# Breast Cancer

## Introduction

Breast cancer is the most common type of cancer in women in the United States, excluding skin cancers. In 2015, there were an estimated 231,840 new invasive breast cancer cases and 60,290 in situ cases diagnosed. The lifetime risk of developing invasive breast cancer is 12.4% (about 1 in 8) for U.S. women. There were an estimated 40,290 deaths from breast cancer in the United States in 2015: it remains the second leading cause of cancer death in women. The lifetime risk of dying from breast cancer for U.S. women is 2.76%. Breast cancer is rare in men.

## Epidemiology and Risk Factors

Breast cancer incidence increases with age. The incidence per decade of life is listed in **Table 37**. The median age of diagnosis in women is 61 years. Incidence rates are highest in non-Hispanic white and black women. Other risk factors for breast cancer are listed in **Table 38**.

Patients with deleterious *BRCA1* or *BRCA2* gene mutations have a 50% to 85% lifetime risk of breast cancer. Patients who received chest wall irradiation between ages 10 and 30 years for treatment of Hodgkin lymphoma have a 30% to 50% risk of breast cancer. Atypical breast lesions, such as atypical hyperplasia or lobular carcinoma in situ, result in a cumulative 30-year breast cancer risk of up to 35%.

Patients with possible hereditary breast cancer syndromes should be referred to a genetic counselor for assessment and possible genetic testing. The criteria for genetic testing are outlined in **Table 39**.

**KEY POINTS**

- Breast cancer incidence increases with age, with the highest incidence in non-Hispanic white women and second highest in black women.
- Women with possible hereditary breast cancer syndromes should be referred to a genetic counselor for possible genetic testing for breast cancer susceptibility genes, such as *BRCA1* and *BRCA2*.

## Chemoprevention and Other Risk Reduction Strategies

Breast cancer screening for average-risk women is discussed in MKSAP 18 General Internal Medicine. The American Cancer Society recommends screening certain women at high risk using annual mammography and breast MRI (**Table 40**).

Women with a 5-year risk of breast cancer of 1.67% or greater are candidates for breast cancer chemoprevention with antiestrogens. A recommended tool for estimating 5-year and lifetime risks of breast cancer is the Gail Model Risk Assessment Tool (www.cancer.gov/bcrisktool/). All patients with atypical hyperplasia or lobular carcinoma in situ (LCIS) are candidates for chemoprophylaxis. At present, there is insufficient evidence to recommend for or against screening with breast MRI in patients with atypical hyperplasia or LCIS.

Tamoxifen and raloxifene are selective estrogen receptor modifiers (SERMs) that block estrogen uptake in breast tissue. Exemestane and anastrozole are aromatase inhibitors that prevent the conversion of androgens into estrogens. These agents proportionally decrease the risk of breast cancer by 28% to 65% and are given for 5 years. **Table 41** summarizes these chemoprophylaxis options.

For women with *BRCA1* or *BRCA2* mutations, breast cancer screening with breast MRI should start at age 25 years and with mammography at age 30 years. The benefit of tamoxifen prophylaxis in *BRCA1* and *BRCA2* mutation carriers is not clear, although limited retrospective data suggest a benefit. Surgical prophylaxis options for *BRCA1* and *BRCA2* mutation carriers include prophylactic bilateral mastectomies, which decrease the risk of breast cancer by greater than 90%, and prophylactic bilateral salpingo-oophorectomy (BSO), which decreases the risk of ovarian, fallopian tube, and primary peritoneal cancers by greater than 80% and all-cause mortality to age 70 years by 77%. If done while a woman is premenopausal, prophylactic bilateral salpingo-oophorectomy also decreases the risk of breast cancer by 50% and is recommended between ages 35 and 40 years, after completion of childbearing. Because *BRCA2* mutation carriers on average develop ovarian cancer 8 to 10 years later than *BRCA1* carriers, bilateral salpingo-oophorectomy can be delayed until age 40 to 45 years in women who have had prophylactic mastectomies.

**TABLE 37. Breast Cancer Risk per Decade of Life for U.S. Women[a]**

| Decade of Life | Fractional Risk for Being Diagnosed with Breast Cancer in the Next 10 Years |
|---|---|
| 20s | 1 in 1674 |
| 30s | 1 in 225 |
| 40s | 1 in 68 |
| 50s | 1 in 42 |
| 60s | 1 in 28 |
| 70s | 1 in 26 |
| 80s | 1 in 33 |

[a]All Races.

Data from Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2012/. Based on November 2014 SEER data submission. The Surveillance, Epidemiology, and End Results Program (SEER) Website. Updated November 18, 2015. Accessed February 7, 2018.

**TABLE 38. Breast Cancer Risk Factors**

| Breast Cancer Risk Factor Category | Breast Cancer Risk Factors | Increase in Breast Cancer Risk or Lifetime Breast Cancer Risk |
|---|---|---|
| Reproductive factors | Early menarche, late menopause, first full-term pregnancy after age 30 years, or nulliparous | RR 1.2-3.5 |
| Lifestyle | Obesity (BMI ≥30), lack of regular exercise, vitamin D deficiency, alcohol intake | RR 1.2-1.6<br>Obesity: RR, 1.6 for BMI >30.7 versus BMI <22.9 in postmenopausal women[a]<br>Regular exercise: RR decreased by 25% in physically active women compared with the least active women[b]<br>Vitamin D deficiency: Postmenopausal breast cancer risk decreased by 12% for each 5 ng/mL (12.5 nmol/L) increase in 25(OH)D levels between 27 and 35 ng/mL[c] (67.4 and 87.4 nmol/L)<br>Alcohol intake: mildly increased risk (RR 1.05) with 2 to 3 drinks per week. RR 1.41 for women consuming 2 to 5 drinks per day[d] |
| Treatment related: radiation | Prior chest wall radiation in patients younger than age 30 years (e.g., mantle radiation for Hodgkin lymphoma) | RR 5.0, with highest risk for younger age at radiation therapy; risk remains increased for at least 40 years after radiation therapy, with 30% to 50% lifetime risk of breast cancer[e] |
| Treatment related: HRT | Combination estrogen and progesterone HRT after menopause | RR 1.2-1.4; increased risk begins after 3 years of therapy[a] |
| Breast density[f] | Increased breast density | Risk increases with each category of breast density; for ≥75% density, RR is 4.7 compared with <10% density[g] |
| Atypical breast lesions | Atypical ductal or lobular hyperplasia, LCIS | RR 3.8-5.3 for atypical hyperplasia[h] and RR 5.4-8.0 for LCIS[i]; 30% to 35% lifetime risk of breast cancer (bilateral risk)[h,i] |
| Family history of breast cancer and familial breast cancer syndromes | *BRCA1/2* mutation represents the most common familial breast cancer syndrome (5% to 10% of all breast cancer tumors); others are rare | *BRCA1/2* mutations (RR 3.0 to 7.0) confer a 50% to 87% lifetime risk of breast cancer and a 20% to 45% lifetime risk of ovarian cancer |

25(OH)D = 25-hydroxyvitamin D; *BRCA1/2* = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; HRT = hormone replacement therapy; LCIS = lobular carcinoma in situ; RR = relative risk.

[a]Data from Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med. 2001 Jan 25;344 (4):276-85. Erratum in: N Engl J Med. 2001 Jun 7;344(23):1804. [PMID: 11172156]

[b]Data from Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. Recent Results Cancer Res. 2011;186:13-42. [PMID: 21113759]

[c]Data from Bauer SR, Hankinson SE, Bertone-Johnson ER, Ding EL. Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. Medicine (Baltimore). 2013 May;92(3):123-31. [PMID: 23625163]

[d]Data from Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol. 2013 Feb;24(2):301-8. [PMID: 22910838] and Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohor studies. JAMA. 1998 Feb 18;279(7):535-40. [PMID: 9480365]

[e]Data from Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012 Aug 1;30(22):2745-52. [PMID: 22734026]

[f]Breast density refers to the amount of radiologically dense breast tissue appearing on a mammogram.

[g]Data from Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007 Jan 18;356(3):227-36. [PMID: 17229950]

[h]Data from Degnim AC, Visscher DW, Berman HK, et al. Stratifications of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol. 2007 Jul 1;25(19):2671-7. [PMID: 17563394] and Marshall LM, Hunter DJ, Connolly JL, et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev. 1997 May;6(5):297-301. [PMID: 9149887]

[i]Data from Bodian CA, Perzin KH, Lattes R. Lobular neoplasia. Long term risk of breast cancer and relation to other factors. Cancer. 1996 Sep 1;78(5):1024-34. [PMID: 8780540]

**KEY POINTS**

- Women at high risk for breast cancer should be screened with annual mammography and breast MRI; this includes women with a *BRCA1* or *BRCA2* gene mutation or with a first-degree relative with a *BRCA1* or *BRCA2* mutation, women with a strong family history of breast cancer, those with a history of chest radiation at a young age, and those with a rare hereditary breast cancer syndrome.

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**KEY POINTS *(continued)***

- Women with a 5-year risk of breast cancer of 1.67% or greater or with lobular carcinoma in situ or atypical hyperplasia are candidates for breast cancer chemoprophylaxis.
- Surgical prophylaxis options for *BRCA1* and *BRCA2* mutation carriers include prophylactic bilateral mastectomy and prophylactic bilateral salpingo-oophorectomy.

**TABLE 39. Highlights of NCCN[a] and USPSTF[b] Recommendations for Breast and Ovarian Cancer Syndrome Genetic Testing**

| **Individuals with a Personal History of Breast or Ovarian Cancer** |
|---|
| Breast cancer diagnosed at or before age 45 years |
| Breast cancer diagnosed at or before age 50 years with one or more relatives[c] with breast cancer, pancreatic cancer, or prostate cancer with Gleason score ≥7 at any age |
| Women with two primary breast cancers, with the first diagnosed at or before age 50 |
| Breast cancer diagnosed at any age with one or more relatives[c] diagnosed with ovarian cancer |
| Triple negative breast cancer[d] diagnosed at or before age 60 years |
| Breast cancer in women of Ashkenazi (Eastern European) Jewish ancestry |
| Men with breast cancer diagnosed at any age |
| Ovarian cancer diagnosed at any age |
| **Individuals without a Personal History of Breast or Ovarian Cancer** |
| Family history of a known deleterious *BRCA1/2* mutation |
| Two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger |
| Three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis |
| More than three family members[c] with breast cancer, ovarian cancer, pancreatic cancer, and/or aggressive prostate cancer |
| A combination of both breast and ovarian cancer among first- and second-degree relatives |
| A first-degree relative with bilateral breast cancer |
| A combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis |
| A first- or second-degree relative with both breast and ovarian cancer at any age |
| A history of breast cancer in a male relative |
| Women of Ashkenazi (Eastern European) Jewish ancestry with a first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer |

*BRCA1/2* = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; NCCN = National Comprehensive Cancer Network; USPSTF = U.S. Preventive Services Task Force.

[a]Full testing guidelines can be accessed at www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[b]Full testing guidelines can be accessed at www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing.

[c]First-degree, second-degree, or third-degree relatives on the same side of the family.

[d]Negative for estrogen and progesterone receptors and *HER2* amplification.

**TABLE 40. American Cancer Society Recommendations for MRI Breast Cancer Screening**

| |
|---|
| Women with *BRCA1/2* mutations |
| Women who are a first-degree relative of a *BRCA1/2* carrier but are untested[a] |
| Women with a strong family history of breast cancer with a lifetime breast cancer risk of ≥20% to 25% as calculated by models[b] largely dependent on family history |
| Women who had radiation to the chest wall between ages 10 and 30 years (e.g., mantle radiation therapy for Hodgkin lymphoma) |
| Women with a history of other rare familial breast cancer syndromes |

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes.

[a]Testing for the *BRCA1* or *BRCA2* mutation that is present in the family is strongly recommended, but some patients decide to defer testing. In this situation where their carrier status is unknown, breast MRI screening is recommended. If they are later tested and do not carry the mutation, MRI screening should be stopped.

[b]Models that can be used to estimate lifetime risk of breast cancer to determine if MRI screening is appropriate (please note that the Gail Model is not recommended for this use):

- BRCAPRO: www4.utsouthwestern.edu/breasthealth/cagene/default.asp
- Claus model: Claus EB, Risch N, Thompson WD. The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. Breast Cancer Res Treat. 1993 Nov;28(2):115-20. [PMID: 8173064]
- Tyrer-Cuzik (also called IBIS Breast Cancer Risk Evaluation Tool): www.ems-trials.org/riskevaluator/

TABLE 41. Primary Chemoprevention for Breast Cancer

| Considerations | Tamoxifen | Raloxifene | Exemestane | Anastrozole |
|---|---|---|---|---|
| Mechanism of action | SERM | SERM | Aromatase inhibitor | Aromatase inhibitor |
| Breast cancer risk reduction | 43% at 7 years[a]<br>28% at 10 years[b] | As effective as tamoxifen at reducing the risk of invasive cancers, but less effective at reducing noninvasive cancers[c] | 65% at 3 years[d] | 53% at 5 years[e] |
| Important toxicities | Vasomotor symptoms, cataracts, vascular events (stroke, TIA, DVT/PE), and endometrial cancer and uterine sarcoma in postmenopausal women | Vasomotor symptoms, cataracts, vascular events (25% lower risk of vascular events than with tamoxifen) | Vasomotor symptoms, arthralgia, headaches, and insomnia | Vasomotor symptoms, arthralgia, carpal tunnel syndrome, dry eyes, and hypertension |
| Indicated for use in premenopausal women | Yes | Not studied; should not be used unless part of a clinical trial | Not effective in premenopausal women | Not effective in premenopausal women |
| Other | Contraindicated in women with prior thromboembolic events; 32% reduction in osteoporotic fractures[a] | Contraindicated in women with prior thromboembolic events | At 3-year follow-up, no increase in osteoporosis, fractures, endometrial cancer, vascular events, or cardiac disease | At 5-year follow-up, no increase in thromboembolic events, fractures, cerebrovascular events, or myocardial infarction |

DVT = deep venous thrombosis; PE = pulmonary embolism; SERM = selective estrogen receptor modulator; TIA = transient ischemic attack.

[a]Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005 Nov 16;97(22):1652-62. [PMID: 16288118]

[b]Cuzick J, Sestak I, Cawthorn S, et al; IBIS-I Investigators. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015 Jan;16(1):67-75. [PMID: 25497694]

[c]Vogel VG, Costantino JP, Wickerham DL, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 2006 Jun 21;295(23):2727-41. Erratum in: JAMA. 2006 Dec 27;296(24):2926. [PMID: 16754727]

[d]Goss PE, Ingle JN, Alés-Martínez JE, et al; NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011 Jun 23;364(25):2381-91. Erratum in: N Engl J Med. 2011 Oct 6;365(14):1361. [PMID: 21639806]

[e]Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014 Mar 22;383(9922):1041-8. Erratum in: Lancet. 2014 Mar 22;383(9922):1040. [PMID: 24333009]

## Staging and Prognosis of Early-Stage Breast Cancer

Breast cancer is most commonly staged by the TNM system. Breast cancer staging and prognosis are presented in **Table 42**. In addition to the excellent prognosis for small tumors with neither lymph node involvement nor distant metastases, the presence of hormone receptors, absence of human epidermal growth factor 2 (*HER2*) overexpression, and absence of lymphovascular invasion also favorably affect prognosis. Estrogen receptors, when detected, imply a better differentiated tumor and suggest response to hormone antagonist therapy. Tumors with a genetic mutation that leads to *HER2* overexpression imply an unfavorable prognosis, although monoclonal antibodies such as trastuzumab that block those receptors are effective therapy and have markedly improved the prognosis for these women.

For asymptomatic patients with newly diagnosed stage 0 to II (early-stage) breast cancer, current guidelines recommend against using imaging studies such as PET, CT, or bone scan, or measuring serum markers such as CA15-3 or CA27-29, for staging. These studies have little diagnostic yield for patients with stage I to II breast cancer who do not have symptoms, findings on examination, or laboratory evidence of metastases. One large series showed that the incidence of bone metastases in stage I to III breast cancer was 5% to 6% for stage I to II and 14% for stage III; for liver metastases, the incidence was 0% in stage I to II and 0.7% in stage III; and for lung metastases, incidence was 0% in stage I to II and 7% in stage III. Imaging studies for staging are recommended in patients with stage III disease or in patients with earlier-stage disease who have signs or symptoms suggestive of metastatic disease.

Advances in breast cancer diagnosis and treatment have led to markedly improved survival rates during the past 40 years. Surveillance, Epidemiology, and End Results (SEER) data from 1975 to 2013 show a 34% decrease in deaths from breast cancer. The 5-year relative survival for all invasive breast cancer stages in patients diagnosed from 2006 to 2012 is 90.8%.

**KEY POINTS**

- Clinical features associated with a more favorable prognosis of early-stage breast cancer include hormone receptor–positive cancer, absence of *HER2* overexpression, small tumor size, low tumor grade, and negative lymph nodes.

*(Continued)*

**TABLE 42. Staging and Prognosis of Invasive Breast Cancer**

| Stage | Definition | 5-Year Relative Survival[a] Rates |
|---|---|---|
| 0 | Ductal carcinoma in situ (negative lymph nodes) | 99% |
| I | IA: Tumor ≤2 cm and negative lymph nodes | 95% |
| | IB: Tumor ≤2 cm and 1 to 3 micrometastatic positive lymph nodes (0.2-2 mm) | |
| IIA | Tumor ≤2 cm with 1 to 3 positive lymph nodes (>2 mm) *OR* | 85% |
| | Tumor 2-5 cm with negative lymph nodes | |
| IIB | Tumor 2-5 cm with 1 to 3 positive lymph nodes *OR* | 70% |
| | Tumor >5 cm with negative lymph nodes | |
| IIIA | Tumor ≤5 cm with 4 to 9 positive lymph nodes *OR* | 52% |
| | Tumor >5 cm with 1 to 9 positive lymph nodes | |
| IIIB | Tumors with skin or chest wall involvement with 0 to 9 positive lymph nodes | 48% |
| IIIC | Tumors with 10 or more positive lymph nodes | Not stated |
| IV | Distant metastatic disease | 22% |

[a]Relative survival is an estimate of the percentage of patients who would be expected to survive the effects of their cancer.

Data from Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2012/. Based on November 2014 SEER data submission. The Surveillance, Epidemiology, and End Results Program (SEER) Website. Updated November 18, 2015. Accessed February 7, 2018.

**KEY POINTS *(continued)***

HVC
- Imaging studies such as PET, CT, or bone scan for staging are not recommended in asymptomatic patients with newly diagnosed stage 0 to II breast cancer.

# Primary Breast Cancer Therapy

## Ductal Carcinoma in Situ

Ductal carcinoma in situ (DCIS), classified as stage 0 breast cancer, is a noninvasive breast cancer that usually presents as calcifications on mammography (see **Figure 19**). Its incidence has increased greatly, from 3% of breast cancers before the era of mammographic screening to 20% to 25% of breast cancers today. Infrequently, DCIS presents as a palpable mass.

Because more than half of local recurrences of DCIS are invasive cancers, the goal of treatment has been to eradicate the area of DCIS and decrease the risks of local recurrence and deaths from breast cancer. Surgical treatment has traditionally been either wide excision (lumpectomy), often followed by breast radiation or mastectomy. Radiation may be omitted in some cases of low-grade or intermediate-grade DCIS. Mastectomy is usually recommended if the DCIS is more extensive and cannot be fully removed by a wide excision.

Recent studies have questioned the benefit of these approaches. An observational study of more than 100,000 women with DCIS showed that although adding radiation to wide excision decreased the risk of local recurrence from 4.9% to 2.5%, it did not decrease the 10-year breast cancer–specific mortality of 0.9%. Similarly, patients who had mastectomies had a lower risk of local recurrence than patients who had lumpectomies but no decrease in the risk of death from breast cancer. Women younger than 35 years, black women, women younger than 40 years presenting with a palpable mass, and women with DCIS that is either estrogen receptor negative or *HER2* positive have a worse prognosis.

In women with estrogen receptor–positive DCIS, tamoxifen and aromatase inhibitors decrease the risks of local recurrence and contralateral breast cancers. Tamoxifen is the

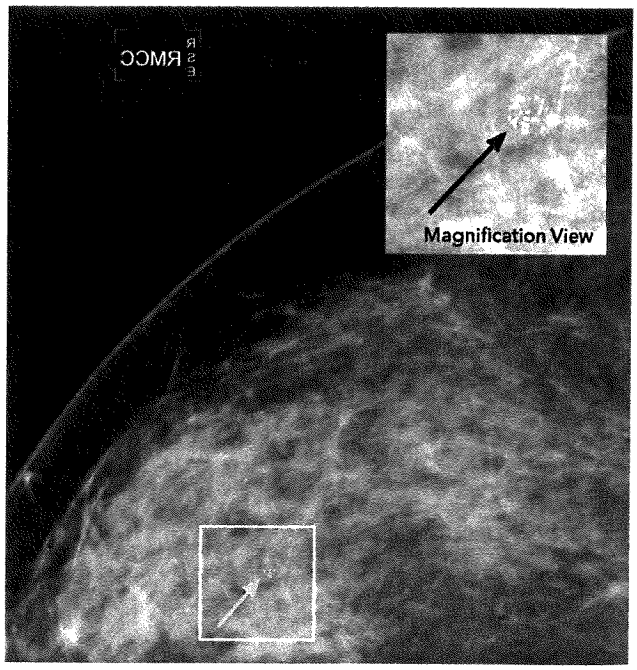


**FIGURE 19.** Ductal carcinoma in situ presenting as calcifications on mammography.

appropriate treatment in premenopausal women. For postmenopausal women, both tamoxifen and anastrozole are effective options, with anastrozole being superior in women younger than age 60 years. Both hormonal therapies are equally effective in women age 60 years or older. Unlike with hormone receptor–positive invasive cancers, antiestrogen treatment of DCIS does not have a survival benefit.

Patients with DCIS should have annual mammography starting 6 to 12 months after radiation therapy, if given, and follow-up visits every 6 to 12 months for 5 years after diagnosis.

**KEY POINTS**

- Although mastectomy or postlumpectomy radiation decreases the risk for local recurrence when compared to wide excision in women with ductal carcinoma in situ, neither improves overall 10-year survival.
- In estrogen receptor–positive DCIS, tamoxifen and aromatase inhibitors further decrease the risks of local recurrence and contralateral breast cancer but do not improve overall survival.

### Invasive Breast Cancer

Most early-stage invasive breast cancers are treated with initial excision, followed by radiation and systemic adjuvant therapy. There are two surgical options for invasive breast cancer. Breast conservation therapy involves wide excision followed by breast radiation and is typically used in patients with cancers 5 cm or less in size, without skin involvement, and with clear margins after excision. Mastectomy is recommended for larger cancers, cancers with skin involvement, and inflammatory breast cancers. Mastectomy may also be chosen in situations where radiation is contraindicated, or in women with *BRCA1* or *BRCA2* mutations or strong family histories of breast cancer where there is a high risk of subsequent breast cancers. For some patients with large tumors, neoadjuvant chemotherapy or endocrine therapy can be given before surgery to decrease the cancer to a size that allows for breast conservation.

In patients with clinically negative axillary lymph nodes, a sentinel node biopsy is done at the time of breast surgery. In patients having breast conservation surgery who will receive chemotherapy or antiestrogen therapy as well as whole breast radiation, axillary dissection is not required if no more than two sentinel nodes are involved. For patients with clinically involved axillary nodes or three or more positive sentinel nodes, an axillary dissection is recommended. The sentinel node procedure has a lower risk of lymphedema, sensory loss, and shoulder abduction defects than axillary dissection.

Primary breast radiation usually consists of radiation to the whole breast, although partial breast radiation is an option in some patients. Postmastectomy radiation is recommended for cancers greater than 5 cm in size, inadequate or positive margins or skin involvement, inflammatory breast cancers, or four or more positive axillary nodes. Depending on other risk factors, it may be recommended in women with one to three positive axillary nodes. Postmastectomy radiation decreases both the risk of local recurrence and the risk of distant metastases and increases overall survival.

For women older than age 70 years with cancers less than 2 cm in size, no clinically involved lymph nodes, and estrogen receptor–positive breast cancer, wide excision followed by antiestrogen therapy alone is an acceptable treatment option. Whole breast radiation in this situation decreases the risk of local recurrence from 9% to 2% at 12 years, but has no impact on the risk of distant metastases, breast cancer-specific survival, or overall survival.

**KEY POINTS**

- Breast-conserving therapy is effective for patients with tumors 5 cm or less in size, without skin involvement, and with clear margins after excision in women who do not have hereditary syndromes that place them at high risk for subsequent breast cancer.
- For patients undergoing breast conservation surgery followed by chemotherapy or antiestrogen therapy and whole breast radiation, axillary node dissection is not required if no more than two sentinel nodes are involved. HVC
- Postmastectomy radiation is recommended for cancers greater than 5 cm in size, positive margins or skin involvement, inflammatory breast cancers, and many patients with positive axillary lymph nodes.

## Adjuvant Systemic Therapy for Nonmetastatic Breast Cancer

Patients with stage I to III (potentially curable) breast cancer receive adjuvant systemic therapy to eradicate occult microscopic foci of breast cancer and decrease the risk of local and distant recurrence. The type of adjuvant therapy used depends on the biology and stage of the breast cancer. Antiestrogen therapy has the additional benefit of decreasing the risk of contralateral breast cancer.

### Adjuvant Endocrine Therapy

Approximately 75% of breast cancers are hormone receptor positive (positive for the estrogen receptor, progesterone receptor, or both). Patients with hormone receptor–positive breast cancers are recommended to receive adjuvant antiestrogen therapy for at least 5 years. The Early Breast Cancer Trialists Collaborative Group meta-analysis of adjuvant tamoxifen showed a 39% proportional reduction in breast cancer recurrence at 15 years and a 30% proportional reduction in breast cancer mortality. In postmenopausal women, aromatase inhibitors compared to tamoxifen resulted in a further 29% proportional decrease in breast cancer recurrence. Both tamoxifen and aromatase inhibitors also decrease the risk of contralateral breast cancer.

Tamoxifen is a selective estrogen receptor modulator that blocks estrogen uptake by breast cancer cells. It is effective in

both premenopausal and postmenopausal women. The aromatase inhibitors letrozole, anastrozole, and exemestane have similar efficacy and prevent conversion of adrenal androgens to estrogen but do not inhibit ovarian estrogen production. They are thus not effective in premenopausal women unless ovarian suppression is given concomitantly.

For postmenopausal women, aromatase inhibitor therapy provides superior results to using tamoxifen alone. Patients may take tamoxifen for 2 years and then change to an aromatase inhibitor for at least 3 to 5 years, or they can take 5 years of an aromatase inhibitor. A 2016 study showed the benefit of extending aromatase inhibitor use to a total of 10 years, whether or not tamoxifen was given initially, with an improvement in disease-free survival at 5 years from 91% to 95% but no difference in overall survival. Recommending extended aromatase inhibitor treatment will depend on a patient's quality of life, the toxic effects of treatment, and the risk of recurrence.

For premenopausal women with low-risk breast cancer who do not require adjuvant chemotherapy, tamoxifen for at least 5 years and preferably 10 years is recommended. Extending tamoxifen use to 10 years decreased the absolute risk of recurrences between 5 and 14 years after diagnosis from 25% to 21.4% and reduced the risk of breast cancer mortality from 15% to 12.5%. Patients who become postmenopausal while taking tamoxifen may be changed to an aromatase inhibitor.

For premenopausal women who receive adjuvant chemotherapy for higher-risk hormone-positive breast cancer and who remain premenopausal, ovarian suppression achieved by surgical oophorectomy or pelvic irradiation in addition to either tamoxifen or an aromatase inhibitor is superior to tamoxifen alone. In the Suppression of Ovarian Function Trial (SOFT), adding ovarian suppression to tamoxifen improved absolute 5-year breast cancer-free survival by 4.5%. Breast cancer-free survival was improved by 7.7% with the use of ovarian suppression and exemestane compared to tamoxifen alone. The benefit was particularly dramatic in patients younger than age 35 years. Patients treated with ovarian suppression had more hot flushes, vaginal dryness, decreased libido, insomnia, depression, arthralgia, hypertension, glucose intolerance, and osteoporosis.

Tamoxifen side effects include endometrial cancer in women older than age 55 years, hot flushes, vaginal discharge, sexual dysfunction, venous thromboembolic events, and stroke.

Aromatase inhibitor side effects include arthralgia; vaginal dryness; sexual dysfunction; and higher risks of osteoporosis, fractures, cardiovascular events, and hyperlipidemia. Compared to tamoxifen, they have a lower risk of venous thrombosis and endometrial cancer. Up to one third of women develop aromatase inhibitor-associated symmetric arthralgia, joint stiffness, and bone pain. This musculoskeletal syndrome is managed with NSAIDs, a treatment break and change to an alternate aromatase inhibitor, or a change to tamoxifen.

**KEY POINTS**

- Premenopausal women with low-risk breast cancer who do not require adjuvant chemotherapy should receive tamoxifen for at least 5 years and preferably 10 years.
- Premenopausal women with higher-risk hormone-positive breast cancer who receive adjuvant chemotherapy should also receive ovarian suppression in addition to either tamoxifen or an aromatase inhibitor.
- Postmenopausal women should receive an aromatase inhibitor for 5 years and preferably 10 years, whether or not tamoxifen was given initially.

## Adjuvant Chemotherapy

Increasingly, the use of adjuvant chemotherapy for early breast cancer is based more on tumor biology rather than on stage. The behavior of hormone receptor-negative and of *HER2*-positive cancers is more aggressive and there is benefit to adjuvant chemotherapy for cancers that are greater than 5 mm in size, lymph node positive, or both.

For hormone receptor-positive, *HER2*-negative breast cancers with zero to three positive axillary nodes, the use of multigene assays that predict the risk of recurrence with antiestrogen therapy alone has significantly decreased the use of adjuvant chemotherapy. The most commonly used molecular prognostic profile in the United States is the 21-gene recurrence score. Tumors with low-risk scores have a favorable prognosis with antiestrogen therapy alone and do not benefit from the addition of chemotherapy.

Clinicopathologic factors that suggest benefit to adjuvant chemotherapy include high tumor grade, extensive lymphatic invasion, very large primary tumor size, skin or chest wall involvement, and involvement of more than four axillary nodes.

Women with hormone receptor-negative, *HER2*-negative cancers (triple-negative breast cancer) have a 50% proportional reduction in the risk of recurrence and of breast cancer mortality with adjuvant chemotherapy. Adjuvant chemotherapy is recommended for triple-negative cancers larger than 5 mm in size or with positive lymph nodes.

When adjuvant chemotherapy is given for high-risk hormone receptor positive cancers or triple-negative cancers, typically two or three agents are given for four to eight cycles. The most common chemotherapies used for adjuvant treatment are anthracyclines (doxorubicin or epirubicin), cyclophosphamide, and the taxanes (paclitaxel or docetaxel).

Adjuvant chemotherapy combined with *HER2*-targeted treatment such as the monoclonal antibody trastuzumab or the combination of trastuzumab and pertuzumab is recommended for *HER2*-positive cancers that are greater than 5 mm in size, node positive, or both. Chemotherapy with trastuzumab decreases the risk of cancer recurrence by 53% and the risk of death by 34%. The main toxicities of trastuzumab are infusion reactions such as fever, chills, and cardiomyopathy. The addition of pertuzumab in treatment of cancers that are greater than 2 cm in size, node positive, or both, improves 5-year

disease-free survival from 81% to 86%. For *HER2*-positive breast cancers that are smaller than 3 cm in size and node negative, treatment with paclitaxel and trastuzumab is a less toxic option, with a 3-year disease-free survival rate of 98.5%.

Acute side effects of adjuvant chemotherapy include bone marrow suppression with anemia and neutropenia, alopecia, allergic reactions, neuropathy, nausea, and premature menopause and infertility in premenopausal women (see Effects of Cancer Therapy and Survivorship). Women of childbearing age who wish to preserve fertility should meet with a fertility specialist before chemotherapy. Serious long-term toxicities include cardiomyopathy, neuropathy, myelodysplasia, and acute myelocytic leukemia. The risk of cardiomyopathy after four cycles of an anthracycline is 1.5%. The risk of acute leukemia after regimens containing an anthracycline or cyclophosphamide is 0.5%.

For women of advanced age with higher-risk early breast cancer, it is important to consider estimated life expectancy, functional status, and medical comorbidities before administering adjuvant chemotherapy. There is a higher risk of cardiotoxicity in older women.

**KEY POINTS**

- Patients with hormone receptor–positive tumors, zero to three positive axillary lymph nodes, and low-risk scores on the 21-gene recurrence assay have a favorable prognosis with antiestrogen therapy alone and do not benefit from the addition of chemotherapy.
- Adjuvant chemotherapy is most appropriate for patients with triple-negative tumors greater than 5 mm in size, skin involvement, or positive axillary lymph nodes.

HVC
- For women of advanced age with higher-risk early stage breast cancer, consider life expectancy, functional status, and medical comorbidities before administering adjuvant chemotherapy.

## Locally Advanced and Inflammatory Breast Cancer

Locally advanced breast cancer includes a subset of clinical stage IIB cancers (T3N0M0), as well as stages IIIA to IIIC cancers. These cancers have high-risk characteristics such as skin involvement, chest wall involvement, extensive lymph node involvement, or inflammatory changes.

Inflammatory breast cancer is a type of locally advanced breast cancer that presents with swelling, thickening, and erythema of the skin overlying the breast, classically with a peau d'orange (orange peel) appearance (**Figure 20**). Patients often present with breast enlargement or swelling developed during a few weeks or months and may have been treated for presumed mastitis. It is important to consider that inflammatory breast cancer may be the underlying cause in patients who do not respond to antibiotics for an apparent mastitis. A palpable breast mass may be present. The skin changes are due to the obstruction of dermal lymphatic vessels by cancer cells,

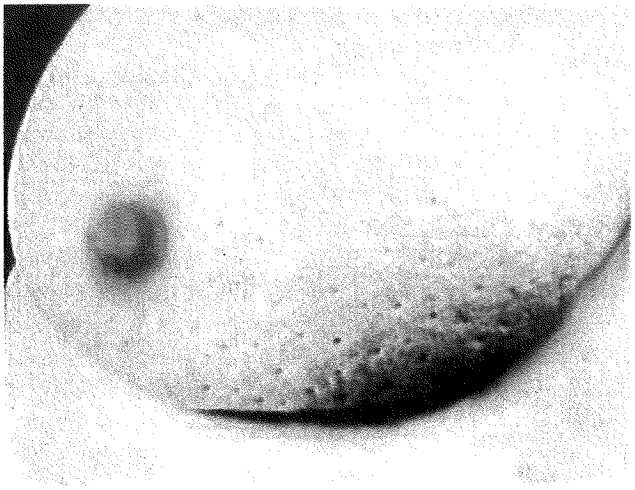

**FIGURE 20.** Inflammatory breast cancer often has a characteristic "p'eau d'orange" (orange peel) appearance of the skin, due to tumor emboli in the dermal lymphatics. Erythema is often present as well.

although demonstrating dermal lymphatic invasion on biopsy is not necessary for the diagnosis. One third of patients have distant metastases at diagnosis, and nearly all have lymph node involvement. For this reason, these patients should have routine CT and bone scan imaging, even in the absence of symptoms of metastatic disease.

Locally advanced cancers are usually treated initially with neoadjuvant chemotherapy, followed by surgery, and then radiation. In some situations, neoadjuvant antiestrogen therapy can be used instead of chemotherapy, although this is typically limited to postmenopausal women who are not candidates for chemotherapy. Tumors with skin involvement or inflammatory cancers require mastectomy, but in other cases, neoadjuvant therapy will often decrease the size of the primary breast cancer to allow for breast-conserving lumpectomy. All patients should have an axillary dissection at the time of mastectomy or lumpectomy and should receive radiation therapy afterward. The amount of residual cancer after neoadjuvant chemotherapy has prognostic significance, particularly in triple-negative or hormone-negative, *HER2*-positive cancers. Patients with complete pathologic responses have the lowest risk of recurrence.

Patients with hormone receptor–positive cancers should receive at least 5 years and ideally 10 years of antiestrogen therapy. Patients with *HER2*-positive cancers should complete one year of trastuzumab therapy.

**KEY POINTS**

- Inflammatory breast cancer, characterized by swelling, thickening, and erythema of the skin overlying the breast, classically with a peau d'orange (orange peel) appearance, may be mistaken for infectious mastitis and delay evaluation and treatment of the underlying malignancy.
- Locally advanced cancers are usually treated with neoadjuvant chemotherapy, surgery, and radiation.

## Breast Cancer Follow-up and Survivorship

In 2016, there were more than 2.8 million women alive in the United States with a previous or current diagnosis of breast cancer. Once patients with nonmetastatic breast cancer complete surgery, radiation, and chemotherapy, they are monitored for local recurrence, distant recurrence, second primary cancers, and physical and psychosocial long-term effects of breast cancer and treatment. Patients with hormone receptor–positive breast cancer remain on antiestrogen treatment for at least 5 years and up to 10 years and require management of menopausal symptoms and other toxicities during that time. Guidelines recommend that patients be evaluated for a detailed cancer-related history and physical examination every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then annually.

Patients should have annual mammograms of remaining breast tissue. Screening breast MRIs are needed only if patients meet criteria for screening MRIs (see Chemoprevention and other Risk Reduction Strategies). Patients should not have routine blood tests at follow-up visits or other routine imaging studies as these are not helpful for diagnosing recurrences earlier. Laboratory and imaging studies other than breast imaging should be guided by a patient's symptoms or findings on examination that raise concern for recurrence.

Patients should be evaluated at each visit for changes in family history of cancers and referred for genetic counseling as appropriate. Patients on tamoxifen should have annual gynecologic examinations and be evaluated by a gynecologist for any abnormal vaginal bleeding. Patients on aromatase inhibitors should have bone density studies every 2 years and should receive treatment of osteoporosis, ideally with a bisphosphonate, if their T score is -2.5 or lower.

For patients with breast asymmetry, reconstruction options can be offered and are often fully covered by insurance. Patients should receive physical therapy for lymphedema or decreased arm mobility after surgery or radiation to axillary nodes. Menopausal symptoms should be managed with nonhormonal options, such as gabapentin for nocturnal hot flushes. Depression, anxiety, and sexual dysfunction are not uncommon in this population and should be appropriately assessed and managed. For patients taking tamoxifen, it is important to avoid medications with strong CYP2D6 inhibition, such as bupropion or fluoxetine, as these may decrease tamoxifen activation.

**KEY POINTS**

- After completion of treatment, follow-up monitoring should be every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then annually, with annual mammography for all survivors, and breast MRI for those at high risk of recurrence.

*(Continued)*

**KEY POINTS *(continued)***

- Patients with hormone receptor–positive breast cancer remain on antiestrogen treatment for at least 5 years and up to 10 years.
- Surveillance blood tests and other imaging tests for breast cancer should not be routinely performed and should be guided by a patient's symptoms or findings on examination that raise concern for recurrence. **HVC**
- Breast cancer survivors should be monitored and treated for the side effects of treatment.

## Metastatic Breast Cancer

Approximately 5% of patients with breast cancer present with initial stage IV disease and up to 30% with early-stage disease develop metastases. Metastatic breast cancer is not curable, but systemic therapy can improve survival, relieve symptoms, and maintain quality of life. Treatment and prognosis are related to whether visceral metastases are present, the number of sites involved, the interval between initial diagnosis and metastases (intervals of less than 2 years have a poorer prognosis), the patient's performance status, and tumor biology. The median overall survival for patients with metastatic breast cancer is 2 years but is longer for women with hormone receptor–positive cancer or *HER2*-positive cancer some of whom may have prolonged survival, in part related to more treatment options.

It is important to biopsy a site of initial metastasis both to confirm the diagnosis and to assess hormone receptor and *HER2* status. Because there may be discordance in the receptors in the metastatic lesion compared to the primary breast cancer in 10% to 15% of patients, the selection of systemic therapy might be altered.

In postmenopausal women with hormone receptor–positive, *HER2*-negative breast cancer, initial treatment is usually hormonal therapy; aromatase inhibitors are superior to other agents as first-line treatment. Fulvestrant, which inhibits estrogen receptor function, and tamoxifen are other options. Premenopausal women can receive tamoxifen, ovarian suppression alone, or ovarian suppression combined with either tamoxifen or aromatase inhibitors as initial treatment. Patients who respond are usually treated with sequential hormonal therapies. In patients with rapidly progressive disease or extensive visceral metastases, initial chemotherapy may be used because of its higher response rate.

Combining targeted agents such as the CDK4/6 inhibitor palbociclib or the mammalian target of rapamycin (mTOR) inhibitor everolimus with antiestrogens improves the response rate and duration of response to hormonal therapy. In patients who develop metastatic breast cancer during adjuvant therapy with an aromatase inhibitor, palbociclib plus fulvestrant is usually the recommended first-line therapy. For women who develop metastatic breast cancer after having completed adjuvant therapy with an aromatase inhibitor, palbociclib plus an aromatase inhibitor is usually given as the initial systemic therapy.

In *HER2*-positive advanced breast cancer, treatment should include *HER2*-directed therapy such as trastuzumab given with either chemotherapy or antiestrogen therapy, depending on the hormone receptor status of the cancer and the sites of disease. First-line treatment with dual *HER2*-targeted therapy with trastuzumab and pertuzumab added to the taxane docetaxel has been shown to improve overall survival, with median overall survival of 56 months in a phase 3 clinical trial. Ado-trastuzumab emtansine is an innovative antibody-drug conjugate that links trastuzumab to the microtubule inhibitor emtansine, delivering chemotherapy more specifically to *HER2*-overexpressing cells.

Triple-negative breast cancers have a higher relapse rate than hormone receptor–positive cancers; recur earlier, with a peak at 3 years after diagnosis and a very low risk of relapse after 5 years; and have a higher risk of locoregional recurrence and brain and lung metastases. Advanced triple-negative breast cancer is treated with chemotherapy. These cancers may be particularly responsive to platinum agents, particularly in *BRCA1* mutation carriers.

Chemotherapy agents used in patients with advanced breast cancer include taxanes, capecitabine, eribulin, gemcitabine, ixabepilone, and liposomal doxorubicin. Single-agent chemotherapy is usually given, with combination chemotherapy reserved for patients with extensive visceral metastases where a higher response rate is important.

In patients with *BRCA1* or *BRCA2* mutations, poly (ADP-ribose) polymerase (PARP) inhibitors have shown encouraging results. These agents cause "synthetic lethality" by producing an increase in double-strand DNA breaks that would usually be repaired by the *BRCA* pathway.

For all subtypes of metastatic breast cancer, bone-modifying agents such as zoledronic acid or denosumab are recommended for patients with bone metastases to decrease skeletal-related events (fractures, pain, and need for radiation). Palliative radiation can be used to treat painful bone metastases as well as other sites of tumor-related pain or obstruction. Triple-negative breast cancers and *HER2*-positive cancers have a higher risk of brain metastases, which are treated with whole brain radiation, stereotactic radiation, or surgery. Palliative care teams can be helpful for managing symptoms of pain, nausea, anorexia, and fatigue. Throughout the course of advanced breast cancer, discussions with patients about their goals of care should take place, focusing on their values and preferences as they are treated for an incurable illness.

**KEY POINTS**

- Metastatic breast cancer is not curable, but it can be treated with systemic therapy with the goals of improved survival, palliation of symptoms, and maintaining quality of life.
- The site of initial metastasis should be biopsied to confirm the diagnosis and to assess hormone receptor and *HER2* status, which can be discordant from the primary breast cancer.

# Ovarian Cancer

## Epidemiology and Risk Factors

Ovarian cancer, the leading cause of gynecologic cancer deaths, will be newly diagnosed in approximately 22,000 women in 2016 in the United States, with an estimated 14,000 deaths. This chapter will focus on the 95% of ovarian cancers that are of epithelial origin.

Risk factors for ovarian epithelial cancer include inheritance of ovarian cancer susceptibility genes, increasing age, infertility, nulliparity, endometriosis, polycystic ovary syndrome, use of an intrauterine device, and cigarette smoking.

The most common ovarian cancer susceptibility genes are *BRCA1*, *BRCA2*, and the mismatch repair (MMR) genes associated with hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome. Approximately 10% to 15% of women with ovarian cancer carry a mutation in one of these genes, and all women with epithelial ovarian cancer should be offered genetic testing for *BRCA1* and *BRCA2* mutations. In patients with a personal or family history of other HNPCC-related cancers (colorectal, small bowel or endometrial cancers or transitional cell cancers of the renal pelvis or ureter), HNPCC testing is recommended as well. There are different criteria for HNPCC genetic testing, including criteria and prediction models based on the number of affected relatives and age of onset, as well as tumor-based strategies often used in colorectal and endometrial cancers involving testing for microsatellite instability (MSI) or immunohistochemistry staining for mismatch repair proteins. The cumulative lifetime risk of ovarian cancer is 1.4% in patients without a susceptibility gene, 45% in *BRCA1* carriers, 12% in *BRCA2* carriers, and 3% to 13.5% in MMR gene mutation carriers.

**KEY POINT**

- Genetic testing for *BRCA1*, *BRCA2*, and mismatch repair gene mutations is recommended for all women with ovarian cancer.

## Screening and Risk-Reduction Strategies

Ovarian cancer screening with transvaginal ultrasonography or serum CA-125 testing is not effective and is not recommended for patients of average, or even high, risk.

For women with *BRCA1*, *BRCA2*, or MMR gene mutations, prophylactic bilateral salpingo-oophorectomy (BSO) is recommended after completion of childbearing. Prophylactic BSO is recommended by age 35 to 40 years for *BRCA1* carriers and by age 45 years for *BRCA2* carriers. For *BRCA1* or *BRCA2* carriers, prophylactic BSO decreases the risk of ovarian, fallopian tube, and primary peritoneal cancers by greater than 80% and decreases all-cause mortality to age 70 years by 77%. Recommendations for genetic testing for breast and ovarian cancer syndromes are discussed in Breast Cancer. In women