lesion), the HPV status of the patient, the age of the patient, and whether this is the first abnormal finding or a persistent abnormality. A full discussion of all the treatment recommendations based on these factors is beyond the scope of this chapter. Some of the diagnostic procedures recommended for evaluation of nonpregnant women are contraindicated in pregnancy, and the indications for some procedures are modified in the setting of pregnancy. Suffice it to say that the evaluation of women with abnormal cervical cytology in pregnancy should be referred to knowledgeable and experienced gynecologists or gynecologic oncologists.

Cervical intraepithelial neoplasia is a slowly progressive lesion and has a low risk of progression to invasive cancer during pregnancy (~0.4%), and many low-grade lesions (36–70%) regress spontaneously. Accordingly, some physicians defer definitive diagnostic procedures in pregnant women until 6 weeks postpartum unless they are at high risk for invasive disease. If invasive disease is suspected and the pregnancy is between 16 and 20 weeks, a cone biopsy may be performed to make the diagnosis and may be curative for some lesions; however, the procedure may cause heavy bleeding due to the increased vasculature in the gravid cervix and increases the risk of premature rupture of membranes and preterm labor two- to threefold. Cone biopsy should not be done within 4 weeks of delivery. The only indication for therapy of cervical neoplasia in pregnant women is the documentation of invasive cancer.

Management of invasive disease is guided by the stage of disease, the gestational age of the fetus, and the desire of the mother to have the baby. If the disease is in early stage and the pregnancy is desired, it is safe to delay treatment regardless of gestational age until fetal maturity allows for safe delivery. Abortion followed by definitive therapy is recommended for women with advanced, but potentially curable, cancer in the first or second trimester **(Chap. 117)**. If the disease is in an advanced stage in early pregnancy and the patient declines pregnancy termination to permit prompt definitive therapy, she must be informed of the fact that the maternal safety of delaying therapy is unproven. In women in the third trimester with advanced disease, the mother should be treated with betamethasone to accelerate fetal lung maturation and the baby should be delivered at the earliest possible gestational age followed immediately by stage-appropriate therapy. Most women with invasive cancer have early-stage disease. If the disease is microinvasive, vaginal delivery can take place and be followed by definitive treatment, usually conization. If a lesion is visible on the cervix, delivery is best done by caesarian section and followed by radical hysterectomy.

BREAST CANCER DURING PREGNANCY

Breast cancer complicates approximately 1 in 3000 to 10,000 live births. About 5% of all breast cancers occur in women age 40 years or younger. Among all premenopausal women with breast cancer, 25–30% were pregnant at the time of diagnosis. It has been recognized for some time that breast cancer associated with pregnancy generally seems to have a poorer prognosis for both overall survival and progression-free survival. The definition of *pregnancy-associated breast cancer* (PABC) has differed in various publications, but a generally accepted definition is breast cancer diagnosed during pregnancy or within 1 year of delivery. There are likely several reasons for the observation of the poorer prognosis. Breast cancers diagnosed during pregnancy are often diagnosed at a later stage of disease and so have a poorer outcome. The late diagnosis is often due to the fact that early physical signs of the disease are missed or attributed to the changes that occur in the breast normally as a function of pregnancy. However, a discreet breast mass in a pregnant woman should never be assumed to be normal. Another reason is the more aggressive behavior of the cancer possibly related to the hormonal milieu (estrogen increases 100-fold; progesterone increases 1000-fold) of the pregnancy. However, about 70% of the breast cancers found in pregnancy are estrogen receptor–negative. About 28–58% of the tumors express HER2, a biologically more aggressive breast cancer subset. Another factor is that aggressive, definitive chemotherapy and radiation therapy are often delayed due to concerns about the consequences of those treatments for the fetus. Younger women with breast cancer have a higher likelihood of having mutations in *BRCA1* or *BRCA2*.

TABLE 124e-3 DIFFERENCES IN BREAST CANCERS IN PREGNANT AND NONPREGNANT WOMEN

	Pregnant	Nonpregnant
Tumor size	3.5 cm	2 cm
Estrogen receptor +	30%[a]	67%
HER2 +	Up to 58%	10–25%
Stage II, III	65–90%	45–66%
Lymph node +	56–89%	38–54%

[a]Lower measured levels could be in part artifactual due to the increased levels of estrogen in the milieu.

Differences in presentation between PABC and breast cancers diagnosed in nonpregnant women are shown in **Table 124e-3**. About 20% of breast cancers are detected in the first trimester, 45% in the second trimester, and 35% in the third trimester. Some argue that stage for stage, the outcome is the same for breast cancer diagnosed in pregnant and nonpregnant women. Primary tumors in pregnant women are 3.5 cm on average, compared to <2 cm in nonpregnant women. A dominant mass and a nipple discharge are the most common presenting signs, and they should prompt ultrasonography and breast MRI exam (if available) followed by lumpectomy if the mass is solid and aspiration if the mass is cystic. Mammography is less reliable in pregnancy due to the increased breast density. Needle aspirates of breast masses in pregnant women are often nondiagnostic or falsely positive. Even in pregnancy, most breast masses are benign (~80% are adenoma, lobular hyperplasia, milk retention cyst, fibrocystic disease, fibroadenoma, or other rarer entities).

Many studies comparing outcomes among women with PABC to those of nonpregnant women have small sample sizes, and there is considerable heterogeneity among the study results, but a formal meta-analysis including multiple adjustments and sensitivity analyses confirms the clinical impression of poorer outcomes for women with PABC. The hazard ratios were 1.44 for poorer overall survival and 1.60 for poorer disease-free survival.

Although having had a pregnancy is a protective factor against breast cancer in women in general, it is questionable as to whether it retains its protective effect in carriers of *BRCA1* and *BRCA2* mutations. Cullinane et al. (Int J Cancer 117:988, 2005) found a statistically insignificant difference (odds ratio 0.94) in breast cancer risk among *BRCA1* carriers who had ever been pregnant versus those who never had a pregnancy. Stratifying the risk of breast cancer according to the number of prior pregnancies versus no pregnancies, no statistically significant protective trend was observed. For *BRCA2* carriers, there was a marginally statistically significant increased risk of breast cancer among women with prior pregnancies. In an international study with more than 65,000 person-years of observation (Andrieu J: Natl Cancer Inst 98:535, 2006), there was no significant effect in either direction of pregnancy on breast cancer risk for carriers of either mutation. Staging the axillary lymph nodes is currently somewhat controversial. Sentinel lymph node sampling is not straightforward in pregnant women. Blue dye has been carcinogenic in rats, and fetuses cannot be shielded from administered radionuclides. For this reason, many surgeons favor axillary node dissection to stage the nodes. Largely due to the typical delay in diagnosis, axillary nodes are more often positive in pregnant than in nonpregnant women.

As with other types of cancer in pregnant women, counseling following diagnosis in the first trimester should include a discussion of pregnancy termination to allow definitive therapeutic intervention at the earliest possible time without the potential for permanent injury to a surviving fetus. While definitive local surgery can safely be performed in the first trimester, radiation therapy and chemotherapy are considerably more risky. Delay in administration of systemic therapy can increase the risk of axillary spread. In the second and third trimesters,