although these groups vary in their recommendations regarding intervals for rescreening.²⁶⁵ The U.S. Preventive Services Task Force, an independent panel of private-sector experts in prevention and primary care, recommends that women aged 40 years and older be screened for breast cancer with mammograms every 1 to 2 years.^{311a}

At present, data are insufficient to recommend a specific surveillance strategy for high-risk women. Earlier initiation of screening, screening at shorter intervals, and screening with additional modalities, such as ultrasound and MRI, may be advised.²⁸⁵

The cost-effectiveness and efficacy of screening mammography in women age 70 years and older have come under examination. It has been suggested that the small gain in life expectancy is a variable that must be factored in when a woman decides about screening.¹⁶³

Some experts suggest that screening, including mammography, should be continued as long the woman's life expectancy is more than 5 years. The challenge remains for the physician to accurately estimate an older person's life expectancy based on individual health status, including concomitant comorbidity.¹³³

Genetic Testing. Inherited mutations of *BRCA1* and *BRCA2* do increase the lifetime risk of breast (and ovarian) cancer, but genetic testing is not advised for everyone. Having an inherited gene mutation does not mean breast cancer is inevitable. Women who have a positive family history of breast cancer before the age of 40 years should seek genetic counseling. Testing may be advised for anyone with a family history described previously in the section on Risk Factors for this disease.

There are many considerations when considering genetic testing. A negative test for a mutation may be dif-

ficult to interpret if the family history is unknown. Coping with the results if they are positive and weighing all the options can be challenging. Although most states have genetic privacy laws to prevent discrimination by health insurers, the guidelines do not always apply to life or disability insurance. Testing is done by a simple blood test, but the test may be expensive and is not always covered by insurance.

DIAGNOSIS. Clinical examination, mammography, and ultrasonography are all used to detect breast abnormalities. Tissue biopsy is the standard for a definitive diagnosis, and sentinel lymph node mapping to identify micrometastases has become standard practice to identify and remove only the first node or nodes that cancer cells reach after leaving the breast. This eliminates unnecessary dissection (see discussion of biopsy technique in the section on Diagnosis in Chapter 9). Only women whose sentinel nodes indicate the spread of cancer will need to undergo more extensive biopsy.

Imaging Technology. As mentioned, mammography is an important tool for the detection of a lesion before the mass (cancerous or benign) is large enough to be palpable but is not a substitute for biopsy because by itself it is not diagnostic and it may not detect cancer in very dense breast tissue.

Digital Mammography. Updated technology, such as digital mammography (computerized x-rays), may improve early detection of breast cancer. With the added capability of transmitting results electronically to specialists worldwide for consultation, this technology may reduce further misdiagnosis and unnecessary surgery. Mammography does not detect all breast cancers, and it cannot distinguish well among the various kinds of breast cancer. A more precise, noninvasive screening technique that does not involve the use of radiation is the ultimate goal of investigators developing improved breast cancer screening. Breast cancer can remain dormant for years before becoming clinically apparent, so long-term follow-up is mandatory for all women, especially anyone with a previous history of breast cancer.³⁵

Ductal lavage is another new method to detect early changes in ductal cells for women at high risk for developing breast cancer. Epithelial cells that line the ductal and lobular system of all milk ducts are collected using a microcatheter inserted into the milk ducts through the nipple surface. Results of this test may be able to diagnose abnormal ductal cells before cancer becomes evident on a mammogram or in a physical examination.^{72,86}

Magnetic Resonance Imaging. Scientists are adapting MRI and positron emission tomography (PET) scanning, two imaging technologies that are good at distinguishing malignant from benign tissue, for use in breast cancer diagnosis (staging), although these remain too costly to use in general screening programs. MRI scans do find cancers that mammograms miss, especially in high-risk women, perhaps because breast cancer occurs in these women at a younger age when breast tissue is denser. About 3% of new cases of breast cancer have malignant tumors in the contralateral breast that can only be detected by MRI. The cost of MRI prohibits its use as a screening tool, but it is cost-effective and recommended for use

to improve the detection of cancer in women already diagnosed.^{177a}

New guidelines from the ACS recommend MRI scans and mammograms once a year starting at age 30 for high-risk women. High risk is defined as a 20% to 25% or higher chance of developing breast cancer over the course of a lifetime. The average lifetime risk for women in the United States is 12% to 13%.

The high-risk group includes women who had radiation treatment to the chest between ages 10 and 30 years (e.g., for Hodgkin's disease); women who are prone to breast cancer because of the presence of genetic mutations, such as *BRCA1* or *BRCA2*; or those whose mothers, sisters, or daughters carry those mutations.

Ultrasound. Ultrasonography is primarily used to differentiate a cystic from a solid lesion. Real-time elastography (elastogram), an experimental ultrasound technique, is on the horizon. This technology distinguishes harmless lumps from malignancy and provides results in minutes. The technique was pioneered at the University of Texas Medical School at Houston in the 1990s.³⁶

Ultrasound elastography is capable of imaging tissue strain even before tissue stiffness associated with pathologic change occurs. Some areas that appear as shadows on sonograms show up as discrete masses on elastograms. The technique may be able to replace tissue biopsy in the diagnostic process.^{303,323}

Biomarkers. The protein (oncogene) *c-erbB-2*, also known as HER2/neu, is a prognostic breast cancer marker assayed in tissue biopsy specimens from women diagnosed with malignant tumors. Current studies suggest that soluble fragments of this oncogene may be released from the cell surface and become detectable in the saliva of men and women with the recurrence of breast cancer.²⁹⁴ Other biomarkers are under investigation, including one ECM component called *tenascin-C*. Expression of this large glycoprotein is suppressed in the normal adult mammary gland but is induced in breast cancer and is present in preinvasive cancer, as well as invasive breast cancer.¹⁰⁴ Researchers are investigating the use of minimally invasive tests to seek out biologic markers in blood or other fluids before a tumor develops.

Staging. Once the diagnosis is established, the clinical stage is ascertained in order to determine optimal management, including selection of candidates for adjuvant systemic therapies (Table 20-3). Staging is done most often using *sentinel lymph node biopsy* (SLNB), which consists of the removal of one to three nodes; the removal of more than three nodes is considered a *dissection*.

Stage 0 (preinvasive cancer), referred to as *in situ*, means that the cancer remains "in place" and has not spread from its point of origin. Stage I disease is marked by a tumor 2 cm in size or smaller. Stage II disease is marked by a tumor between 2 and 5 cm in size without nodal metastases or a tumor less than 5 cm with homolateral axillary lymphatic metastases (the nodes are movable). A tumor larger than 5 cm is classified as stage III, as is a tumor fixed to the pectoral muscle or fascia or if the diseased axillary lymph nodes are fixed to adjacent tissues. Stage IV disease is a tumor fixed to the chest wall or skin or any tumor with metastases to the homolateral

Table 20-3 Stages of Breast Cancer and Prognosis

Stage	Description	5-Year Relative Survival Rate
0	Early cancer that has not spread (inside or outside breast), called DCIS, LCIS, or breast cancer in situ.	100%
I	No larger than 2 cm, has not spread outside the breast.	100%
IIA	Between 2 and 5 cm, does not involve lymph nodes, has not spread to distant sites.	92%
IIB	Between 2 and 5 cm, has spread to axillary lymph nodes, has not spread to distant sites.	81%
IIIA	Smaller than 5 cm, has spread to axillary and other lymph nodes; has not spread to distant sites.	67%
IIIB	Cancer has spread to tissues near the breast (skin, chest wall, ribs, muscles) and to lymph nodes inside the chest wall along the breast bone, has not spread to distant sites.	54%
IIIC	Can be any size, spread to 10 or more axillary lymph nodes or 1 or more infraclavicular/supraclavicular or internal mammary lymph nodes, has not spread to distant sites.	*
IV	Can be any size, metastases to other parts of the body (e.g., bones, lungs, liver, brain) or to skin and lymph nodes inside the neck.	20%

Data from American Cancer Society and the Health Alliance Cancer Services, 2007.

DCIS, Ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

*Survival rates for IIIC breast cancer are unavailable; this stage was only defined a few years ago.

infraclavicular or supraclavicular nodes, with upper extremity edema, or with any distant metastasis.

The TNM classification of breast cancer has been revised and changed considerably, based on important developments that have occurred in breast cancer diagnosis and management. For example, the average size of breast tumors when first detected has decreased significantly. Immunohistochemical (IHC) staging and molecular biology techniques (e.g., reverse-transcriptase polymerase chain reaction [RT-PCR]), increasing knowledge of the importance of total positive axillary lymph nodes, and new information about clinical outcomes associated with metastases have led to greater refinement in TNM staging.²⁸³

TREATMENT. Once the diagnosis of breast cancer is made, most of the treatment is the same for men as for women. The treatment plan depends on the type of cancer, stage

at diagnosis (early or advanced), hormonal sensitivity (ER-positive or progesterone receptor-positive [PR-positive]), and presence of the growth-promoting protein Her-2/Neu, which appears to produce tamoxifen resistance. Treatment options include surgery, chemotherapy, radiation therapy, and hormonal manipulation.

The NCCN publishes an annual update of its original 1996 NCCN Breast Cancer Treatment Guidelines. The Guidelines address the treatment of all stages of breast cancer. With constant changes in the adjuvant therapy for breast cancer, a supplement to the Guidelines from the NCCN Breast Cancer Adjuvant Therapy Task Force is available.⁴²

Radical mastectomy was the most commonly employed procedure until the 1970s. This technique included removal of the entire breast, pectoral muscles, axillary lymph nodes, and some additional skin. Postsurgical problems included lymphedema, restricted shoulder mobility, impaired muscle function, and paresthesia.

Likewise, axillary node dissection is no longer performed routinely since it has been shown that the therapeutic benefit of a complete dissection has no effect on survival rate or risk of metastasis but only local control of the tumor. Instead, intraoperative lymphatic mapping and sentinel lymph node dissection are replacing complete lymph node dissection as the preferred procedure for the management of early-stage disease.¹³⁷

Breast-Sparing Therapy. More recent treatment recommendations for women with stage I or II breast cancer include breast-conserving surgery (BCT), or lumpectomy to remove only the tumor and a surrounding margin of normal tissue with preservation of the breast, and radiation therapy (Fig. 20-16). Lumpectomy may be an option for women with larger tumors who have neoadjuvant chemotherapy (before surgery) to shrink the tumor.

Up to 50% of women with early breast cancer in the United States are now treated with BCT. In some geographic areas, modified radical mastectomy, which spares the pectoralis major muscle, is also a commonly used procedure with the primary advantage being avoidance of radiation therapy. However, radiotherapy, now an integral part of BCT, should not be withheld.^{95,138}

BCT may not be appropriate for women whose breasts are so small a simple lumpectomy would be too disfiguring, making a simple mastectomy the more feasible option. Breast conservation is not appropriate when there are multiple areas of cancer, a tumor too large to excise, and previous history of radiation to the breast.^{199a}

Mastectomy is usually reserved for women with more extensive disease; although the surgeon may recommend mastectomy for some women with early breast cancer if, for example, cancer is found in more than one location in the breast. Some women choose mastectomy to avoid radiation or for greater peace of mind.

Breast reconstruction with an implant is an option for women who have mastectomies. This is a two-stage process; first, a balloonlike tissue expander is placed under the chest wall muscle. Every 2 or 3 weeks for several months, saline is injected into the expander to gradually stretch the overlying chest wall muscles and skin.

The expander is replaced in a second surgery with a permanent saline implant. Although silicone implants

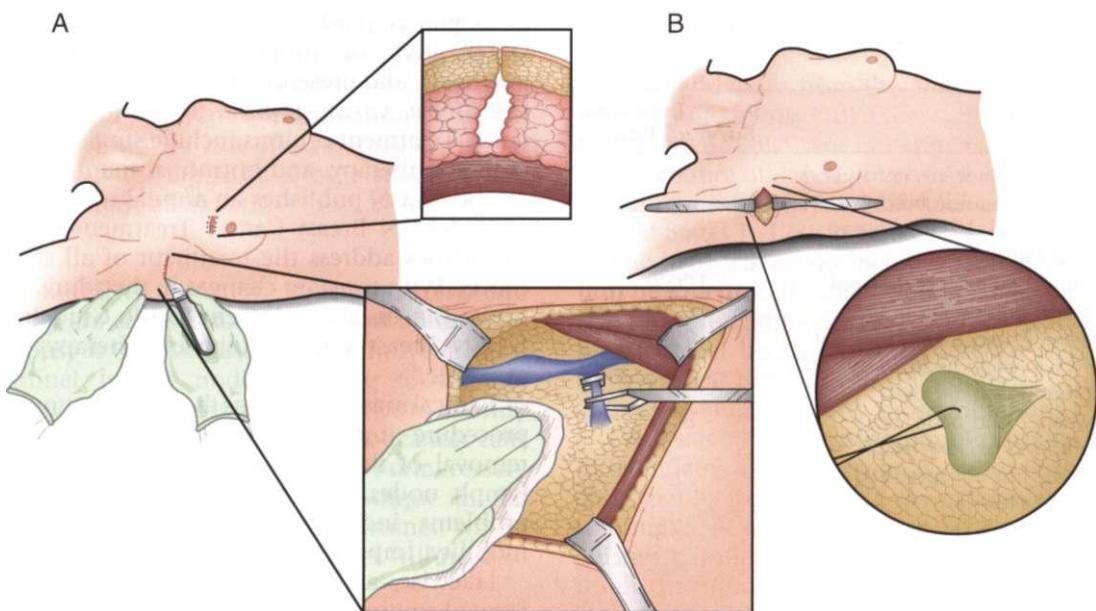


Figure 20-16

Breast-conserving therapy (BCT). **A**, Incisions to remove malignant tumors are made directly over the tumor without tunneling. A transverse incision in the low axilla is used for either the sentinel node biopsy or the axillary dissection. The inset shows the excision cavity of the lumpectomy; no attempt is made to approximate the sides of the cavity, which will fill with serous fluid and gradually shrink. **B**, In the sentinel node biopsy, a similar transverse incision is made and extended through the clavipectoral fascia and the true axilla entered. The sentinel node is located by virtue of its staining with dye or radioactivity, or both, and dissected free as a single specimen. (From Townsend CM: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2004, WB Saunders.)

were banned in 1992, after reviewing years of evidence and research concerning silicone gel-filled breast implants, the Institute of Medicine (IOM) has not found any increased risk of adverse health outcomes. The use of silicone-based implants has been reinstated once again.

Silicone breast implants may be contraindicated or used with caution in women with existing malignant or premalignant cancer of the breast. Silicone gel-filled breast implants have not been clinically tested in women who have had radiation to the breast after implantation. For a complete discussion of this topic, the reader is referred to the IOM's publications.^{144, 144a}

Alternately, muscle-flap procedures use tissue from the back or abdomen to either form a breast or create a pocket for an implant. The most popular flap procedures are the latissimus dorsi (back) flap, the transverse rectus abdominis muscle (TRAM) flap (Fig. 20-17), and the free flap. Free flaps use little or no muscle; a plastic surgeon trained in microvascular technique is needed for this procedure.

More recently a new procedure, the deep inferior epigastric perforator (DIEP) flap, uses skin and fatty tissue from the abdomen to reconstruct the breast without sacrificing the underlying abdominal muscles. Blood vessels (deep inferior epigastric artery) harvested to supply the new breast tissue do not travel within the abdominal muscles. Less disruption of the abdominal tissue results in far fewer abdominal impairments.^{47, 109, 110}

A similar procedure, the gluteal artery perforator (GAP) flap, allows transfer of tissue from the buttock, also with minimal donor-site morbidity. Like the DIEP, the superficial inferior epigastric artery (SIEA) flap transfers the

same tissue from the abdomen to the chest for breast reconstruction as the TRAM flap without sacrificing the rectus muscle or fascia (Fig. 20-18).^{109, 110}

After surgery, the treatment plan may include radiation therapy, chemotherapy, hormone therapy, or a combination of these approaches. Chemotherapy is used when a tumor is larger than 1 cm or when smaller tumors have spread to the lymph nodes. The primary objective of these treatments is to reduce the odds of occult metastases developing into disease.

Chemotherapy. Women with harder to treat ER-negative breast tumors benefit much more from chemotherapy than do women with ER-positive tumors. Almost all women with ER-negative breast tumors should receive chemotherapy, whereas women with ER-positive tumors are better served by hormonal therapy; chemotherapy adds little additional improvement for ER-positive women.²³

Increased disease-free survival time after combination chemotherapy has been noted consistently in premenopausal women with metastases to the axillary lymph nodes. Combination chemotherapy combines two or more drugs and is given in multiple courses over 3 to 6 months. The addition of hormone therapy or ovarian ablation for premenopausal women to stop estrogen production is more effective than chemotherapy alone in women whose tumors contain estrogen receptors.

The majority of women with early-stage breast cancer are advised to receive chemotherapy in addition to radiation and hormonal therapy, yet research has not demonstrated that chemotherapy benefits everyone equally. The development of molecular profiling tests (a technique

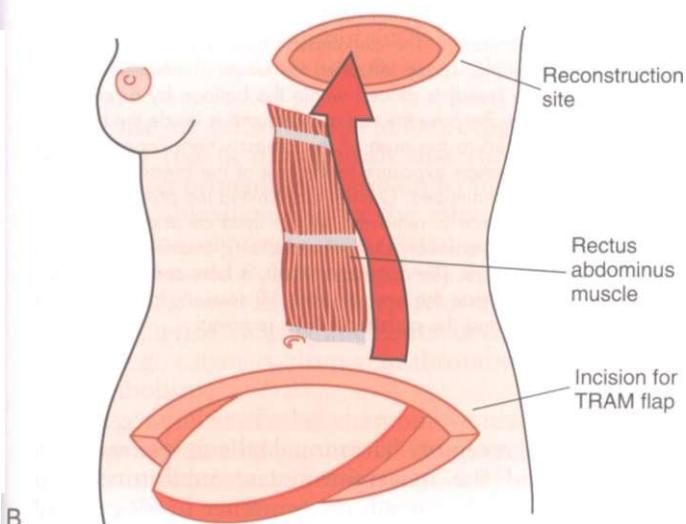
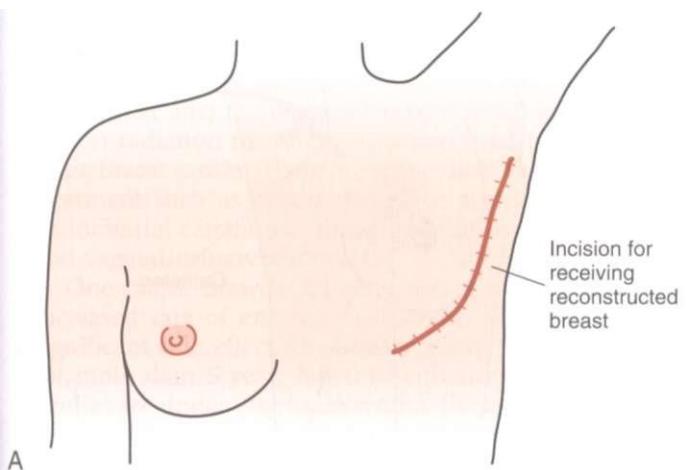


Figure 20-17

Transverse rectus abdominis myocutaneous (TRAM) flap. **A**, After mastectomy of the involved breast, **(B)** a breast is reconstructed using the lower abdominal skin and fatty tissue. In a pedicled TRAM, the tissue's own blood supply remains attached and the lower abdominal tissue is rotated into position on the chest. The tissue is tunneled under the skin to the chest area, where it is brought through the mastectomy incision. The reconstructed tissue is shaped to form a matching breast and placed in the mastectomy skin pocket. A free TRAM flap refers to using skin and tissue that are completely disconnected from their own blood supply, moved from the abdomen to the new site, and then reconnected to different blood vessels. A nipple and areola can be tattooed on later after healing has taken place.

that examines many genes simultaneously) may be able to spare women unnecessary treatment if chemotherapy is not likely to be of benefit to them.^{153,207}

Gene Profiling. Testing, or Trial Assigning Individualized Options for Treatment (TAILORx), is underway to determine the most effective current approach to cancer treatment with the fewest side effects for women with early-stage breast cancer using gene profiling assays. Two such diagnostic tests now available for gauging a woman's

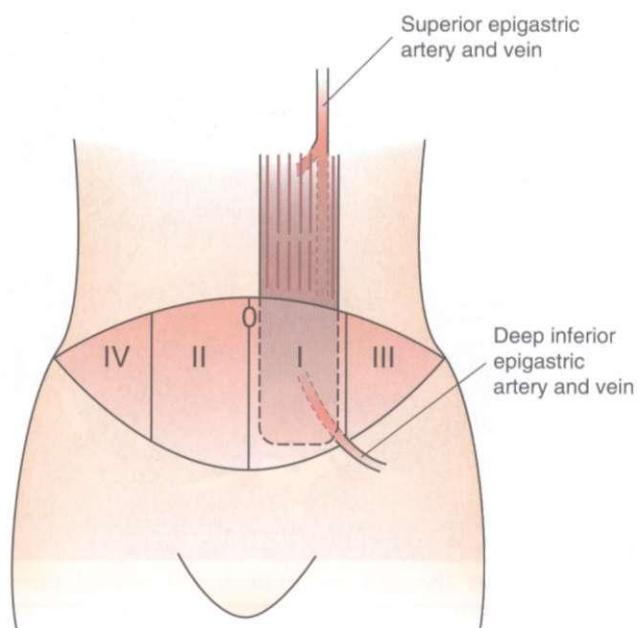


Figure 20-18

Vascular territories of the abdominal wall provided by unilateral transverse rectus abdominis myocutaneous (TRAM) flap. Studies show that the most reliable cutaneous portion is directly overlying muscle zone I, followed by zones III, II, and IV, respectively. A deep inferior epigastric perforator flap (DIEP) is an alternative procedure to the TRAM. The rectus abdominis muscle is dissected to harvest the blood vessels, but the muscle is preserved because no muscle or overlying muscle fascia is used. The DIEP flap relies on blood vessels that perforate the rectus abdominis muscle (e.g., deep inferior epigastric artery and vein). [From Townsend CM: Sabiston textbook of surgery, ed 17, Philadelphia, 2004, WB Saunders.]

risk of breast cancer recurrence are Oncotype DX and MammaPrint gene profiling tests.

The Oncotype DX test can be performed in women of all ages with early-stage node-negative, ER-positive tumors. The MammaPrint assay is used only for women 55 years or younger who have early ER-positive or ER-negative tumors. Using this test to obtain characteristic genetic information, called a *genetic signature*, about the tumor can predict rate of metastasis and disease-free survival.

Researchers have found that women classified as high risk by the Oncotype DX test gain substantially from chemotherapy with a 90% 10-year disease-free survival rate when treated with chemotherapy compared to 65% with tamoxifen alone.²³⁷ Neither test is intended for use in women with either carcinoma in situ (precancerous) or metastatic breast cancer; the tests are not 100% accurate or fool-proof.

Radiation Therapy. Most women receive radiation therapy after a lumpectomy to eradicate any cancer cells that may remain in the affected breast or nearby lymph nodes. Usually, radiation is delivered to the whole breast once a day, 5 days a week, for about 6 weeks (Fig. 20-19).

Software algorithms used to produce discriminating radiation fields conform the radiation to the breast, chest wall, and/or regional lymph nodes to achieve a homog-

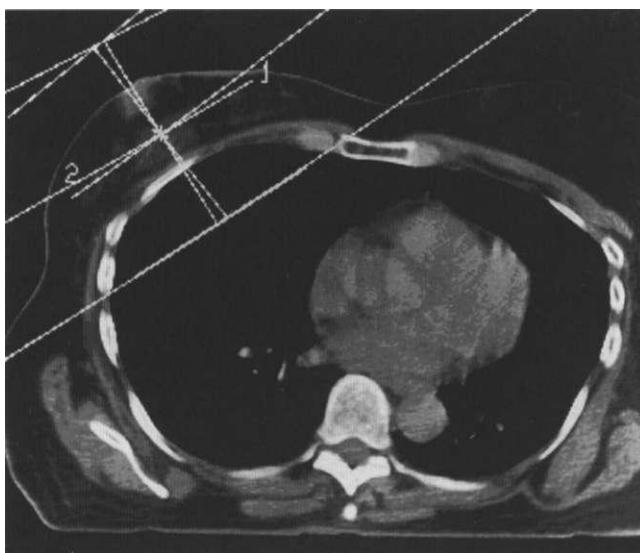


Figure 20-19

The standard radiation field configuration for breast cancer. Two tangentially directed fields encompass the breast with a minimal amount of underlying lung tissue. The contralateral breast and all of the critical structures are avoided. (From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Churchill Livingstone.)

enous dose to the breast and decrease or avoid doses to the ribs, lung, and heart. This technology has allowed greater adaptation to a variety of breast and chest wall shapes.³³

Women who have a mastectomy may also be treated with radiation if the tumor is more than 8 cm or if the tumor is close to the rib cage or chest wall, or if there were many positive axillary lymph nodes.

The use of partial-breast radiation to target the tissue immediately around the tumor where cancer is most likely to recur is on the rise. Radiation beams can be targeted at the tumor site instead of the breast, cutting down the usual 6-week treatment to 5 days (Fig. 20-20). Studies are underway to determine who is the best candidate for this treatment and what treatment protocol works best. A 1-day method that permanently implants radiation seeds inside the breast to kill stray cancer cells is also in use. The pellets emit radiation for about 2 months until they run out; the implant remains under the skin with no further effects.^{158,244}

Stem Cell Transplantation. In 1998, breast cancer was the most common indication for stem cell transplant in North America, accounting for nearly one-third of all transplants. However, subsequent reports have concluded that high-dose chemotherapy plus autologous bone marrow transplantation does not improve survival in women with metastatic breast cancer.^{24,288} Thus a gentler approach using trastuzumab (Herceptin) was developed with better outcomes and fewer side effects.

Hormonal Therapy. Knowing that estrogen promotes the growth of ER-positive breast cancers, several methods are used to block the effect of estrogen or to lower estrogen levels. **Antiestrogens** prevent estrogen from causing the growth of cancer cells by binding directly to and blocking

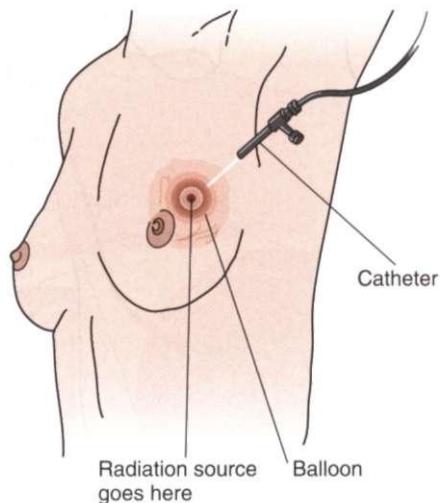


Figure 20-20

Balloon brachytherapy. The MammoSite device approved for partial breast radiation in the treatment of early-stage breast cancer. A single-balloon catheter is inserted in the breast to deliver a site-specific, prescribed dose of radiation. The deflated balloon is placed inside the lumpectomy cavity (the space left after the tumor is removed). A tiny radioactive source (seed) is placed within the balloon by a computer-controlled machine. Because the radiation source is inside the balloon, radiation is delivered to the area of the breast where cancer is most likely to recur. Radiation exposure to the rest of the breast, skin, ribs, lungs, and heart is minimized. Once it has emitted the prescribed dose of radiation, the source is removed. When used as primary therapy (i.e., the only form of radiation after a lumpectomy) treatments are twice a day for up to 5 days. The applicator shaft, a tube connected to the balloon, remains outside the breast. After 10 sessions in 5 days, the balloon is deflated and the catheter is then removed.

the estrogen receptor. Hormonal therapies, such as tamoxifen and the newer aromatase inhibitors, help prevent the growth, spread, or recurrence of ER-positive tumors by preventing estrogen from reaching them. Women with ER-positive tumors may benefit from hormonal therapy without needing chemotherapy. Hormonal therapy does not work against ER-negative tumors.

Tamoxifen (Nolvadex) has been the definitive standard of antiestrogen hormonal therapies for the last 30 years because of its documented efficacy in preventing ER-positive breast cancers from coming back and its reasonable safety profile. Tamoxifen prevents estrogen from entering cells, whereas some newer antiestrogens, such as fulvestrant (Faslodex), work by reducing the number of estrogen receptors. Tamoxifen is typically used as a chemopreventive agent to reduce the risk of recurrence. It is administered for 5 years after surgery for premenopausal and postmenopausal women with early-stage breast cancer. It has a proven track record when administered postoperatively in stages I and II disease of a 50% or more reduction of invasive and noninvasive breast cancer in all age groups and all categories of estrogen-sensitive breast cancer.

Tamoxifen is a preferred drug used to prevent breast cancer recurrence in premenopausal women. Some women over age 70 years with ER-positive breast cancer

who choose hormonal therapy may be able to avoid radiation therapy after lumpectomy. Tamoxifen is used to reduce the risk that the tumor will recur locally or metastasize after the woman has completed local surgical and/or radiation treatment. It is also used to treat metastatic breast cancer. There are some disadvantages to this treatment such as cancer resistance and toxicities (e.g., endometrial carcinoma, thromboembolism, hot flashes, and vaginal/urinary symptoms).¹⁸⁸

One major drawback to the use of tamoxifen is the increased rate of endometrial cancer. Weight gain is a significant side effect for some women. Giving the drug for more than 5 years failed to enhance its effect; more studies are under way to determine the optimal duration of tamoxifen administration, especially in relation to the concomitant development of endometrial cancer in some women.

Tamoxifen does not appear to benefit women with tumors that can grow without estrogen and progesterone as they are unresponsive to hormonal blockers. More study is needed to develop chemotherapeutic agents that target progesterone receptors similar to how tamoxifen is used to treat ER-positive tumors by blocking the estrogen pathway.

The use of raloxifene, a SERM drug approved for women at risk of osteoporosis that shows promise in breast cancer prevention, is also under investigation. Like tamoxifen, raloxifene blocks the effect of estrogen on breast tissue and breast cancer. Initial results of the Study of Tamoxifen and Raloxifene (STAR) showed that raloxifene works as well as tamoxifen with the added benefit of fewer uterine cancers and fewer overall serious side effects (e.g., cataracts, deep vein thrombosis, or pulmonary embolism).^{175,228,318}

A large number of other chemopreventive agents under investigation include other SERMs, cyclooxygenase-2 inhibitors, aromatase inactivators/Gn-RH agonists, isoflavones, and vitamin D derivatives.^{87,179} Aromatase inhibitors (AIs) are a new class of endocrine agents that block an enzyme necessary to convert other hormones to estrogen in the breast. AIs cannot stop the ovaries of premenopausal women from making estrogen, so they are only effective in postmenopausal women.

Third-generation drugs (e.g., letrozole [Femara], anastrozole [Arimidex], and exemestane [Aromasin]) in this group have also been approved for first-line treatment based on studies that show at least a 90% estrogen suppression effect. Some researchers are investigating the use of several aromatase inhibitors in women with mild symptoms and slow disease progression.^{33,297} Exemestane after tamoxifen reduces breast cancer recurrence by about half.¹⁸⁸

Biologic Therapy. Trastuzumab (Herceptin) is highly effective in treating breast tumors that produce too much HER2, a protein that spurs the growth of cancer cells. Herceptin is a humanized IgG monoclonal antibody, and the first biologic therapy approved for use that attacks cancer at its genetic roots. It targets a defective growth-promoting oncogene, known as HER2/neu, found in about 30% of women with aggressive breast cancer.

HER2/neu is a protein that often appears on the surface of breast cancer cells. HER2-positive tumors are like a car

with the accelerator stuck to the floor with constant signaling to grow contributing to cell proliferation. After the antibody attaches to the protein, it is taken into the cell, where it interferes with basic cell function and eventually kills the cells but spares other fast-growing cells. HER2-positive breast cancers are more aggressive and less likely to respond to conventional therapies.

When administered to women with metastatic breast cancer along with standard chemotherapy, trastuzumab delays the progression of the disease for several months and produces a greater regression in existing tumors without additional side effects. Unfortunately, Herceptin eventually stops working for many women with advanced breast cancer. Its use also has been linked with heart failure and is not recommended for women with impaired heart function.

There is another drug, lapatinib (Tykerb) under investigation that targets tumors without killing healthy cells. Like Herceptin, Tykerb targets the protein HER2/new. Herceptin blocks the protein on the cell surface; Tykerb blocks it inside the cell and blocks another abnormal protein as well.¹⁰²

Bevacizumab (Avastin), a targeted drug that cuts off the blood supply to cancer cells, has been approved to treat advanced colorectal cancer and may be helpful in late-stage breast cancer when given in combination with paclitaxel (Taxol). At the time of this writing, Avastin had not yet been approved by the FDA for use in breast cancer. All of these targeted drugs are very expensive (up to \$100,000 per year).

The role of cannabis (specifically, δ^9 -tetrahydrocannabinol [THC] in marijuana) in the treatment of breast cancer is also under investigation. Studies in mice have shown an inhibition of breast cancer when exposed to THC.¹⁸⁰ THC exhibits antitumor effects on various cancer cell types, but its use in chemotherapy is limited by its psychotropic activity.

Uncertainties remain about how to treat node-negative women, particularly when the tumor is small; how to treat DCIS; who should receive preoperative systemic therapy; and who should be given tamoxifen. Despite these unresolved issues, medical advances have saved the lives of many people and will continue to progress with further reduction in morbidity and mortality.

Ovarian Ablation. Removing estrogens from premenopausal women by surgically removing the ovaries is another effective way of treating ER-positive breast cancer. Drugs can be injected monthly as an alternate (nonsurgical) method of stopping ovary function without removing the organ.

PROGNOSIS. Prognosis is dependent on when the lump is discovered, how large it is, and the involvement of lymph nodes. This is true for men and women, although some studies have found lower survival rates for men with advanced breast cancer. This may be the result of older age, coexisting diseases, and lower life expectancy of men at the time of diagnosis. When cancer stage and grade are matched, survival rates for men and women with breast cancer are equal.

The presence of three or more comorbid conditions has been associated with a fourfold higher rate of all-

cause mortality at 3 years for women compared to women with primary breast cancer with no comorbid conditions. Similar comparisons have not been made for men.²⁶⁹

Cancer prognosis and risk of recurrence is dependent on the age of the client, stage of disease, menopausal status, race/ethnicity (blacks and Hispanics are often diagnosed at later stages), activity level (sedentary has a poorer prognosis), and body mass index (BMI; risk is increased when BMI is greater than 30).

The status of the axillary nodes is an important prognostic factor in breast cancer and determines the selection of treatment. Breast tumors that lack estrogen responsiveness have had a poor prognosis because of the cancer's poor response to current treatment available.¹⁷⁴ However, for the 70,000 U.S. women diagnosed each year with nonhormonal cancer, advances in conventional IV chemotherapy have improved survival rates.²⁵

Pathologic characteristics of the primary tumor are also prognostic (e.g., high grade, aneuploid DNA content, presence of tumor necrosis factor [TNF], negative estrogen (ER-negative and PR levels, and Her2/neu over-expression).¹⁹⁸ Newer findings offer more evidence that a tumor's "personality characteristics" are more important than size and how much the cancer has spread. Whether the tumor is fueled by estrogen is also a factor in how fast it grows and spreads, affecting outcomes.

If detected early before metastases, breast cancer is curable. There has been a reduction in mortality of 1% to 2% annually in the United States and other industrialized countries, possibly related to changes in lifestyle (e.g., diet, exercise, and reproductive behavior), early diagnosis, and improved success of treatment.⁷¹ More than one-half of all cases reported are diagnosed as stage 0 or I disease.

The 5-year survival rate for localized tumors is 92%; survival rate drops considerably if there is nodal involvement; and metastatic disease is incurable and results in an overwhelming death rate.¹¹² Ten-year survival rate for stage I disease is 85%, for stage II 66%, for stage III 36%, and for stage IV 7%.²⁸

Negative prognostic indicators for bone metastases include aggressive nature of primary lesion (i.e., advanced breast cancer that is poorly differentiated), lytic or multiple bone lesions, metastases to multiple systems, high tumor markers, overall poor health of the individual, and a short period of cancer-free status.²⁰⁰

Advancements in technology make early detection possible with a higher survival rate; even so, more than 40,000 women died from this disease in the last year. Many women experience secondary complications of the disease and its treatments, including decreased quality of life, weight gain, sleep disturbances, poor body image, fatigue, increased risk for osteoporosis, cardiovascular disease, premature menopause, and lymphedema.²⁶

RECURRANCE. Breast cancer recurs in 20% to 25% of women deemed by current tests to be at low risk. The probability of recurrence is higher with histologically positive axillary nodes and increases with each additional positive node. Other risk factors for recurrent disease include premenopausal status, estrogen status, tumor size (>2 cm), high grade, and other histopathology.¹

Despite treatment with chemopreventive drugs like tamoxifen, some women have recurrences because the cancer cells develop resistance to the drug. It may be possible to switch from one drug to another to increase the odds of long-term survival for women at risk for recurrence. Herceptin has been shown to cut the risk of relapse by 50% for women with aggressive breast cancer when used in the early stages of disease.^{243,260}

Patterns of recurrence and metastases are similar for men and women, usually occurring within 2 years of the initial diagnosis and treatment. For example, DCIS in stage 0 at the time of diagnosis is usually considered cured after treatment. Even though the highest risk of recurrence is in the first 2 years, small stage I cancers can reappear years later in a more lethal form. Stage IV breast cancer has the poorest prognosis; tumors have spread to other parts of the body.

Molecular profiling studying the genetic characteristics of breast cancer will help identify women at greatest risk of breast cancer recurrence. Genomic testing will help identify women as low-, medium-, or high-risk of cancer recurrence with a high degree of accuracy. Treatment and surveillance for these individuals will likely be more aggressive. Microarray technology may make it possible to examine the genomic profile of the primary tumor, identify the presence of micrometastatic cells, and determine the best drug to elicit a positive response based on pharmacogenetic data.^{116,142}

Men are less likely than women to develop cancer in the opposite breast, but recurrence of cancer does happen. Local recurrence is treated with surgical excision or radiotherapy combined with chemotherapy, especially if hormonal therapy has failed. A key to recognizing women whose cancer is most likely to recur might be a tumor-suppressing protein called *maspin*, produced by cells in the breast and an effective inhibitor of angiogenesis. Women who have high levels of maspin in the bone marrow tend to remain disease-free for 2 years, whereas those with low concentrations are more likely to have a recurrence.^{184,338} The most powerful predictor of recurrence remains whether or not the cancer has spread to the lymph nodes, although 20% of women whose nodes are clear still relapse.

New drugs on the market, such as letrozole (Femara) an anti-aromatase agent, have also been found to reduce the risk of relapse in older or postmenopausal women. Letrozole, like tamoxifen, works by interfering with estrogen. Whereas tamoxifen blocks estrogen receptors on the cells, letrozole inhibits the creation of estrogen.

SPECIAL IMPLICATIONS FOR THE THERAPIST 20-11

Breast Cancer

PREFERRED PRACTICE PATTERNS

4B: Impaired Posture

4C: Impaired Muscle Performance

6H: Impaired Circulation and Anthropometric Dimensions Associated with Lymphatic System Disorders

There are many considerations for the therapist working with men and women who report upper

quadrant symptoms of unknown origin or who have been diagnosed with breast cancer, both before and after treatment. Besides the considerations discussed in this section, limited literature evaluating physical therapy and breast cancer is available.^{117,143,201} See also the section on Lymphedema in Chapter 13.

Screening for Disease and Cancer Recurrence

When treating a woman with a history of breast cancer, an awareness of the symptoms and signs associated with breast cancer is important. Local and distant metastases occur most frequently within 3 years of the initial diagnosis. Typical sites of metastasis in women with breast cancer are lymph nodes, bone, lung, liver, and brain.¹⁴⁸

Approximately 10% of women with breast cancer will develop cancer in the opposite breast. After surgical removal of all malignant breast tissue, there is still a risk of breast cancer recurrence in the breast and along the chest wall. In 40% of the cases, cancer recurs at the original location of the primary tumor.²⁰⁰

A local recurrence of breast cancer will present most commonly as a new lump or mass. A lump that is painless, hard, and with irregular edges is very suspicious and must be evaluated. Palpation of a lump or mass in these areas or new onset of edema or swelling in the upper quadrant should raise concern on the therapist's part and lead to further questioning regarding the clinical findings.²⁰⁰

Therapists examining the shoulder and shoulder girdle region need to be aware of the nonmusculature structures (including breast tissue and regional lymph nodes) located in these areas. The upper, outer quadrant of the breast can extend up toward the glenohumeral joint, and more cancerous masses occur in this area of the breast than in any other part of the breast.

In addition, approximately 50% of women with breast cancer have metastasis to the axillary nodes at the time the diagnosis is made. Breast tumor metastases to lymph nodes can involve the axillary, supraclavicular, and mediastinal lymph nodes. Disease spread to these lymph nodes groups may cause compression of adjacent structures, resulting in referred pain to the shoulder, upper extremity, and/or chest wall.^{110a,200}

If the mass lies in the pectoralis major muscle, the mass should change during palpation when the muscle is actively contracting. Metastases to the thorax are common in breast cancer, and pulmonary symptoms can be very similar to pulmonary abnormalities that occur after radiotherapy. If the therapist is in doubt regarding any reported or observed manifestations, the client should be evaluated by a physician (see the section on Lymphedema in Chapter 13).

Bone metastases occur in up to 70% of women with advanced breast cancer.²⁰¹ The humerus is the most common upper extremity site for bone metastasis, and pathologic fractures can occur. The femur is the most common lower extremity site. Any report of new (or increased) bone pain, especially at night and/or with weight-bearing activities, should be carefully assessed. Other common sites for breast cancer metastases

include brain, liver, lymph nodes, bone marrow, and lungs.

The therapist must remain aware of and monitor for risk factors for bone metastases for individuals with breast cancer. Positive nodal status, large tumor size, ER-positive status, and age under 35 years are significant risk factors for bone metastases in this population. Individuals who use tobacco, have a poor diet and nutrition, report decreased physical activity, and engage in alcohol abuse are much more likely to develop metastases.^{57,88}

Preoperative Considerations

Preoperative evaluation is recommended for all women undergoing surgical intervention for breast cancer whether the intervention is axillary node dissection, lumpectomy, or mastectomy of any kind. Therapists have a great amount of work to do to provide evidence-based research supporting the role of the physical therapist in preoperative assessment and education. Educating surgeons, radiation oncologists, and medical oncologists regarding the benefits of mobility and soft tissue mobility is essential.

Upper quadrant motion, posture, joint range of motion (including accessory motions), flexibility, and soft tissue movement should be assessed. Identification of current physical activity level and exercise regimen is important. Preoperative education is included to teach safe movement and exercise techniques to be used in the early postoperative phase. Lymphedema precautions are also important (see Table 13-2).

Starting with the preoperative diagnosis and throughout the recovery process the therapist can guide women into physical activity and exercise routines that help them maintain endurance, function, flexibility, and strength; reduce pain and fatigue; and prevent musculoskeletal injury or debilitation, especially during adjuvant treatment such as chemotherapy or radiation. Helping women cope with the emotional challenges of living with a life-threatening and body-altering disease is integral to the healing and recovery process.

If BCT or reconstruction has not been discussed with the woman, the therapist may want to encourage the woman to discuss this with her surgeon before the scheduled procedure. A recent study has shown that only about 25% of general surgeons refer most of their clients with breast cancer for a reconstructive surgery consultation at the time of treatment planning. A multidisciplinary approach involving clinicians in different specialties is needed to help women understand all of their surgical options.^{104a}

Side Effects of Treatment

Women receiving adjuvant therapy (chemotherapy, radiation therapy, or hormonal therapy) may experience numerous side effects that could interfere with rehabilitation (see Chapters 5 and 9). Potential side effects of therapy are listed in Table 9-8; see also Tables 5-7 and 5-8).

Continued.

There has been an increased frequency of rheumatoid symptoms reported after breast cancer treatment. Significant joint pain and swelling of the upper extremity, morning stiffness lasting less than 1 hour (41%) or more than 1 hour (26%), and prolonged joint pain and stiffness have been documented.¹⁰

CHEMOTHERAPY

Women receiving chemotherapy will likely be fatigued and experience flulike symptoms. This has been minimized to some extent with erythropoietin (EPO) used to treat anemia by stimulating bone marrow production of red blood cells. For the individual with low nadir (lowest point of blood cell production after neutrophil and platelet count have been depressed by chemotherapy) and/or anemia, the timing of scheduled therapy visits is important to maximize productivity during the session.

Exercises and functional activities may have to be paced or therapy visits shortened to accommodate the woman's energy level. An exercise program to improve endurance in order to perform activities of daily living is important.

RADIOTHERAPY

Radiotherapy to the left breast is associated with higher rates of chest pain, coronary artery disease, and myocardial infarction. Cardiotoxic drugs such as Adriamycin and Herceptin may compound the problem. The therapist can screen women treated for breast cancer for cardiac symptoms and risk factors such as blood pressure and smoking. Regular cardiac surveillance is important for all breast cancer survivors regardless of whether they had radiation therapy because of the increased risk of cardiac disease with aging.¹²²

HORMONAL THERAPY

Although tamoxifen has a protective effect on bone mineral density, the majority of AIs have been linked with an increase in osteoporosis. Future reports may bear out a significant difference in fractures as well.¹⁷² To date there are no standard guidelines on the prevention and management of osteoporosis for these clients. The therapist must be alert to the need for referral for baseline studies, use of bisphosphonates, and preventive exercise in these individuals.¹⁷² All of the clinical trials using adjuvant AIs have shown an increase in arthralgias and myalgias. Symptoms are usually mild and include joint pain and muscle aches that seem to respond to antiinflammatories.¹⁷²

Postoperative Considerations

Breast surgery (lumpectomy, modified regional mastectomy, breast conserving mastectomy, or breast reconstruction) combined with radiation therapy and chemotherapy are common treatment interventions that can contribute to postoperative problems such as pain, decreased range of motion, weakness, movement impairment, swelling, neuropathy, radiation fibrosis, fatigue, and lymphatic cording.^{278a,335}

Recovery after each individual surgical procedure may vary. Differences exist even among the different choices for reconstruction (e.g., pedicled TRAM flap,

free TRAM flap, or DIEP free flap). Every woman is different in her recovery, depending on the total treatment process. Most centers have postoperative protocols for each procedure available for review.¹⁷⁰

BREAST CONSERVING THERAPY

BCT usually does not affect the pectoralis major or overlying fascia, but the therapist should read the operative report to be certain; lobular breast cancer can go deep to the chest wall requiring deep resection. Keep in mind that the muscles are not spared by radiation therapy.

MASTECTOMY

Mastectomy without reconstruction will be different from mastectomy with reconstruction. Women who have undergone mastectomy should be instructed postoperatively and assisted with breathing and coughing exercises to prevent pulmonary complications. In addition, lower extremity exercises are also important to prevent thromboemboli. More specific rehabilitation recommendations based on specific oncologic treatment are available.¹⁰¹

About 40% of women undergoing mastectomy or level 1 and 2 lymph node removal with nerve resection experience a neuropathic pain phenomenon called *postmastectomy pain syndrome* (PMPS) or *postbreast therapy pain syndrome* (PBTPS). PMPS/PBTPS is thought to arise from damage to the axillary nerves during surgery, specifically the intercostobrachial nerve, a peripheral nerve with tributaries that branch into the armpit and upper arm.²⁹⁵

The pain occurs at the incision site, axilla, arm, or shoulder and is experienced as burning, numbness, tingling, or stabbing. Severity ranges from mild to extremely distressing; onset and frequency are highly variable (immediate to after 3 months or continuous, daily, weekly, and monthly). Because PMPS/PBTPS seems to be on the rise, it is important to ask about postmastectomy pain. Prognostic risk factors that predispose an individual to PMPS/PBTPS are unknown, with the possible exception of age (more common in women younger than 30 years).^{44,287} In addition to medications for pain, a program to prevent loss of mobility and to prevent adhesive capsulitis must be initiated.

Sensory stimulation to the skin with a variety of techniques (e.g., deep pressure, light touch, and sharp or vibratory stimulation) and nerve gliding techniques may be helpful. For the person who cannot tolerate the touch of clothing against the skin, medications (e.g., Neurontin or Elavil) may be considered. Some women have relief from symptoms with the application of Lidocaine patches to the nerve root region while waiting for nerve regeneration to take place.

BREAST RECONSTRUCTION

The TRAM flap has an incision that runs laterally from hip to hip and may weaken the abdominal wall. Women with chronic back problems are usually not good candidates for this procedure without adequate preoperative rehabilitation. Other complications of TRAM include failed vasculature of the breast and fat

necrosis (small areas of scar tissue formed by necrotic fatty nodules), abdominal wall hernias, and flap failure.

Risk factors for postoperative complications include smoking and peripheral vascular disease for a higher incidence of wound infection and preoperative radiation therapy for increased rates of seroma.²⁷⁷ A postoperative strengthening program is essential to prevent further back-related musculoskeletal complications. Although uncommon (occurring in 1% to 5% of cases), the most serious complication of the flap procedure is a loss of blood circulation to the transferred tissue, leading to necrosis and the loss of all or part of the reconstructed breast.

BREAST IMPLANTS

Women who receive breast implants for reconstruction after mastectomies may experience surgical complications caused by tissue damage from the cancer surgery and follow-up chemotherapy and radiation to the surrounding tissue. These alterations in tissue may prevent the implant from being fit in where the breast tissue was excised, thus affecting the way scar tissue forms around the implant. Scar-tissue formation that deforms or hardens the implant, called *capsular contraction*, is the most common complication, followed by implant rupture or malfunction, bruising, infection, and chronic pain.⁹⁶

AXILLARY NODE DISSECTION

Numbness under the arm (axillary area) is often a clue that axillary node dissection was done; many times, the woman does not know how many nodes were removed. The therapist must read the pathology report to assess the level of risk for lymphedema and other complications. Postoperative deficits following axillary lymph node dissection can become chronic conditions for many breast cancer survivors.¹¹⁸ Most of these problems develop within 3 months of surgery and have not resolved up to 2 years later.¹¹⁶

Lymphatic cording, also known as *axillary web syndrome* (AWS) associated with surgical removal of axillary lymph nodes is not uncommon. Lymphatic cording is described as a visible and palpable web or fibrous cord of subcutaneous tissue extending from the axilla into the medial arm (Fig. 20-21). The network of cords usually extends to the cubital space and even below with occasional cording to the base of the thumb.²⁴⁷

The cords are most visible in the axilla when the shoulder is abducted or in the antecubital space when the elbow is extended (Fig. 20-22). Radiating pain down the arm during shoulder abduction and limitation of shoulder abduction and/or elbow extension are the most common symptoms.

Typically there are two or three palpable cords under the skin that are hard and painful but not erythematous. It is usually self-limiting, often resolving within 3 months' time.²⁴⁶ However, some women do report persistent discomfort in the chest wall or axillary for a long time after surgery and may not continue to report this to their physicians because they have been told it will go away or to "live with it."



Figure 20-21

Axillary web syndrome (AWS) 2 weeks after initiation of physical therapy intervention. The cording is less prominent but still visible as the skin is pulled back by the cord. This effect can make the arm look swollen as if there is some swelling from lymphedema. Edema can also accompany cording. (Courtesy Jane Kepics, MS, PT, CLT-LANA, Phoenixville Hospital, Phoenixville, PA.)

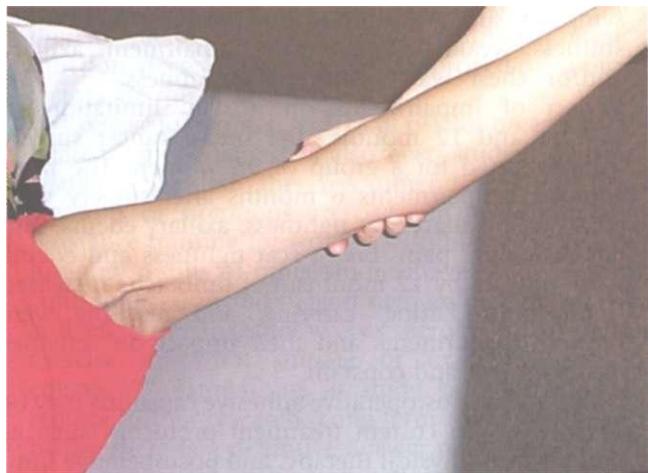


Figure 20-22

Photo shows a pretreatment axillary cord that limits shoulder abduction. This client had a biopsy of a swollen axillary lymph node. The biopsy was benign, but the woman had pain and limited range of motion for about 6 weeks. (Courtesy Jane Kepics, MS, PT, CLT-LANA, Phoenixville Hospital, Phoenixville, PA.)

The physical therapist may be very instrumental in finding out about unreported or unresolved AWS. Physical therapy intervention may have a role in reducing the length of time clients suffer from this condition, especially for women for whom the condition persists beyond the expected time due to concurrent cancer care.³³⁵ Clinicians report good success with myofascial release and soft tissue mobilization techniques directly to the cords and to the surrounding tissues. Increased range of motion and decreased discomfort can be attained quickly in most cases. An

Continued.

individual's low tolerance for pain may require additional time and intervention to resolve.

This condition is thought to occur from lymphatic disruption after breast or axillary surgery. The exact mechanism is unknown but may be attributed to lymphovenous injury (e.g., lymph vein rupture, superficially dilated veins with thrombi inside, or lymphatic outflow obstruction) from prolonged positioning during surgery or lymphovenous stasis from removal of nodes in the axilla. The cords may represent thrombosed lymphatics after an inflammatory phase with thickening of the vessels, temporary shortening, and tightening, which later remits.^{161,178,215}

It is important to differentiate articular or postoperative muscular shortening, as well as the fear-avoidance behavior (i.e., fear of pain from movement), from AWS. The woman usually has a good postoperative course but begins to report intense pain along with limited range of motion, especially shoulder abduction (less than 90 degrees in 74% of cases).^{215,247}

SHOULDER/UPPER EXTREMITY

Of those who have surgery, seven out of eight experience some ongoing problems with shoulder/arm function; most women present with more than one symptom such as arm and breast swelling, shoulder stiffness, weakness, movement impairment, axillary and/or chest wall pain, and numbness.^{196,295} The impact of impairments on activity limitations 6 months and 12 months after breast cancer surgery were reported for a group of 96 women. The most common impairments 6 months after surgery were breast and axillary scar tightness, axillary edema, and neck-shoulder pain. Breast scar tightness and edema were reduced by 12 months, but limb ache increased significantly. Lifting, carrying, and reaching were limited; impairments and their impact on activities were frequent and constant.¹⁵⁶

The risk of postoperative adhesive capsulitis may be decreased with current treatment protocols, such as preoperative physical therapy, and postoperative limitations in shoulder range of motion until 5 days after the drain is removed. Too much movement while the drain is in can cause increased drainage. The downside of this situation is that women are advised to limit their motion so they can get stiff throughout the entire upper quadrant on the affected side. Scarring with facial tightness complicates the therapist's treatment intervention.

Releasing cordage associated with AWS may also be preventive but this statement is made on the basis of clinical observation rather than evidence-based clinical studies. A home program of stretching and encouraging functional tasks may help to maintain range of motion in preparation for radiation with its known effects on soft tissue. Some therapists have observed increased adhesive capsulitis with the use of hormonal therapy with anastrozole, but this has not been reported in the literature to date.

There is a great need for a functional assessment tool and rehabilitation protocols specific to breast

cancer survivors. The use of functional scales adapted for the breast cancer client, including the visual analogue scale (VAS) and Scale for Breast Cancer Patients (based on the Oswestry Low Back Pain Disability Questionnaire), has been documented.¹⁵⁶

Subtle changes in upper extremity function are difficult to quantify, potentially leading to an under-reporting of functional deficits.²⁰⁵ Many of the problems unique to this population are not captured by standard functional scales (e.g., the Penn Shoulder Score, the disabilities of the arm, shoulder and hand [DASH] questionnaire, and the functional assessment of cancer therapy for breast cancer [FACT-B]) used with other diagnoses.

A newly developed upper limb lift test (ULLT) modified from a previous study¹²⁴ has been pilot tested in women newly diagnosed with breast cancer before medical treatment. Weight used was scaled to the participant's body weight to avoid fatigue. The ULLT appears to be a promising test of gross motor upper extremity function that may provide a quantitative measure of function to guide rehabilitation of women during and after breast cancer treatment.²⁴¹

LYMPHEDEMA

Secondary arm lymphedema remains a chronic and distressing condition for some women after breast cancer treatment. Conservative therapies, such as complex physical therapy, compression bandaging and garments, and exercise, have proved effective in reducing fluid volume and improving subjective arm symptoms and quality of life.²¹⁴ Lymphedema and its treatment are presented in depth in Chapter 13.

Low-level laser treatment has recently been approved by the FDA for the treatment of postmastectomy lymphedema. The laser-beam pulses produce photochemical reactions at the cellular level, thereby influencing the course of metabolic processes and reducing the volume of the affected arm, extracellular fluid, and tissue hardness.⁴¹

The use of low-level laser over areas where carcinoma was originally found has not been investigated. Manufacturers of laser equipment suggest that a history of carcinoma is a contraindication for the use of class 3 laser. Information is lacking regarding the use of class 1 laser. If we consider the method of action of the laser (increased transport across the mitochondrial barrier), prior carcinoma remains a contraindication in the use of laser.³⁰ Research in this area is needed. FDA has approved laser for lymphedema treatment.

Exercise and Breast Cancer

Throughout this text, the benefits of exercise in relation to various diseases, disorders, and conditions have been discussed, including (pertinent to the diagnosis of breast cancer) exercise and immunology (see Chapter 7), exercise and cancer from a variety of viewpoints (see Chapter 9), exercise and the cardiovascular system (see Chapter 12), and exercise and the lymphatic system (see Chapter 13).

Many observational studies show exercise to be inversely associated with risk for breast cancer; the

mechanisms by which exercise may alter breast cancer remain under investigation. Studies show a modest protective effect of strenuous leisure time physical activity (intense enough to make the woman break a sweat) among postmenopausal women who are consistently active throughout their lifetime.⁷⁵

Several theories have been proposed, including reduction of excess body weight, excess body fat, elevated fasting insulin, insulin resistance, and alterations in plasma levels of insulin-like growth factor (IGF). If these factors are part of the biologic basis for breast cancer and they can be improved by exercise training, then breast cancer risk could be modified with exercise.²⁷²

Three separate considerations regarding exercise and breast cancer are presented in this section: the effect of exercise in the prevention of breast cancer, the effect of exercise in the prevention or exacerbation of clinical symptoms associated with breast cancer and/or its treatment (e.g., lymphedema or fatigue), and the effect of exercise on breast cancer recurrence.

EXERCISE IN THE PREVENTION OF BREAST CANCER

A clear relationship between physical activity and exercise and breast cancer prevention has been established.^{31,257,258,306} These studies have all been of white women; there are limited data on black women or women of other ethnic groups, but findings suggest that strenuous physical activity in early adulthood is associated with a reduced risk of breast cancer in black women as well.²

Prescriptive exercise (preventive or otherwise) usually includes type of exercise, intensity, duration, and frequency since these parameters are carefully matched to the underlying pathologic process and clinical presentation. The association of physical activity and exercise to overall and site-specific cancer risk is under investigation, especially in relation to whether any dose-response correlation has been observed.

A review of 41 studies, including 108,031 breast cancer cases, identified an observed inverse association with a dose-response relationship between physical activity and breast cancer. Moderate activity (defined as >4.5 metabolic equivalents [MET]/week) was shown to have a protective effect against breast cancer in premenopausal and postmenopausal women.³⁰⁷

Physical activity corresponding to 15 MET/week or higher at age 10 to 24 years has been shown to significantly reduce breast cancer at age 51 to 60 years in a small number of women.¹³⁰ Women who consistently exercise even minimally have a 35% lower risk of developing breast cancer *in situ*; this does not apply to women with a family history of breast cancer.

Other investigators reviewed number of hours per week, suggesting that breast cancer rates were 20% lower among women who exercise an average of 1 hour per day (or more), compared with those who exercised less than 1 hour per week.²⁵⁸ Much more investigation in this area is both warranted and underway.

EFFECT OF EXERCISE DURING BREAST CANCER TREATMENT

Exercise during adjuvant treatment for breast cancer is regarded by some as a supportive self-care intervention that results in improved physical fitness and thus the capacity to perform activities of daily living, which might otherwise be impaired due to inactivity during treatment.¹⁹⁰ Benefits of exercise for clients with breast cancer include but are not limited to the following²⁵²:

- Increased functional capacity
- Improved mood and coping
- Decreased nausea
- Increased self-esteem and self-efficacy
- Increased natural killer cell activity
- Improved body image
- Decreased fatigue

The therapist should keep in mind that exercise interventions for sedentary individuals requires behavior change, which can be a significant challenge when prescribing appropriate exercise for the individual.

The impact of all types of aerobic exercise is significant in maintaining functional ability and reducing fatigue in women with breast cancer receiving chemotherapy or radiation therapy.^{167,274} Moderate-intensity aerobic exercise has been shown effective during radiation for breast cancer to increase peak Vo₂ and therefore aerobic capacity reserves. Improved physical function, decreased fatigue, and improved psychologic factors are the final outcomes.⁷⁶

Exercise for women with or at risk for breast cancer-related lymphedema has also been studied. Previous results suggested the recommendation to avoid vigorous or strenuous exercise and upper extremity resistance training for women with breast cancer. Preliminary results of other studies have challenged this contraindication and suggest such exercise may be safe and effective. In other words, aerobic or strenuous exercise may not initiate or exacerbate lymphedema.^{26,196} Limitations in study size and methods require further research. Long-term results are needed before there is a definitive answer regarding the total effect of exercise in this population.

Supervised exercise in women with breast cancer not receiving chemotherapy increases aerobic capacity and reduces body weight.²⁷⁶ For those who are post-operative, research indicates that range of motion exercises can be delayed immediately after surgery without significant long-term consequences to range of motion/pain. Delaying exercises until the Jackson-Pratt (JP) drain comes out (7 to 10 days) reduces infection and seroma rates.^{93,168,182,282} See also the section on Exercise During and After Chemotherapy in Chapter 9.

EFFECT OF EXERCISE ON BREAST CANCER RECURRENCE

It has been proposed that the extent to which breast cancer survivors can improve body composition, insulin, and IGF axis proteins through exercise intervention may result in reduced cancer recurrence and improved survival.²⁷² In a study of nearly 3000 women with breast cancer, women who exercised 3 MET hours/week after diagnosis were less likely to die of

Continued.

their disease.¹³⁴ Twice-weekly weight training has been shown effective in increasing muscle mass and decreasing body fat, which may have implications in preventing cancer recurrence. Weight training may have some advantages over aerobic exercise because it has been shown to positively alter body composition, glucose/insulin dynamics, and IGF axis proteins. Adherence to exercise interventions may be more likely with this type of exercise.²⁷²

Concerns that upper body resistance activity may increase the risk of lymphedema have not been proved. Investigations thus far support the use of this type of supervised exercise program even for breast cancer survivors. Further study is needed to determine whether exercise leads to physiologic change of lymphatic structure and/or function, as well as timing between exercise and change in lymphedema.³

Personality factors as they relate to exercise participation across the breast cancer experience have come under scrutiny. Personality may be an important determinant of exercise after breast cancer diagnosis.²⁴⁸ Women with outgoing personalities who are conscientious and have low scores of neuroticism were better

able to discriminate when and how to exercise during and after cancer treatment, as well as better able to recognize changes in exercise stage across the cancer experience (prediagnosis through treatment to posttreatment).²⁴⁹

Women with high scores of neuroticism especially engaged in maladaptive exercise patterns.²⁴⁹ In addition, unsatisfactory coping and defending mechanisms are linked with increased breast cancer risk.²³⁴ This type of information can be potentially helpful to the therapist when assessing the individual woman's needs and abilities as they relate to designing an effective interventional prescriptive program of exercise.

References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 341 cited references and other general references for this chapter.

CHAPTER 21

Transplantation

CHRIS L. WELLS • CATHERINE C. GOODMAN

Transplantation for the treatment of end-stage organ failure has been one of the major medical advances of the last 20 to 30 years. The success of this form of treatment has improved dramatically with better understanding of the rejection process and the introduction of more effective immunosuppressive medications.

There have been further advances in the prevention and management of bacterial, viral, and fungal infections so that recipients of transplanted organs or cells live longer. A number of people have survived for well over 25 years. Unadjusted survival rates at 5 years range from 90% for recipients of living related kidney transplants to 40% for the small number of heart-lung recipients, with the 5-year survival rate averaging 70%.^{215,316}

The fiftieth anniversary of the first successful live-donor kidney transplantation was celebrated at the 2004 National Kidney Foundation's U.S. Transplant Games in Minnesota. Dr. Murray and Dr. Harrison performed a live-donor kidney transplantation between identical twins.

By the end of the 1960s, the great advances in surgical techniques combined with immunologic and pharmacologic discoveries led to further successful organ transplantation, including the first heart, liver, and pancreas. With the commercial introduction of cyclosporine in 1983, the world of transplantation has made remarkable strides in becoming an acceptable medical intervention in the treatment of various end-stage organ diseases, including lung transplantation.²²⁶

In the past 2 decades we have seen great advances in the preservation of donor organs and surgical techniques to transplant multiple organs. There also have been advances in the detection of early rejection; further advances in immunotherapy and management of infections have made treatment even more successful. Over 350,000 lives have been saved or enhanced by transplantation.³¹⁶

INCIDENCE

Transplantation remains limited by an acute worldwide shortage of available and suitable human organs. In 2006 there were over 92,000 people waiting for transplants. It is estimated that every day 19 people die while waiting

on the United Network for Organ Sharing transplant list. In 2005 an estimated 12,000 to 15,000 deaths in the United States had the potential to yield suitable organs, yet only 7593 deceased individuals donated organs.

Each cadaveric donor can donate up to 25 organs and tissues to help as many as 50 recipients. This means up to 500,000 organs should be available for transplantation each year, but only approximately 25,000 transplants are performed (Table 21-1).

One positive highlight in the incidence of transplantation has come from the increase in living related organ donation. In 2001 the number of live-donor organs recovered was more than the number of deceased- or cadaver-donor organs. In 2005 almost 7000 individuals donated a kidney or a portion of their liver, lung, or pancreas to provide an opportunity for another to survive an end-stage organ disease.³¹⁶

TYPES OF TRANSPLANTATION

Many types of tissues and organs can be donated and therefore transplanted, including the heart, lungs, liver, pancreas, kidneys, intestines, skin, bone and bone marrow, umbilical cord blood, veins, soft tissues, heart valves, corneas, and eyes.

Ovarian cryopreservation and transplantation is under investigation. Considering that more than 50,000 reproductive-age women are exposed to sterilizing chemotherapy and radiotherapy annually in the United States alone¹⁵² and thousands lose their ovarian function due to gynecologic surgery, larger trials of ovarian cryopreservation and transplantation are strongly justified.

Many different terms are used to describe types of transplantations (Box 21-1). *Allograft* (homograft) transplantations are between individuals of the same species (e.g., human being to human being). *Autologous* transplantations are within the same individual (e.g., skin graft from leg to hand; blood or bone marrow for own use later).

Xenogeneic (heterograft) transplantations are between individuals of different species (e.g., pig to human being). *Allogeneic* transplantation is one in which the source comes from a human leukocytic antigen (HLA; see Chapter 7) matched donor (usually a sibling). *Syngeneic*

Table 21-1 National Waiting List for Organ Transplantation

Organ	YEAR			
	2008	2004	2000	1995
Kidney	76,090	57,910	44,636	29,036
Liver	16,351	17,133	16,125	5,521
Heart	2,668	3,237	3,944	3,413
Lung	2,118	3,851	3,519	1,861
Heart-lung	101	171	202	202
Kidney-pancreas	2,288	2,403	2,364	1,145
Pancreas (including PAK)	1,621	1,477	767	315
Intestine	233	196	137	82
TOTAL (candidates)	101,470	86,378	71,694	41,575

Data from the 2008 United Network for Organ Sharing, an online database system called UNet containing data regarding every organ donation and transplant event in the United States. Available at www.unos.org/data/.

PAK, Pancreas after kidney.

Box 21-1

TYPES OF TRANSPLANTS

- **Allogeneic:** between individuals of the same species but of different genetic constitution (e.g., human being to human being)
- **Allograft (homograft, homologous, autologous):** between individuals of the same species (e.g., human being to human being)
- **Autologous:** within the same individual (e.g., transfer of skin from one site to another on the same body; donation of blood or bone marrow for own use later)
- **Heterologous (heterograft; xenogeneic):** between individuals of different species (e.g., pig to human being)
- **Heterotopic (autograft):** transfer of organ or tissue from one part of a body of a donor to another area of the body of a recipient
- **Homologous (homogenous):** corresponding or similar in structure, position, origin (e.g., pig heart, human heart)
- **Orthotopic:** tissue transplant grafted into its normal anatomic position
- **Syngeneic (isograft):** between genetically identical members of the same species (identical twins)
- **Xenogeneic (heterograft):** between individuals of different species (e.g., pig to human being)

transplants are between genetically identical members of the same species (identical twins); the syngeneic transplant is also called an isograft.

Orthotopic homologous transplantation refers to the surgical placement (grafting) of the donor organ into the normal anatomic site. In the *heterotopic homologous* transplantation, the recipient's diseased organ is left intact and the donor organ is placed in parallel with anastomoses between the two organs.

Box 21-2

COMBINED ORGAN TRANSPLANTS

- Heart-lung
- Heart-kidney
- Heart-liver
- Kidney-pancreas
- Kidney-liver
- Pancreas-liver
- Pancreas-small intestine (rare)
- Liver-small intestine
- Cluster operation: multiple organs simultaneously (primarily pediatrics)

Combined-Organ Transplantation

Combined-organ transplants from a single donor are uncommon relative to single-organ transplants (Box 21-2). Research to date generally suggests that organ rejection is decreased in cases of combined-organ transplantation compared with single-organ transplantation. Short-term survival in combined-organ transplantation seems to be acceptable, but long-term recipient and graft survival remains unknown at this time. No single center has accumulated a significant experience, and as a result long-term results in the current era are unknown.¹⁷

Organ Retransplantation

Occasionally, retransplantation is necessary because of acute graft failure, graft rejection or infection, or the recurrence of the primary disease as in the case liver or heart and lung transplantation. When the body mounts a defense against the transplanted organ, a clinical picture of chronic rejection presents itself. This form of rejection leads to a destruction of the donor organ over time.

In many cases the immunosuppressive medication is no longer able to suppress the immune response and rejection persists, which will eventually cause organ failure. One option is for the recipient to undergo another transplantation procedure. Transplant recipients in need of a retransplantation once again become organ candidates and must meet certain criteria for transplantation of that specific organ.

There is typically an increase risk of morbidity and/or mortality for these candidates when compared with outcomes of first-time transplantation procedures. For most organs the 3- and 5-year survival is not as high for recipients who have undergone retransplantation.^{234,236}

A model for end-stage liver disease has been developed and tested to predict the outcome of transplantation for liver recipients with advanced liver disease. A similar model to estimate survival after retransplantation is being developed to help identify individuals with a poor expected outcome; this information could be useful in further refining candidate selection criteria.¹⁹⁹ Studies show the model-based allocation system may not benefit candidates who undergo liver retransplantation.²³⁴

Ethical issues centered on the availability (i.e., shortage) of organs are always a consideration with retrans-

plantation. Graft survival after retransplantation is less than for primary transplants, both for immunologic (e.g., rejection) and nonimmunologic (e.g., donor age, donor size, cadaver vs. live donor) reasons, and requires more aggressive monitoring for rejection.

Pediatric Transplantation

Solid-organ transplantation has become accepted therapy for the treatment of end-stage organ dysfunction in children. As with adult organ transplantation, the supply of cadaver pediatric organ transplants is limited. And, like adult organ transplantation, living related donation is on the rise in pediatrics. Close tissue match of the related donor allows a higher compatibility rate and transplantation scheduling before the child is in critical condition improves outcomes.

Children can receive adult organs; in the case of the liver, only a portion of the adult donor liver is needed. Preoperative and postoperative assessment and care are very similar to adult care. Management may be complicated by infections such as hepatitis B and cytomegalovirus. Morbidity and mortality are often attributed to the consequences of long-term immunosuppression and include graft failure, increased incidence of cancer, hypertension, and renal failure or diabetes from overimmunosuppression.

There are known age-related differences in all phases of pharmacokinetics (absorption, distribution, metabolism, elimination); information specifically related to age and differences in the pharmacokinetics of immunosuppressants is very limited at this time. Biologic and psychologic changes common during the transition from childhood to adolescence and adolescence to adulthood present some unique challenges.¹⁴¹

Parent training and education are essential components in the transplantation process. The care team pays special attention to the psychosocial and emotional needs of the child and family. Noncompliance and nonadherence are common behaviors among all age groups but especially among adolescents. The consequences of this behavior include increased rejection, late graft loss, and death. Despite the best 1-year graft survival of any age group, the long-term transplantation outcomes in this age group are not as optimal.^{82,263}

ORGAN PROCUREMENT AND ALLOCATION

Organ Distribution

With the passage of the National Organ Transplant Act (NOTA) in 1984, the U.S. federal government began the process of establishing a comprehensive framework for the development and administration of a national transplant system.²¹⁷

The Organ Procurement and Transplant Network (OPTN) (www.optn.org) was created to maintain a national registry to track the process and outcomes related to organ donation and transplantation. During the past 20 years, nearly 350,000 people have received organ

transplants at 250 U.S. transplantation centers, and the national waiting list has grown from 8400 people to more than 85,000.²⁰⁷

No further legislative progress was made to amend the NOTA because of the lack of agreement as to the federal government's authority to set allocation policy, a task assigned to the OPTN. Then in 2004, the Organ Donation and Recovery Improvement Act (ODRIA, Public Law 108-216) was signed with a legislative provision to establish a federal grant program to provide assistance to living donors for travel and other expenses.

Instead of tackling disagreements over how to establish fair and equitable organ allocation policies, the Act focuses on strengthening efforts to increase donation rates, including ways to make live donation an easier and more financially appealing option. Removing financial barriers from living organ donations may help expand access to transplantation for members of lower socioeconomic groups who may not be able to consider living donation.²⁰⁷

This legislation also grants money to states for organ donor awareness, public education, and outreach activities designed to increase the number of organ donors, establish programs coordinating organ donation activities, and conduct studies of long-term effects associated with living organ donation.³⁴⁰

United Network for Organ Sharing

In order to establish a means to procure and distribute donor organs in an appropriate and ethical manner, the United States was divided into 58 local areas, ranging in population from 1 million to 12 million, and those areas were then divided into 11 regions (Fig. 21-1). Each local area has a designated organ procurement organization (OPO) responsible for recovering and transporting organs to transplantation hospitals in their territories. The local OPO also provides a wealth of medical and public education about organ transplantation and the promotion of donation.

On the national level the United Network for Organ Sharing (UNOS; www.unos.org) is a private, non-profit organization that provides critical services in the area of organ transplantation. UNOS administers the national organ waiting list, coordinates the matching and distribution of donor organs via the local OPO throughout the United States, tracks outcomes, establishes physician training for the medical and surgical management of transplant recipients, and provides public education.³¹⁶

UNOS is composed of every transplantation center, tissue-matching laboratory, and OPO within the United States, which are required to report a massive amount of data to UNOS. The OPTN is given these data, which analyzes in relation to the transplantation candidates, recipients, and living and deceased donors.

Great detail in the process to match candidates with a donor organ(s) has been developed to ensure equity based on medical need. There are two large processes occurring simultaneously to match and allocate organs. One side involves the identification and management of the potential transplantation candidate (someone waiting for an organ) through the transplantation center; on the

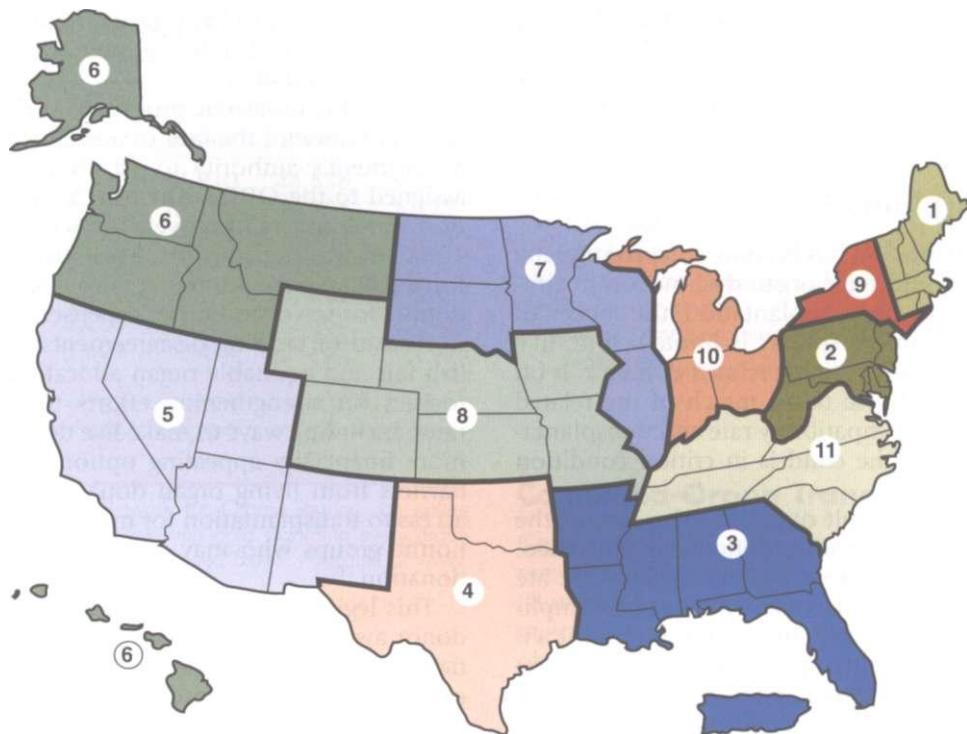


Figure 21-1

The United Network for Organ Sharing (UNOS) is divided into 11 geographic regions. (Courtesy United Network for Organ Sharing, Richmond, VA, 2006.)

other side is the identification and procurement of viable organs for donation.

After a thorough evaluation the transplantation center reports vital medical information about each candidate to UNOS. When a possible deceased organ donor has been identified, the local OPO will obtain and report valuable medical information about the donor to UNOS. The UNOS computer system will search for a suitable match between the donor and candidate.

A list of potential candidates will be provided in a priority order, and the organ is offered to the candidate who has the highest medical need as well as the greatest likelihood of a successful outcome based on the analysis of prior transplantation.

This allocation begins with the transplantation center being contacted at the local level, but if a local candidate does not match the donor organ or has a lower medical need, the organ will be offered to a candidate in the region where the donor organ was procured and then to adjacent regions and then finally nationally, with the goal to utilize every suitable organ.³¹⁷

Allocation Policy. The allocation of deceased donor organs has significantly changed over the years, with the goal to ensure that people who have the most urgent medical need will be given priority despite the amount of waiting time a person has on the UNOS list.³¹⁹ The change in allocation policy is known as *transplant benefit*.

The policy is intended to balance anticipated duration of survival on the transplantation list with length of benefit from receiving a transplant. Priority for transplanted organs will go to those candidates most urgently needing a transplant and expected to receive the most

survival benefit from the transplant. Under earlier organ allocation policy, priority was based on the amount of time candidates had been on the waiting list.

This distribution system is also designed to decrease the disadvantage some people had due to the progressive nature of their disease or the uneven distribution of transplantation centers within the United States. The new policy considers the waiting list urgency and transplantation benefit of each candidate based on individual clinical diagnostic factors. The improved computerized organ-matching system has made these important changes possible.

Organ Donation

Death is usually the circumstance under which organs are procured, either when complete and irreversible loss of all brain and brainstem activity occurs or when the heart stops in the case of cardiac death. The specific neurologic event that has resulted in brain death may include blunt traumatic injury to the head, intracranial hemorrhage, or penetrating traumatic injury.

Deceased organ donation continues to be the primary source for available organs. There has been a collaborative effort (Organ Donation Breakthrough Collaborative) by the U.S. Department of Health and Human Services Health Resources and Services Administration. The goal of the program is to unite the various agencies involved in transplantation and to define their roles and efforts to increase the identification of potential organs.

The transplantation center, donor hospitals, and the local OPO have teamed up to increase their efforts in

procuring organs to save and enhance the lives of people who are dying from end-stage organ disease. This collaborative effort, which began in 2003, has resulted in the largest 1-year increase (11%) in deceased organ donor in the past 10 years.³¹⁶

In the same time period there has been a 3% increase in living donation. The year 2004 was the first year since 2000 that the number of deceased donors exceeded 7000 in number and also exceeded the number of living donors.³¹⁶

Source of Organ Donations

The characteristics of deceased and living donors have changed over the years, and the effect of these changes on the outcome for the recipient is not fully known. Early on it was typical that the deceased donor was a young individual who was declared brain dead from a traumatic brain injury. Today more deceased donations are from the older person who has suffered a fatal cerebral vascular injury from stroke or aneurysm.³¹⁶

There is also an increased use of organs harvested from non-heart-beating deceased donors, especially in kidney transplantation. Most transplantation centers are still reluctant to transplant other organs from the non-heart-beating donor due to the risk of ischemic injury to the organs.¹²³

There has also been an increased utilization of organs from what is referred to as an extended donor pool. These are deceased donors that fall outside the general criteria to be an acceptable donor, such as older individuals, individuals with diabetes, those with some forms of cancer, and individuals who are positive for the hepatitis B or C virus. There are reports of promising results when organs from this extended donor pool have been used.

Individuals previously considered unacceptable transplantation candidates may be offered a donor organ from this extended donor pool. Seropositive hepatitis B or C candidates can now receive a transplant from a positive donor. In the past these individuals were not considered acceptable candidates for transplantation.⁴⁵ Successful kidney transplants have been completed from deceased donors who have a medical history of diabetes.³

Many so called "marginal" or "suboptimal" organs have been discarded by centers while people die each day while on the waiting list. Marginal organs can provide a viable solution to organ shortage. When used with appropriate surgical techniques and immunosuppression protocols, suboptimal organs can increase the supply of donor organs by 25% to 30%.²

The source of organ donation is also changing in regard to the living donation. In previous years living donation was conducted primarily between relatives. There are currently transplantation centers beginning to perform transplants using unrelated living donors.³¹⁶ Finally, transplantation centers are exploring the possibility of ABO-incompatible renal transplantation in candidates who have undergone a splenectomy, plasmapheresis, immunoabsorption therapy, and plasma exchange to remove antibodies, thereby decreasing the antibody-antigen reaction that would cause graft or organ failure.¹⁶⁰

Guidelines for Donor Candidates

There are general guidelines or standard criteria that are used when determining the acceptability of a donor, and the criteria will vary slightly based on organ type. These guidelines have been expanded as procedures to procure organs improve and as transplantation centers become more effective at the surgical procedure and medical management of transplant recipients.

Donor age is a consideration, with the majority of donors being under 50 years of age, although this is being extended because of the need for donors, further advancement in postoperative management, and type of organs that are available for procurement. For example, in order for the deceased donor to donate the lungs, the donor must typically be younger than 55 years (or 65 years if there is no history of smoking), with a clear chest x-ray, an absence of chest trauma, no thoracic surgery, clear bronchoscopic examination, and no aspiration or sepsis.

Smoking history must be less than 30 pack-years (see section on lung cancer in Chapter 15), with acceptable oxygenation measured as a PO₂ greater than 300 mm Hg. A living related donor must be ABO compatible with the candidate, without a history of lung disease, no previous thoracic surgeries, and larger size than the recipient (weight, height, chest size); the latter requirement is required because only two lung lobes will support the recipient's full pulmonary function.

Other criteria for donors vary according to the organ being harvested, but overall there must be no evidence of malignancy, human immunodeficiency virus (HIV) or hepatitis B, or sepsis (Box 21-3). Hepatitis C present in the donor is considered a precaution but not a contraindication. If the candidate already has hepatitis C or is critically ill, the risk of developing hepatitis C is not considered a contraindication in the decision to progress with the procedure.

Body weight must be within 20% of the ideal (using the body mass index [BMI] for heart and lung organ donation; see discussion of BMI in Chapter 2) because of the ischemia-perfusion injury associated with obesity.¹⁷³ Biologically related donors are preferred with clear and altruistic motivation (as opposed to coerced by the family or guilt driven).

Testing will be performed to assess the function for each of the donor organs being considered for procurement. For potential renal donors, urinalysis, creatinine,

Box 21-3

CRITERIA FOR ORGAN DONOR

- Age <50 years, extended pool up to 60 years
- No evidence of malignancy, human immunodeficiency virus (HIV), hepatitis B, sepsis
- No evidence of other contraindicated illness or disease (e.g., cirrhosis for liver transplant, pulmonary hypertension for heart transplant, pulmonary diseases)
- Within 20% of ideal BMI
- Left ventricular ejection fraction >40% (heart donor)

and blood urea nitrogen will be completed along with tests to assess liver function. To assess the function of the heart, an echocardiogram, 12-lead electrocardiogram, serial arterial blood gas (ABG) measurements, and possibly a right and left catheterization will be ordered. Pancreatic function will be assessed with amylase and lipase studies, serial ABGs, sputum Gram stain, and bronchoscopy to inspect the airways to assess the function of the lungs.^{236,310,317}

Organ Recovery

Hearts and lungs can be preserved for up to 6 hours, livers up to 24 hours, and kidneys up to 72 hours. Lungs cannot be preserved outside the body for any extended period of time. This length of allowable ischemic time helps determine allowable distances between centers.

Efforts are being made to improve organ harvest and preservation techniques and the number of organs harvested. For example, eliminating medical failures before donation through aggressive resuscitation, coagulopathy control, invasive monitoring, and dedicated intensive care unit (ICU) management while implementing a rapid brain death determination protocol has been documented as successfully increasing the number of donor organs available.^{153,316}

Technology to improve organ recovery, maintain organ perfusion, and recover normal cell metabolism is under investigation utilizing a kidney transporter, a portable organ preservation device. The ability to maintain and monitor organ viability over an extended period of time may allow live donors to avoid traveling to the recipient's location for explant surgery. Eventually, this type of technology may be extended to include transport devices for all other organs.

Efforts to obtain consent for donation continue to improve as part of the Collaborative's efforts. Public education now includes National Donor Awareness Week and the choice to indicate organ donation on a driver's license. According to Health Care Financing Administration regulations, hospitals are now required to report every death and impending death to their local OPO in order to continue receiving Medicare benefits.⁹⁴

Early referral of all imminent deaths to OPOs can result in the OPO conferring with the medical team regarding the best medical plan of care for the recipient, including specific needs of the family as well as procedures necessary for the donor once consent is obtained. These steps will help ensure that care of potential organ donors continues without premature termination.²⁷¹

A new approach to obtaining family consent is being utilized. Instead of informing the family of the individual's death and at a later time discussing organ donation (referred to as decoupling), now most families are approached about organ donation at the time when they are making end-of-life decisions. The discussion about organ donation has become a team approach between the OPO staff, physicians, nurses, and clergy. In 2005, 57% of families approached about donation consented, which is up 17% from 2001.³¹⁶

During this critical period of time assessing a potential donor, personnel from the OPO will be requesting medical evaluation from various specialists (e.g., cardi-

ologist, pulmonologist, nephrologist, gastroenterologist, and surgeon) to determine the viability of the organs that were consented for harvesting and to provide instructions for continued medical care to ensure adequate organ function until the procurement process begins.

Criteria for Organ Candidates

People waiting for transplants (candidates) are listed at one or more of the transplantation centers where they plan to have surgery. A national, computerized waiting list of potential transplantation candidates in the United States is maintained by UNOS with active input from treatment centers. UNOS maintains a 24-hour telephone service to aid in matching donor organs with people on the waiting list and to coordinate efforts with transplantation centers.

Each possible transplantation candidate undergoes various testing, and many of these test results, such as organ(s) needed, blood type, body size, various organ function, walking ability, life support need, virology, and other pertinent comorbidities will be reported to UNOS.

There are criteria for most organs to classify candidates into levels of medical urgency or status based on the medical workup. When a donor becomes available, UNOS is notified and a list of potential organ candidates for that region is identified. UNOS notifies the OPO, which in turn notifies the transplantation center to verify that the candidate is currently medically appropriate and has consented to the transplantation process. Arrangements are then made to transport the donor organ and candidate to the transplantation center and proceed with the surgery.

UNOS has developed a status coding or allocation system to prioritize the candidates waiting for transplantation when a donor organ has been recovered. The goal of these allocation systems is to promote an equitable system that will save as many lives as possible. Each waiting list and the prioritization of possible candidates varies from organ to organ.

In response to a perceived unfairness in organ allocation, Congress issued a "Final Rule" in 1998. The rule called for a more objective ranking of potential recipients on a waiting list and more equality in disease severity among transplant recipients across OPOs. To date, little progress has been made in eliminating geographic inequities. Potential organ candidates in the smallest OPOs continue to receive transplants at a lower level of disease severity.⁶⁷

The purpose of ranking or assigning the candidate a status is to consider beyond just the waiting time key medical information that has been determined to aid in the prediction of mortality while waiting and to predict the survival posttransplant. The goal is to decrease the number of deaths while waiting on a transplantation list and optimize the utilization of these precious organs.

For example, it is known that an individual who has a cardiac index of less than 1.8 l/min/m^2 and who is on a high dose of one or more inotropic medications has a shorter life expectancy than someone who is only on oral medication with compensated heart failure. In this see-

Box 21-4**UNOS ORGAN ALLOCATION STATUS LIST****Heart**

- Status 1A
 - Mechanical circulatory support (intraaortic balloon pump, total artificial heart, ECMO)
 - VAD (for 30 days once patient is medically stable)
 - Complications involving VAD, including mechanical failure or infection
 - High dose or multiple inotropes (dobutamine or milrinone) with an indwelling arterial catheter
 - Exceptions are reviewed on an individual basis
- Status 1B
 - Inotrope support but not on high dosage
 - VAD support after 30 days
- Status 2
 - Meet the criteria for transplant and have an expected 1-year mortality risk of more than 15%
 - Not on inotrope support
 - Not on VAD support
- Status 7 temporarily inactive

Lung

Lung Allocation System*

Definition and formulas to calculate Lung Allocation Score (LAS):

- Waiting list Urgency Measure is the expected number of days lived without a transplant during an additional year on the waiting list
- Posttransplant Survival Measure is the expected number of days lived during the first year following transplantation
- Transplant Benefit is the posttransplant survival measure—waiting list urgency measure
- Raw Allocation Score is the transplant benefit measure—waiting list urgency measure

$$\text{Formula: LAS} = 100 \times (\text{Raw score} + 2 \times 365) / (3 \times 365)$$

Factors used to calculate the predicted waiting list survival:

- Forced vital capacity (percent predicted)
- Pulmonary artery systolic pressure
- O₂ required at rest (l/min)
- Age at offer
- BMI
- NYHA functional class

Heart data modified from Bloom RD, Goldberg LR., Wang, AY et al: An overview of solid organ transplantation, *Clin Chest Med* 26:529-543, 2005.

UNOS data modified from 2007 Annual report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network—transplant data, Richmond, Va, 2007.

*This new allocation was implemented in May 2005 and is still under investigation to determine if it meets the goals of the allocation system (e.g., decrease the number of deaths of transplantation candidates and recipients).

nario the first person would be assigned a status 1 A, listed higher on the transplantation listing, and offered an organ before the second person (Box 21-4).

Several factors are taken into consideration in identifying the best-matched candidate or candidates. In general, preference is given to candidates with the most critical status from the same geographic area as the donor because timing is a critical element in the organ procurement process. Waiting for combined-organ transplantation is much more complicated. Once the potential candidate is listed first for transplantation (for either required organ),

- Diagnosis
- 6-minute walk test <150 feet
- Continuous mechanical ventilation
- Diabetes mellitus

Factors used to calculate predicted posttransplant survival:

- Forced vital capacity (percent predicted)
- Pulmonary capillary wedge mean pressure ≥20 mm Hg
- Continuous mechanical ventilation
- Age at transplant
- Serum creatine (mg/dl)
- NYHA functional class
- Diagnosis

Heart-Lung

This allocation system is still in development because of the complexity of managing both the heart and lung waiting lists separately and the timing required to offer both types of organs to one individual. At present the candidate who is waiting for a heart and lung transplantation procedure is placed on both waiting lists. When the individual is identified as the best candidate for the donor organ under that specific allocation system (heart or lung), he or she would receive the other organ by default.

Allocation

- Organs from donors younger than 12 years will be offered to candidates less than 12 years of age by waiting time. If no candidate is found then the organ will be offered to a candidate between 12 and 17 years of age based on LAS score. Waiting time will be used as the tiebreaker in cases where the LAS scores are the same. If no pediatric candidate is found, then the donor organs will be offered to an adult based on the LAS score.
- Organs from donors 12 to 17 years of age will be first offered to a candidate of the same age bracket based on LAS. If no candidate is found in this age group, then the organs will be offered to a pediatric candidate less than 12 years of age by waiting time before beginning offered to an adult candidate base on LAS score.
- Organs from donors over the age of 18 years will be offered to an adult candidate (>18 years of age) by LAS score, then to a candidate between the age of 12 and 17 years of age by the LAS score.

the second organ must be available and no other higher status candidate must be waiting for that second organ.

The transplantation team bears the responsibility to conserve scarce resources for those who can benefit, requiring careful screening of potential candidates. Transplantation centers follow UNOS guidelines, but criteria may vary from center to center; some centers adhere to a medical evaluation for the acceptance of applicants for transplantation.

Other teams have medical and nonmedical criteria with exclusion criteria for people with severely problem-

Box 21-5**CRITERIA FOR ORGAN CANDIDATE****Medical Considerations**

- Matched blood type required
- Body weight (morbid obesity >20% of ideal body weight contraindicated; severe malnutrition <70% of ideal body weight contraindicated)
- Presence of other illness or disease contraindicated
 - Other end-stage organ disease
 - Irreversible renal insufficiency
 - Irreversible hepatic insufficiency
 - Severe pulmonary disease: forced vital capacity >50%; FEV₁ < 60%
 - Fixed pulmonary hypertension
 - At risk for cardiac problems (death, myocardial infarction, coronary angioplasty, bypass surgery, unstable angina)
 - Uncontrolled infection or acute sepsis
 - HIV
 - Malignancy with metastases
 - Malignancy with an expected 5-year survival <75%
 - Irreversible neuromuscular or neurologic disorder
 - Severe peripheral vascular disease or cerebrovascular disease
 - Abdominal aneurysm
 - Peripheral ischemic ulceration
 - Carotid disease
 - Decrease in chest wall mobility
 - Nonambulatory with poor rehabilitation potential

Nonmedical Considerations

- History of noncompliance with medical therapy (last 5 years)
- History of ongoing alcohol or drug dependence
- Active or recent (within last 6 months) cigarette smoking (lung transplant)
- History of psychologic instability
- Financial resources available
- Family and community support available

atic behavior or other psychosocial factors (Box 21-5). There has been a recent trend to recognize the importance of nonmedical issues, such as psychologic stability, family support, and history of compliance or adherence to medical care, when evaluating applicants.

Medical compatibility of the donor and candidate or candidates is determined based on characteristics such as blood type, weight, and age; urgency of need for some organs; and length of time on the waiting list. Any illness that cannot be treated or that will prevent transplantation success must be evaluated carefully. Transplantation is usually not recommended if another illness is predicted to rapidly cause graft failure.

For example, in the case of someone having heart failure who is being considered for heart transplantation, pulmonary arterial pressure will be evaluated. If the pulmonary artery pressure is high and unresponsive to medication, that would dilate the pulmonary vascular bed and reduce pulmonary hypertension; the pressure is considered refractory, or fixed, which can result in failure of the new donor heart.

The donor heart, particularly the right ventricle, will not be able to pump against the high pulmonary pressure and will result in right-sided heart failure. In addition, a previous history of cancer or osteoporosis is considered carefully since postoperative medications can greatly advance these diseases.

A history of problematic behavior, such as adherence to treatment and psychiatric instability, leads to higher posttransplant mortality and morbidity.^{76,185,276} Compliance issues associated with substance abuse usually include personality disorder, living arrangements, and/or global psychosocial factors. A history of substance abuse requires documentation of abstinence; ongoing drug and/or alcohol abuse can potentially impair the success of the transplantation and requires referral for treatment before placement on a transplantation waiting list.

In the case of live-donor transplantation, psychosocial risk to donors must be taken into consideration. Most published reports have indicated an improved sense of well-being and a boost in self-esteem for living donors, but there have been some reports of depression and disrupted family relationships after donation, and even suicide after a recipient's death.¹⁵⁶

Pretransplant Evaluation

Extensive medical testing is required before someone is placed on the transplantation waiting list (Table 21-2). Blood typing, including Rh factor analysis, is used as one of the first eligibility criteria for donor-candidate matching. Predictor values for acute and chronic rejection are evaluated, such as patent reactive antibodies (a measure of the amount of antibodies circulating in the system), and offer some predictive value of hyperacute rejection.

Other serology testing determines exposure to cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex viruses (HSVs), and hepatitis because complications can arise related to individual exposure to viral loading (i.e., the greater the viral replication, the higher the incidence of active infection).

CMV infection may contribute to an increased incidence of chronic rejection; HSV has been associated with an increased incidence of necrotizing pneumonitis and cervical cancer; and EBV has been associated with an increase in posttransplantation lymphoproliferative diseases. (See further discussion of these infectious diseases in Chapter 8.) Transplant recipients are placed on appropriate medications to reduce the risk of infection and undergo repeated serologic testing if clinical signs and symptoms suggest infection or infectious disease (see Box 8-1).

Fasting lipids, liver function studies, prostate-specific antigen levels to determine prostate function, and tests specific to the potential organ transplant are carried out. A person with isolated end-stage organ failure with no other complications has a better chance for selection than someone with other complicating factors. In addition to all the testing procedures, the organ candidate meets with a large team of professionals listed in Table 21-2, including, in some centers, rehabilitation staff such as physical and occupational therapists.

Table 21-2 Referral to Transplantation Center

Bloodwork	Testing*	Consultations*	Other
ABO blood type	Multigated acquisition	Surgeon	Urinalysis
Panel reactive antibodies	Echocardiogram	Pulmonologist	Sputum cultures
Serology	Transesophageal or transthoracic echocardiogram	Cardiologist	Creatinine clearance
Liver function tests	Pulmonary function tests	Nephrologist	Purified protein derivative
Fasting lipids	6-Minute walk test	Transplant coordinator	Mammogram
Prostate-specific antigen	Ventilation-perfusion scan	Social services	Pap Smear
Prothrombin time	ABGs	Credit analysis	
Partial prothrombin time	Diffusion capacity of carbon monoxide	Neuropsychology	
Complete blood count	Organ catheterization (heart, kidney)	Physical therapy	
	Radiographs	Rheumatologist	
	Electrocardiogram	Gynecologist	
	VO ₂ max or VO ₂ peak	Dentist	
	Glucose testing (diabetes mellitus)	Nutritionist	
	Peripheral vascular disease		

*Specific consultants and the special tests orders are determined by the type of organ transplantation planned.

ADVANCES AND RESEARCH IN TRANSPLANTATION

Advances in understanding of immunology and organ preservation, surgical technique, pharmacology, and postoperative care have permitted the rapid development of other organ transplantation procedures than just the heart and lung (e.g., liver, pancreas, intestine).

New transplantation is being developed for other organs, such as pancreatic islet cells for the treatment of diabetes and ovarian preservation for later use in cases of cancer requiring removal of the ovaries. The use of hepatic segments for transplantation (either from cadavers or from living related donors) has decreased the number of people (especially children) awaiting liver transplantation.

The first transplantation of skeletal muscle cells to test whether the cells can repair damaged heart muscle took place at Temple University's heart transplantation program in 2000. Muscle tissue taken from the individual's arm was transplanted into his own heart during a surgical procedure to implant an assistive device while waiting for a heart transplant.⁷⁹

Since then, researchers have successfully injected autologous skeletal myoblast cells into myocardium tissue in human beings undergoing concurrent coronary artery bypass grafting or ventricular-assist device implantation. This potential treatment for end-stage heart disease remains under investigation.⁷⁸

Research is underway to develop transplantable cells for the treatment of human diseases characterized by cell dysfunction or cell death and for which current treatment is inadequate or nonexistent. Scientists are also looking for a way to modulate the human immune system in order to prevent rejection of transplanted cells without the use of immunosuppressive drugs.²²⁸

Additional products under investigation include porcine neural cells for stroke, focal epilepsy, and intractable pain; porcine spinal cord cells for spinal cord injury; engineered blood vessels for use as vascular grafts; neurologic cell transfer for Parkinson's disease or Huntington

chorea; human liver cells for cirrhosis; and porcine retinal pigment epithelial cells for macular degeneration.^{11,228}

The diverse research directions being undertaken around the world will continue to change the field of transplantation in the years to come. Gene therapy (including *in utero*), xenotransplantation, tissue engineering, chimerism, and new fields of study developing daily can only be presented briefly in this text but help represent the overall picture of rapid change in treatment approaches.

Xenotransplantation

Allotransplantation remains the preferred treatment for human organ failure, but shortages of acceptable donor organs and the lack of success in developing suitable artificial organs have led researchers to investigate the use of organs from other species (xenotransplantation). Xenotransplantation is defined more fully as the interspecies transplantation of cells, tissues, and organs or *ex vivo* interspecies exchange between cells, tissues, and organs.¹²

Nonhuman primates are now considered an unethical and unsafe source of donor organs, so other species are being considered, in particular the pig. Baboon organs are too small to sustain human beings for long periods. The risk of transmitting deadly infectious agents from nonhuman primates is greater than from other animal species.

Physicians are already successfully using various pig components (e.g., heart valves, clotting factors, islet cells, brain cells) to treat human diseases. Researchers are now breeding genetically manipulated donor pigs whose cells, tissues, and organs could be permanently transplanted into human beings without being destroyed by the human immune system.¹⁰⁶

Previously, hyperacute rejection or acute vascular rejection was the biggest disadvantage to xenotransplantation. Circulation of recipient blood through the transplanted organ caused graft failure within 24 hours. Recent scientific progress has eliminated this obstacle.²⁸³

Concerns still exist about the potential for transfer of infectious agents from animal to human being, leading to a possible epidemic. Scientists hope that, by using modern biotechnology, it may be possible to generate pigs free of threatening viruses in the future.²⁸³

Considerable progress has been made in recent years, and experimental pig-to-primate organ xenotransplantation has resulted in transplant function for days and weeks rather than minutes. Researchers have successfully implanted pig organs as a short-term bridge (up to 10 hours) until a human donor organ can be found and implanted.¹⁸⁷

Other hurdles to xenotransplantation include anatomic, physiologic, and biochemical differences. The upright position of human beings is unique in nature. Gravity therefore exerts a different impact on the anatomic location of organs such as lung, heart, liver, and kidney. More pronounced are differences on the humoral and enzymatic basis.

Complex interactions existing in allografts are totally disturbed in xenogeneic situations. Regaining physiologic function of the graft in the foreign environment may be prevented by molecular incompatibilities between the donor and recipient, and there is the possibility of transferring infectious diseases from the animal donor graft to the recipient. Virologists and molecular biologists are concerned about the serious potential for introduction of diseases foreign to the human immune system.²⁵⁴

Experts say that before xenotransplantation can become an everyday reality, safeguards must be developed to ensure the minimization of risk to the recipient and to society. The decision to proceed with clinical application of this technique depends on ethical, regulatory, and legal frameworks established by consensus.¹⁰⁶

Issues yet to be resolved include the recipient's right to privacy, selection of the first recipients of xenografts, concern that the socioeconomically disadvantaged will be used as test subjects for the first xenografts, and animal rights are just a few of the concerns expressed by various interest groups.^{12,106,265}

Tissue Engineering

Tissue engineering, the science of growing living human tissues for transplantation and other therapeutic applications, is a rapidly expanding industry—so much so that biomedical engineering and technology has become a college-degree program designed to develop engineers able to bridge the gap between biology, medicine, and engineering. Tissue engineering applies the principles of biology and engineering toward the development of biologic substitutes that restore, maintain, or improve tissue function.

The science of tissue engineering has given birth to a new clinical discipline called *regenerative medicine* aimed at restoring the functions of damaged or defective tissues and organs. Aging, associated with a progressive failing of tissues and organs and the leading cause of many diseases, is one of the primary forces behind a branch of regenerative medicine designed to "rejuvenate" the failing, aging body.^{15,162}

Tissue engineering, or the fabrication of functional living tissue, uses cells seeded on highly porous, synthetic, biodegradable, polymer scaffolds as a new approach toward the development of biologic substitutes that may replace lost tissue function. Over the past decade, the fabrication of a wide variety of tissues has been investigated, including both structural and visceral organs.

Bioengineered skin, bone, ligaments, tendons, and articular cartilage are already available in some clinical settings.¹⁸ Collagen meniscus implants may be used to regenerate or regrow new meniscus-like tissue, with the goals of slowing down and preventing further degenerative joint disease, enhance joint stability, provide pain relief, and return people to activities at their desired level.

Autologous chondrocyte implantation and osteochondral autologous transplantation take plugs of cartilage or bone from one site, multiply the cells in culture, and place them into a lesion or hole in the native cartilage or bone, respectively.

Functional bone tissue with the necessary strength for load-bearing applications is still under development. Injectable hydrogels have resulted in materials with significantly enhanced compressive strength.²⁷⁷ Several growth factors contained in demineralized bone matrix (e.g., bone morphogenetic protein) are now being used to stimulate bone healing. Tissue engineering for bone healing has great potential for many people who experience nonunion, slow-to-heal bone fractures, or traumatic bone loss associated with war injuries.¹¹⁴

Other research is underway to generate stronger bone substitutes either by increasing osteoblast differentiation and mineralization⁷¹ or culturing the engineered tissue for a longer period of time before implantation to allow matrix maturation.⁵⁰ Learning to tailor the strength of tissue-engineered bone to the person's need requires further research.^{73,183}

Other examples of current progress in the area of bioengineering include implants filled with islets for people with diabetes to replace insulin injections, a method to generate natural breast tissue to replace saline implants, heart valves, dental tissue (gums, teeth), skeletal muscle tissue isolated from synthetic polymers, and formation of phalanges and small joints from bovine-cell sources (calves).

Laboratory-grown organs are farther off, with the hope for producing donor tissue and organs for transplantation on demand and developing living prosthetics (incorporating living tissue with electronics) for every organ system in the body.^{184,322} Embryonic and adult stem cells, able to differentiate into all types of cells, remain the hope of many scientists in the treatment of systemic diseases and local tissue defects, as a vehicle for gene therapy, and to generate transplantable tissues and organs in tissue-engineering protocols. There remain many biologic and ethical challenges to overcome before this type of treatment becomes a reality.^{22,162,232}

Medications

Tremendous advancement has been made in the pharmacologic management of transplant recipients. Medica-

Figure 21-2

Cyclosporin (CsA, CYA, Neoral, Sandimmune) and tacrolimus (FK506, Prograf) block the sensitization of T cells. Cyclosporin and tacrolimus inhibit calcineurin in lymphoid tissues and thus inhibit the production of immune mediators such as interleukin-2. In general, sirolimus (Rapamune) structure is similar to cyclosporin but its action is different. It does not interfere directly with the cytokine production but inhibits the growth and proliferation of T and B lymphocytes by inhibiting the lymphocytes from taking action in response to stimulatory signals from certain cytokines. (Courtesy Chris L. Wells, University of Maryland Medical Center, and James H. Dauber, University of Pittsburgh Medical Center-Health Systems.)

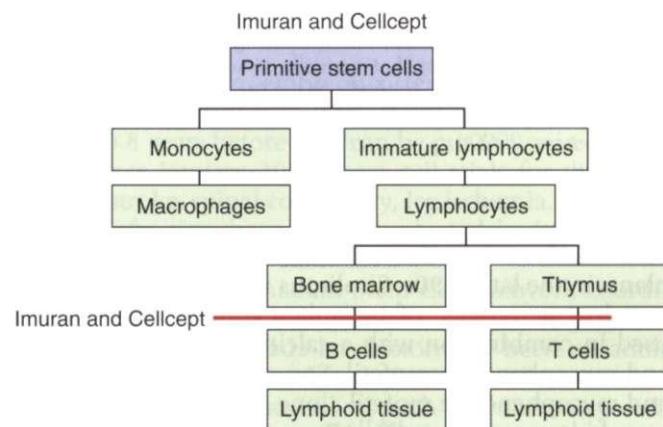
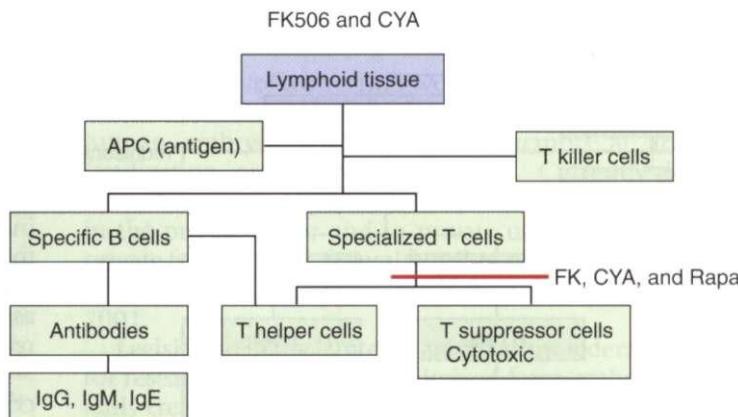
tions are used with transplant recipients to prevent rejection and treat rejection or infection. Research is ongoing to find ways to reduce or eliminate the long-term use and adverse effects of medications, especially immunosuppressants. New discoveries in cellular immunology have led to a greater understanding of the immune system and its implications for tissue transplantation. Immunosuppressive regimens continue to improve, and newer immunomodulatory strategies are evolving. In particular, new immunosuppressive drugs may allow the recipient to overcome or reduce the early antibody-mediated rejections.⁴²

Most transplant recipients are placed on a three-drug regimen to control the incidence of rejection and minimize the adverse effects that are common if any one drug is given in too high a dosage. This drug cocktail commonly consists of a calcineurin inhibitor, an antimetabolite, and a corticosteroid. Great strides are still being made to decrease the dosage and the number of immunosuppressive medications the transplant recipient is exposed to in order to promote long-term, effective graft function.

There has been a decline in the use of cyclosporine and Neoral over the 5 years for most organs. These drugs have been replaced with the administration of tacrolimus (Prograf, FK506). Cyclosporine and tacrolimus are classified as *calcineurin inhibitors*.³⁶ Calcineurin is an enzyme, protein phosphatase, which is responsible for the activating the transcription of interleukin-2 that stimulates the growth and differentiation of T cells. Calcineurin is also linked to the differentiation of fiber types and hypertrophy of muscle fibers.⁶⁶

The mechanism of action for tacrolimus and cyclosporine is similar in that they both inhibit calcineurin, although tacrolimus is more selective in its action and may be one of the reasons its use has become more popular (Fig. 21-2). Both drugs bind to specific lymphoid tissues and block the production of interleukin-2, which is a critical substance in the growth and proliferation of activated T cells and other immune response cells, such as natural killer cells, macrophages, and lymphocytes.⁶⁶

Another classification of drugs commonly used along with a calcineurin inhibiting medication are the antimetabolites. These drugs include azathioprine (Imuran), mycophenolate mofetil (CellCept), and cyclophosphamide (Cytoxan).³¹⁶ There has been an increased utilization

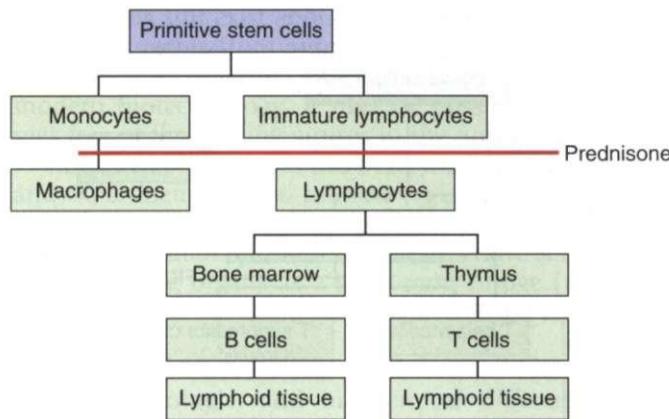
**Figure 21-3**

Azathioprine (Imuran) and mycophenolate mofetil (CellCept) are theorized to block lymphocytes from maturing into T cells. This inhibits the immune-mediated inflammatory response. (Courtesy Chris L. Wells, University of Maryland School of Medicine, and James H. Dauber, University of Pittsburgh Medical Center-Health Systems, 2000.)

of mycophenolate mofetil over other drugs in this classification. Azathioprine works by suppressing the bone marrow (as exhibited by thrombocytopenia, leukopenia, and anemia), and mycophenolate mofetil inhibits the inflammatory response mediated by the immune system (Fig. 21-3).^{190,191} Cyclophosphamide, which is typically thought of as an anticancer drug, has been used in transplant recipients. It inhibits the replication of DNA and RNA in the lymphocytes and other key cells involved in mounting an immune response against the transplanted organ.⁶⁶

The third class of drugs includes prednisone, a corticosteroid with an effect at the level of the macrophages. Prednisone blocks the production of interleukin-2 in the presence of an antigen to stimulate a major histocompatible complex, thus stimulating both B-cell and T-cell response (Fig. 21-4). Work continues to be done to decrease the exposure and utilization of corticosteroids because of the adverse effects of this medication, including diabetes, osteoporosis, and fat deposition.

Sirolimus (rapamycin, Rapamune) is an immunosuppressant that inhibits cytokine-driven cell proliferation and maturation. It was approved for use with renal trans-

**Figure 21-4**

Prednisone works at the macrophage level and is theorized to block the production of interleukin-2, thus preventing the formation of major histocompatible complexes that normally stimulate both B- and T-cell response. (Courtesy Chris L. Wells, University of Maryland School of Medicine, and James H. Dauber, University of Pittsburgh Medical Center-Health Systems, 2000.)

plants and was introduced for use with other organ transplants in the late 1990s. Sirolimus is presently being used in a low percentage of transplant recipients. It may be used in combination with a calcineurin inhibiting drug and mycophenolate mofetil. Some centers use sirolimus and mycophenolate mofetil alone, particularly with pancreas kidney recipients.^{166,316} Recent studies have reported a decrease in chronic rejection in heart transplant recipients with the use of sirolimus.¹⁶⁷

Unlike cyclosporine and tacrolimus, which prevent the body from reacting to the transplant, sirolimus "stalls the engine," disabling the body's ability to reject the transplanted organ. Because of this effect, sirolimus in combination with cyclosporine and steroids not only lowers the incidence of acute renal allograft rejection, but also permits cyclosporine sparing (reduced amounts or eventual elimination) without an increased risk of rejection.

Medication Reduction and Withdrawal

Among individuals who initially received sirolimus in combination with cyclosporine and steroids, those who had steroid treatment stopped 1 month after transplantation had significantly fewer rejection episodes and were spared the numerous toxic side effects associated with long-term steroid administration.¹³⁶

Ongoing research continues to explore and support this practice as early as 4 days after transplantation.^{8,10,338} Steroid withdrawal can increase the risk of acute rejection but reduces the incidence of infection. Maintaining a sufficient immunosuppressive regimen is the key to successful steroid withdrawal.

Withdrawal or marked reduction of corticosteroids is of particular benefit in the case of diabetes mellitus and in the presence of severe osteoporosis or aseptic necrosis of bone. Steroid withdrawal has been shown possible in up to 70% of pancreas transplant candidates who are otherwise maintained on tacrolimus-based immunosuppression.^{143,157}

One other way to reduce the amount of immunosuppression required is through the use of monoclonal antibodies, such as OKT₃, a mouse monoclonal antibody to human T cells. OKT₃ blocks the ability of the candidate's T cells to recognize foreign antigens, thus inhibiting both the generation and the function of cytotoxic T cells responsible for graft rejection. T cells are rapidly decreased in the circulation after the drug is given; by the third day there are usually no detectable circulating T cells. Unfortunately, the use of OKT₃ for induction therapy has an association with chronic rejection in heart transplant recipients.²⁶¹

Research groups are working toward identifying the critical components on particular grafts that are seen as foreign to modify them.³¹ This work will enable the graft to succeed while simultaneously allowing the host immune response to carry out its main tasks. Strategies that teach the immune system to accept the transplanted tissue rather than attack it, a process called *chimerism*, are under investigation (see the section on Future Trends under Blood and Bone Marrow Transplantation in this chapter).^{135,175,288}

Chimerism involves inducing the donor's immune system onto the candidate's so that the candidate's immune system no longer rejects the organ or tissue. In bone marrow transplantation (BMT) chimerism is achieved when bone marrow and host cells exist compatibly without signs of graft-versus-host disease (GVHD).

Researchers studying how the developing fetus avoids destruction may be able to identify protective biologic pathways and then use this model to develop drugs to interrupt the rejection process and promote tolerance of foreign tissue.^{147,312}

BIOPSYCHOSOCIAL IMPLICATIONS

Many different ethical, social, moral, economic, and legal issues are associated with the procurement and allocation of living or bioengineered tissue. In addition, new information concerning the psychoneuroimmune responses (see the section on Psychoneuroimmunology in Chapter 1) in healthy tissues and organs has added new dimensions to understanding the emotional adjustment for recipients of living organ and tissue transplants.

Legal and Ethical Considerations

Before alternate treatment methods can be fully implemented, scientific and medical communities and the general public will have to seriously consider and attempt to resolve legal and ethical issues. For example, federal law prohibits the sale of human organs in the United States, and violators are subject to fines and imprisonment. However, individuals have taken matters into their own hands and established donor matching services on the Internet (Box 21-6).

In some countries of continental Europe, organ donation is governed by "presumed consent" legislation. Unless legally designated otherwise, organ donation is presumed on the death of each individual. Consent leg-

Box 21-6**TRANSPLANTATION RESOURCES**

There are many books, Web sites, and organizations devoted to the topic of organ transplantation. Some focus on the needs of the donors; others provide information to potential recipients. The following is a list of resources we have found helpful. There may be others equally helpful that we do not know about.

- *Transplant Chronicles and Transplant News Digest*: A monthly edition, available in print and PDF formats, containing in-depth articles about worldwide developments in organ, tissue, eye, cell, and bone marrow procurement and transplantation, including business and regulatory news. Also a weekly eNewsletter covering up-to-the-minute developments available at <http://www.trannews.com>.
- National Kidney Foundation (NKF) TransAction Council: the Council was founded to address the unique needs and concerns of all individuals who have received or await transplantation of any type. The Council is open to all recipients and candidates, family members, friends, and health care professionals. Available at <http://www.recipientvoices.org> or <http://www.kidney.org/transplantation/transAction/index.cfm>.
- United Network for Organ Sharing (UNOS) is a nonprofit organization that coordinates U.S. organ transplantation activities. The UNOS Web site contains information and statistics about organ transplantation (<http://www.unos.org>). A separate Web site sponsored by UNOS for patients is available at <http://www.transplantliving.org>. Information about paired exchanges and matching organ donors with candidates can be found by searching for "paired exchange."
- The official U.S. government Web site for organ and tissue donation and transplantation is maintained by the Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, an agency of the U.S. Department of Health and Human Services. Available at: <http://www.organdonor.gov>. At this site you can also learn how to become an organ and tissue donor and download donor cards.
- Matching Donors, a nonprofit organization, matches organ donors with people in need of organ transplants. It is available on-line at <http://www.matchingdonors.com>. The New York Organ Donor Network also has a paired exchange program to match willing donors with organ candidates. More information is available at <http://www.donatelifenyc.org>.
- International Association of Living Organ Donors, Inc., offers another on-line community to match and support living donors, potential donors, their families, and the medical community. Available at: <http://www.livingdonoronline.com>.
- TransWeb: all about transplantation and donation. Available at: <http://www.transweb.org>.
- Finn R, Green R, Lamb L: *Organ transplants: making the most of your gift of life*, New York, 2000, O'Reilly and Associates.

islation has had a proven and positive, sizeable effect on organ donation rates in the last 10 years.¹

Although Western opinion is almost universally against the practice of paid organ donation and the use of organs from judicially executed prisoners, similar laws are not in place worldwide. The ethics of both issues continue to be debated.

Bioethical Considerations

Another area of concern involves researchers growing human cells into tissues using stem cells derived from human embryos left over from attempts at artificial fertilization or following abortions. Currently in the United States embryonic stem cell lines are being made in the private sector and in private universities that use private funding. U.S. federal funding currently is restricted to 22 cell lines that were made on or before August 9, 2001.

Legislation in the United States to allow federal funding for research using stem cells derived from embryos originally created for fertility treatments and willingly donated by consenting adults has been introduced and remains a debated issue. Other countries such as Israel, England, and India and in parts of Asia have moved ahead in this area.

For the most part, embryonic stem cells are only used in fundamental research. It is predicted that it will be at least 5 to 8 years before they can be put to use in clinical trials. Since January 2006, stem cell trials for the treatment of stroke, spinal cord injury, leg ischemia, and myocardial infarction have been conducted in India using bone marrow-derived stem cells.

In Canada, the Canadian Stem Cell Network coordinates Canadian stem cell research at over 70 research sites. Research in Canada has historically been on adult stem cells; however, as of June 2005 a small amount of human embryonic stem cell research was underway with two human embryonic stem cell lines.

The Canadian federal government has passed legislation banning human cloning for reproductive or therapeutic purposes. However, the Assisted Human Reproduction Act allows Canadians to derive new human stem cell lines from embryos left over after fertility treatments. The Act also recommended that an authority be set up to license, inspect, and enforce activities controlled under the act and to foster the application of ethical principles in relation to assisted human reproduction. The Assisted Human Reproduction Agency of Canada was established in 2006.^{127,315}

The United Kingdom established a national bank for stem cell lines, called the UK Stem Cell Bank, to work closely with the clinical and research communities to provide qualified stocks of human stem cell lines of adult, embryonic, and fetal origin for both research use and for use in emerging human therapy.¹²⁸

Many bioethicists and lawmakers still question the appropriateness of this research until the ethical issues and appropriate concerns can be voiced and resolved. Questions about the nature of human life and its protection, the safeguard of human dignity, and the use of genetic material have been raised. However, new discoveries in the rapidly developing field of stem cell research, such as the discovery of master stem cells (see the section on Blood and Bone Marrow Transplantation in this chapter) replacing the use of embryonic tissue, may bypass these bioethical concerns.

Concerns related to animal-derived matrix proteins have also been raised. Some private bioengineering companies are proactively researching ways to develop human

tissue with matrix proteins naturally secreted by the cells rather than developing tissue from animal-derived matrix proteins. In the area of animal organ transplantation (xenotransplantation), rules governing the welfare of animals bred for transplants are being formulated. For example, a ban on having children has been placed on all people receiving animal organ transplantation.

Psychoemotional Considerations

Pretransplant

Transplant applicants face many challenges, including the obvious physical illness, complex assessment protocols, uncertainties about surgery and outcome, the possibility of relocation to obtain transplant services, and large expenses. Waiting for a transplant can be accompanied by a vast range of changing emotions, such as relief, despair, elation, depression, excitement, and apprehension.

No single attitude is common or expected; each person's reaction is a valid expression of his or her experience. Most candidates find waiting for surgery a stressful time and, of course, the longer the wait, the greater the stress. The evaluation process itself and the wait for the results after tests and procedures require complex coping strategies, especially if the person is denied for transplantation. Deciding whether to accept a donor organ or wait for a potentially better one can create considerable psychologic and emotional distress.

When death is a possibility, candidates may worry that negative thinking will harm their health. Others are distressed that someone else must die before an organ will be available for transplantation or that receiving an available organ deprives someone else of life. Candidates are encouraged to focus on the desired outcome without completely ignoring the alternatives for themselves and outcomes for others. Counseling and support groups are often recommended.

Anxiety and depression are common complications of medical illness of any kind and may interfere with the candidate's or recipient's participation in rehabilitation. Symptoms of posttraumatic stress disorder (PTSD) are not uncommon in the recipient or partner after organ implantation or mechanical assist device implantation followed by heart transplantation.^{43,214}

Clinical symptoms of PTSD, anxiety, or depression can be subtle and mimic the individual's health condition, requiring candidate or recipient self-awareness and careful screening by all members of the transplantation team to identify and treat early. Attention to the supporting members of the recipient's family and partners is also advised.⁴³

A condition severe enough to require organ transplantation can sometimes impair concentration, memory, judgment, or ability to process thoughts. In particular, approximately one third of all liver transplant candidates have severe impairment of mental abilities (i.e., hepatic encephalopathy) and may be extremely confused or even delirious at the time of transplantation. Similar mental impairment can occur with heart, lung, and kidney candidates, although it is less common.

Posttransplant

Postoperatively, recipients face a long recovery period, the potential for graft rejection, reintegration into family and work roles, and lifelong changes, such as the need for drug compliance and changes in diet. Adaptation after transplantation is a lifelong process and depends on several factors, such as the success of the transplantation, expectations before the transplantation and perceived outcomes, postoperative complications or side effects of the antirejection drugs, permanent physical changes or changes in appearance, as well as other individual considerations.

Identification of recipients most likely to have compliance and psychiatric problems early after transplant is important in focusing interventions that maximize recipients' psychosocial status in these areas and thus improve long-term physical health outcomes.^{76,296} Pretransplant psychiatric disorders, female gender, longer hospitalization, more impaired physical function, and less social support from caregivers and family in the perioperative period are known risk factors for posttransplant anxiety and depressive and psychologic disorders.⁷⁵

Stress on the family and the need for family support and counseling also affect treatment outcomes. Health care staff may observe a deterioration of family relationships after transplantation (especially between husband and wife or between partners). Older children receiving organ transplantation may face the challenge of parents not allowing or unable to allow the child to grow into adulthood. Support groups can be extremely helpful in these types of situations and should be recommended early by the health care team.

Some recipients experience difficulty accepting the transplanted organ as their own. Others wonder if their new organ carries some donor characteristics. Typical literature available from transplantation centers contains reassurances that a heart, liver, or kidney can be transplanted into another person without the transfer of personal characteristics. Changes reported are often attributed to the normal process associated with overcoming a serious life-threatening illness.

On the other hand, research pioneered by Candace Pert,²⁴⁷ formerly a molecular biologist at the National Institutes of Health, has discovered the biologic basis for emotions. The results of Pert's research have demonstrated that peptides and various other ligands (information carriers) and their receptors are the physiologic substrates of emotion. This work strongly helped establish the field of psychoneuroimmunology (see the section on Psychoneuroimmunology in Chapter 1) and supports the idea that emotions, personal characteristics, behaviors, and thoughts are biochemically derived—not only being actively present within our tissues, but also making up a bodywide system carrying this type of information across cellular barriers.

Following is a brief summary of Pert's research findings. The reader is referred to her book *Molecules of Emotion: the Science Behind Mind-Body Medicine*²⁴⁸ for a more thorough treatise of her findings and similar organ-specific information presented by others.^{237,245,326} The