Breast cancer in men

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INTRODUCTION

Breast cancer in men is rare [1,2]. Although it shares many similarities with cancer of the breast in women, there are also important differences [3,4]. This topic will review issues specific to men with breast cancer. An overview of breast cancer in women and topics related to the treatment of breast cancer are discussed in detail separately.

- (See "Clinical features, diagnosis, and staging of newly diagnosed breast cancer".)
- (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)
- (See "General principles of neoadjuvant management of breast cancer".)
- (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer".)
- (See "Adjuvant systemic therapy for HER2-positive breast cancer".)
- (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer".)
- (See "Overview of the approach to metastatic breast cancer".)

EPIDEMIOLOGY AND RISK FACTORS

In the United States and United Kingdom, male breast cancer represents between 0.5 and 1 percent of all breast cancers diagnosed each year [1,5]. In the United States, breast cancer in men accounts for less than 0.5 percent of all cancer diagnoses in men [5]. By contrast, in Tanzania and areas of central Africa, male breast cancer accounts for up to 6 percent of all breast cancers [6]. Higher rates of male breast cancer in central and eastern Africa may be related to endemic hepatic infectious diseases that lead to hyperestrogenism [7,8].

As with women, the incidence of breast cancer in men rises with age, and men tend to be approximately 5 to 10 years older than women at the time of diagnosis [4,9-14]. The annual incidence of breast cancer in men appears to be rising; one report suggests that incidence has increased 26 percent over the past 25 years [15].

Breast cancers in men appear to share some of the risk factors associated with postmenopausal breast cancer in women [4]. Systematic reviews of the literature have summarized the factors associated with breast cancer in men, and these are reviewed below [16,17]. Despite these reported associations, the vast majority of men with breast cancer have no identifiable risk factors.

Genetics and family history — Men with breast cancer should be referred for genetic counseling and testing, as discussed elsewhere. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes", section on 'Concerning personal or family history'.)

As with breast cancer in women, a family history of breast cancer in a first-degree relative is associated with an increased risk of breast cancer among men. Approximately 15 to 20 percent of men with breast cancer have a family history of the disease compared with only 7 percent of the general male population [11]. As is the case in women, two breast/ovarian cancer genes, *BRCA1* and *BRCA2*, which are inherited in an autosomal-dominant pattern, give rise to the majority of known cases of hereditary breast cancer. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes" and "Overview of hereditary breast and ovarian cancer syndromes".)

The risk for male breast cancer appears to be higher with inherited *BRCA2* rather than *BRCA1* mutations [18-23]. Men who inherit germline *BRCA2* mutations have an estimated 6 percent lifetime absolute risk of breast cancer; this represents a 100-fold higher risk than in the general male population [23,24]. (See "Risk factors for prostate cancer", section on 'Family history and genetic factors' and "Cancer risks in BRCA1/2 carriers", section on 'Male breast cancer'.)

The incidence of *BRCA* mutations varies based upon ethnicity and strength of family history (table 1) [20,25-35]. Of men with breast cancer, up to 14 percent have a deleterious *BRCA2*

mutation; *BRCA1* mutations occur very rarely, except in individuals of Ashkenazi Jewish ethnicity. One study found that 4.5 percent of Ashkenazi Jewish men presenting with breast cancer have a *BRCA1* mutation [25,35]. Because of this, all men diagnosed with breast cancer should be referred for genetic counseling and *BRCA* testing. Cancer surveillance of men with a *BRCA* mutation is discussed separately. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes" and "Cancer risks in BRCA1/2 carriers".)

Genes other than *BRCA* may be involved in predisposition to breast cancer in men: mutations in the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene (Cowden syndrome), tumor protein p53 (*TP53*; Li-Fraumeni syndrome), partner and localizer of *BRCA2* (*PALB2*), and mismatch repair genes (Lynch syndrome) have all been associated with an increased risk of breast cancer in men [36-38]. However, while such findings may raise the relative risk of breast cancer in men in whom the mutation was identified (compared with men without such mutation), the absolute risk of male breast cancer is still quite low. Therefore, we would not advise screening mammography or prophylactic mastectomy in affected male individuals. (See "PTEN hamartoma tumor syndromes, including Cowden syndrome" and "Li-Fraumeni syndrome" and "Overview of hereditary breast and ovarian cancer syndromes", section on 'PALB2' and "Overview of hereditary breast and ovarian cancer syndromes", section on 'MSH1, MLH1, MSH6, PMS2, and EPCAM (Lynch syndrome)'.)

Alterations of the estrogen to androgen ratio — Excessive estrogen stimulation may be due to hormonal therapies (eg, estrogen-containing compounds or testosterone), hepatic dysfunction, obesity, marijuana use, thyroid disease, or an inherited condition, such as Klinefelter syndrome.

Klinefelter syndrome is a rare condition resulting from the inheritance of an additional X chromosome [9,39-41]. Klinefelter syndrome consists of atrophic testes, gynecomastia, high serum concentrations of gonadotropins (follicle-stimulating hormone, luteinizing hormone), and low serum testosterone levels; the net effect is a high ratio of estrogen to testosterone. (See "Causes of primary hypogonadism in males".)

Few carefully conducted epidemiologic studies have been undertaken focusing on this association due to the rarity of both Klinefelter syndrome and male breast cancer. The largest cohort study of 3518 men who were cytogenetically diagnosed with Klinefelter syndrome found 19- and 58-fold increases in incidence of and mortality from breast cancer, respectively, compared with the general population [42]. Additional studies are needed to clarify which men with Klinefelter syndrome are at a high risk of developing breast cancer and to define the contribution of possible predisposing factors, including altered endogenous hormones.

The role of breast cancer screening in men with Klinefelter syndrome is unclear. Although routine mammography is not advocated for all affected men, the importance of patient education, self-examination, and regular clinician examinations is stressed [42]. (See "Sex chromosome abnormalities", section on '47,XXY Klinefelter syndrome'.)

Primary testicular conditions — Testicular conditions associated with an increased risk of breast cancer in men include orchitis, undescended testes (cryptorchidism), and testicular injury [9,13,43]. While speculative, it may be that these conditions may be associated with lower androgen production, resulting in a higher than normal estrogen to androgen ratio.

Prior cancer treatments — Prior chest radiation is a risk factor for breast cancer in females, and one study suggests that it is also a risk factor in males [44]. In a cohort study in 3077 male survivors with Hodgkin lymphoma (HL) treated at age ≤51 years, after a 20-year median follow-up, male HL survivors had a 23-fold increase in breast cancer compared with males in the general population, with a 40-year cumulative breast cancer incidence of 0.7 percent. Treatment with chest radiotherapy was associated with increased incidence of male breast cancer irrespective of whether alkylating chemotherapy was administered.

PRESENTATION

Clinical characteristics — Male breast cancer has typically been diagnosed at a more advanced stage than female breast cancer, most likely due to a lack of awareness that men can develop breast cancer and absence of routine screening exams [45]. Nevertheless, one analysis suggests that the majority of men are diagnosed with early-stage disease (95 percent) and only 3.8 percent present with de novo metastatic disease [46,47].

Most men with breast cancer generally present with a painless, firm mass that is usually subareolar, with nipple involvement in 40 to 50 percent of cases [11,48]. The left breast is involved slightly more often than the right, and less than 1 percent of cases are bilateral. There may be associated skin changes, including nipple retraction, ulceration, or fixation of the mass to the skin or underlying tissues. Axillary adenopathy is typically palpable in advanced cases.

Pathologic characteristics — Although most histologic subtypes of breast cancer seen in women are also present in men, men with breast cancer are rarely diagnosed with lobular carcinomas [49].

Approximately 85 to 90 percent of breast cancers in men are invasive ductal carcinomas [15,46]. By contrast, lobular cancers accounted for 1.5 percent of cases in one series of 2000 men [15] and only 0.5 percent in another series [47], while they account for up to 15 percent of cases in

women [50]. The lack of a lobular histologic subtype is due to lack of acini and lobules in the normal male breast, although these can be induced in the context of estrogenic stimulation. (See "Pathology of breast cancer".)

In addition to differences in the invasive carcinoma, there are differences in the incidence and clinical characteristics of ductal carcinoma in situ (DCIS) (see "Breast ductal carcinoma in situ: Epidemiology, clinical manifestations, and diagnosis" and "Paget disease of the breast (PDB)" and "Inflammatory breast cancer: Clinical features and treatment"):

- DCIS accounts for a significantly higher proportion of breast cancers in women compared with men (approximately 20 versus 7 to 11 percent, respectively) [15,51,52].
- DCIS in men tends to occur at a later age, presents more frequently in an intraductal papillary form, and is more often low grade [52,53].

Paget disease and inflammatory breast cancer have rarely been described in men [54-57].

Breast cancer subtype — As in postmenopausal women, the most common subtype of breast cancer in men is hormone receptor positive [11,14,15,58].

A worldwide consortium effort retrospectively evaluated the characteristics of almost 1500 male breast cancer patients for which tissue was available and found that 99 percent were estrogen receptor positive, 81 percent were progesterone receptor positive, and 97 percent were androgen receptor positive [46]. Immunohistochemistry evaluations from this study found that 42 percent were luminal A-like, 42 percent were luminal B-like, 8.7 percent were human epidermal growth factor receptor 2 (HER2) positive, and 0.3 percent were triple-negative.

There are differences in the molecular characteristics of breast cancer associated with both age and ethnicity, although these do not appear to influence survival outcomes. This was shown in a registry study involving 829 men with primary breast cancer (71, 11, and 7 percent who were non-Hispanic White, Hispanic, or non-Hispanic Black, respectively) [58]. Major findings were:

- Hormone receptor-positive/HER2-negative, HER2-positive, and triple-negative breast cancers were identified in 82, 15, and 4 percent of cases, respectively.
- Younger patients were more likely to be diagnosed with a HER2-positive tumor.
- Non-Hispanic Black men were more likely to have triple-negative breast cancer compared with non-Hispanic White or Hispanic men (9 versus 3 and 6 percent, respectively).

DIAGNOSTIC EVALUATION AND STAGING

The approach to the male patient who presents with a suspicious breast mass is similar to that of women and includes mammography and biopsy. (See "Clinical manifestations, differential diagnosis, and clinical evaluation of a palpable breast mass" and "Diagnostic evaluation of suspected breast cancer" and "Clinical features, diagnosis, and staging of newly diagnosed breast cancer".)

Mammography — The mammogram is abnormal in 80 to 90 percent of men with breast cancer and can usually distinguish between malignancy and gynecomastia [59-61]. In one study, the reported sensitivity and specificity rates of mammography were 92 and 90 percent, respectively [59]. Radiographic features suggestive of malignancy include eccentricity to the nipple, spiculated margins, and microcalcifications. By contrast, gynecomastia typically appears as a round or triangular area of increased density positioned symmetrically in the retroareolar region. In rare cases, concurrent gynecomastia can mask a malignant lesion [60,61]. (See "Breast imaging for cancer screening: Mammography and ultrasonography".)

Biopsy — Any suspicious mass requires biopsy to confirm the diagnosis and to assay for estrogen receptor and progesterone receptor content as well as human epidermal growth factor receptor 2 status. Although fine needle aspiration (FNA) cytology can provide adequate diagnostic material in many cases, avoiding open or surgical biopsy [62-64], up to one-fourth of samples are insufficient for diagnosis [62]. Compared with FNA, core needle biopsy offers a more definitive histologic diagnosis, avoids inadequate samples, and usually distinguishes between invasive versus in situ cancer. If inadequate tissue is obtained, an open biopsy should be performed. (See "Breast biopsy".)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a breast mass in a man includes [65]:

- **Gynecomastia** – Gynecomastia typically presents as bilateral, symmetric breast enlargement with poorly defined borders. Unlike breast cancer, there is usually no evidence of fixation to the underlying chest wall, and it is not associated with skin changes or axillary lymphadenopathy. (See "Epidemiology, pathophysiology, and causes of gynecomastia".)

- **Pseudogynecomastia** – In contrast to gynecomastia, pseudogynecomastia represents an increase in breast fat rather than glandular tissue, which can generally be appreciated on

clinical exam. (See "Clinical features, diagnosis, and evaluation of gynecomastia in adults", section on 'Pseudogynecomastia'.)

- **Infections** – This includes breast abscess or other skin infections involving the chest wall. Typically, it presents as a localized and painful inflammation, often associated with systemic symptoms (eg, fever and malaise). (See "Primary breast abscess".)

- **Lipoma** – These are ovoid-shaped breast masses comprised of fat. Lipomas are the most common benign soft-tissue neoplasm and rarely cause symptoms. (See "Overview of benign lesions of the skin", section on 'Lipoma'.)

- **Pseudoangiomatous stromal hyperplasia** – Pseudoangiomatous stromal hyperplasia (PASH) is characterized as a benign, stromal proliferation. It presents as either a mass or thickening and on imaging is characterized as a solid, well-defined, noncalcified mass. (See "Overview of benign breast diseases", section on 'Pseudoangiomatous stromal hyperplasia'.)

- **Granular cell tumor** – Granular cell tumors are usually benign, submucosal tumors that arise from Schwann cells. They most commonly occur in the oropharynx, skin, subcutaneous tissue, or breasts. The clinical presentation and imaging evaluation of these tumors can mirror invasive breast cancer. Therefore, diagnosis often requires tissue analysis, which is obtained at core needle biopsy. (See "Benign lesions of the esophagus", section on 'Granular cell tumors'.)

- **Fibromatosis** – Fibromatoses (or desmoid tumors) are locally aggressive tumors with no known potential for metastasis or dedifferentiation. The diagnosis requires histologic examination of a biopsy specimen. (See "Desmoid tumors: Epidemiology, molecular pathogenesis, clinical presentation, and diagnosis".)

- **Metastatic disease** – Although rare, metastases from another primary cancer can present as a breast mass. A biopsy is necessary to rule out a primary versus metastatic lesion.

Other rare tumors that occur in men include schwannoma, myofibroblastoma, and hemangiomas. In addition, other benign breast lesions that are more commonly seen in women should be considered. These are discussed in more detail separately. (See "Overview of benign breast diseases".)

STAGING WORKUP

The diagnostic evaluation and staging system used for breast cancers in men are the same as for women with breast cancer. (See "Clinical features, diagnosis, and staging of newly diagnosed breast cancer".)

Breast cancer is classified according to the eighth edition Tumor, Node, Metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) and endorsed by the Union for International Cancer Control (UICC) [66]. (See "Tumor, node, metastasis (TNM) staging classification for breast cancer".)

As in women, stage, tumor size, and axillary lymph node status are the most important factors influencing outcome in breast cancers in men. (See 'Prognosis' below.)

NON-METASTATIC DISEASE

Differences compared with the approach in women — In general, the approach to early breast cancer in men mirrors that for women. However, there are noteworthy exceptions. In particular:

- Men with early-stage breast cancer typically proceed with simple mastectomy rather than breast-conserving therapy because of their small volume of breast tissue. However, decision-making between the two options should proceed in an analogous fashion as for women. Specifically, men who have sufficient breast tissue to permit breast conservation may proceed with this strategy, barring any contraindications, followed by adjuvant radiation. (See 'Surgical treatment' below and "Breast-conserving therapy", section on 'Absolute contraindications for BCT' and "Breast-conserving therapy", section on 'Relative contraindications for BCT'.)

- For those with hormone receptor-positive disease, we suggest adjuvant tamoxifen rather than an aromatase inhibitor (AI), given insufficient evidence to support AI monotherapy for men [67], and fewer side effects compared with AI with gonadotropin-releasing hormone agonists (GnRHa). For those with contraindications to tamoxifen (eg, hypercoagulable state), an AI with GnRHa may be administered. (See 'Endocrine therapy' below.)

Surgical treatment — The surgical approach to treatment of breast cancer in men is similar to that of women and depends on the extent of disease at presentation. This is discussed below.

Early-stage disease — Although there have been no randomized trials, most men with early-stage disease (T1 to T2, N0 to N1) undergo a simple mastectomy rather than a mastectomy with

pectoral muscle removal. For men who want to avoid mastectomy, limited data suggest that breast-conserving surgery is a reasonable alternative, provided there is enough breast tissue to ensure that adequate surgical margins can be obtained.

Data from retrospective studies comparing modified radical mastectomy with its radical counterpart (which included taking the muscle) consistently show the procedures result in an equivalent local recurrence rate and survival outcomes [12,68-70]. Additional support for simple mastectomy can also be drawn from studies in women that also demonstrated therapeutic equivalence of these two surgical procedures. Nipple- and skin-sparing mastectomy techniques have emerged as valuable tools in female breast cancer, but these have not been explored in male breast cancer, likely due to the constraints of tumor location and nipple involvement. However, the psychosocial distress described below suggests that greater attention to the cosmetic outcomes for men should not be ignored. Indeed, breast reconstruction has been performed in men seemingly for exactly this indication [71]. (See "Mastectomy".)

Although most men have a small volume of breast tissue, some have sufficient breast tissue to permit breast conservation therapy [72]. In a review of data from the Surveillance, Epidemiology, and End Results Program (SEER), 1541 cases of male breast cancer were identified, and almost 20 percent were treated with breast conservation [73]. While this study did not report outcomes, a subsequent SEER database analysis suggested that breast-conserving surgery is an acceptable alternative to mastectomy in some male patients (table 2) [74]. Furthermore, one retrospective study of seven men treated with breast-conserving therapy followed for a median of 67 months reported that none experienced a recurrence of disease [72]. (See "Breast-conserving therapy".)

For most men who opt to proceed with breast-conserving surgery, adjuvant radiation therapy (RT) is thought to be essential. This is based on consistent results showing that adjuvant RT after breast-conserving surgery for women confers a survival advantage. However, extrapolating from data in older women with clinically node-negative, hormone receptor-positive breast cancer treated with adjuvant endocrine therapy, we offer men in the analogous clinical situation the option of omitting RT. Data in female breast cancer suggest that this approach yields similar overall survival and rates of distant metastases, although local recurrences are more frequent. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer", section on 'Possible omission of RT for select ER-positive, HER2-negative cancers'.)

Management of the regional nodes — Assessment of the regional nodes is an important aspect of surgical breast cancer management, as it is in women. We agree with an expert panel convened by the American Society of Clinical Oncology (ASCO) and feel that sentinel lymph node

biopsy (SLNB) for men with clinically node-negative breast cancer is "acceptable" [75], and we suggest this approach over full axillary dissection in this setting.

Although the role of SLNB is established in women with clinically node-negative breast cancer, its proven role in men is less robust due to the rarity of male breast cancer. Although large studies establishing the sensitivity and specificity of SLNB in men with clinically node-negative breast cancer have not been carried out, smaller reports suggest it is feasible and accurate [76,77]. For example, as reported in a retrospective case review of 32 patients, 19 percent had an involved sentinel node, and there were no axillary recurrences at a median follow-up of 30 months [76]. SLNB in men is becoming more widely adopted. (See "Overview of sentinel lymph node biopsy in breast cancer".)

Men with a negative SLNB do not require further surgery. However, the role of a complete axillary node dissection for men with a positive SLNB is controversial. Given the lack of data to inform this issue, the approach to patients with a positive SLNB mirrors that for women. (See "Overview of sentinel lymph node biopsy in breast cancer".)

Locally advanced disease — Men who present with locally advanced disease (T3N0 or stage III disease) or inflammatory breast cancer are treated similarly to women who present in this way. We offer these patients neoadjuvant chemotherapy because randomized trials of neoadjuvant chemotherapy followed by surgery versus primary surgery followed by adjuvant chemotherapy, which have been predominantly performed in women, demonstrate that neoadjuvant chemotherapy is associated with high rates of clinical response and a higher likelihood for allowing cosmetically acceptable surgery without compromising survival outcomes. (See "General principles of neoadjuvant management of breast cancer".)

Additionally, patients with earlier-stage disease may be appropriate candidates for neoadjuvant therapy if they have triple-negative breast cancers or human epidermal growth factor receptor 2 (HER2)-positive tumors, since these patients generally receive chemotherapy at some point in their treatment course anyway, and these subtypes are associated with a high likelihood of response. (See "General principles of neoadjuvant management of breast cancer", section on 'Patient selection'.)

Following completion of chemotherapy, we proceed with a mastectomy in most patients, provided they have a sufficient response to make surgery feasible. For patients who do not have a sufficient response, an alternative regimen should be administered. (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer", section on 'Locally advanced breast cancer' and "Inflammatory breast cancer: Clinical features and treatment" and

"General principles of neoadjuvant management of breast cancer", section on 'Poor response to or progression on neoadjuvant therapy'.)

Adjuvant therapy — As in women, adjuvant treatments may include RT, endocrine therapy, chemotherapy, and anti-HER2 therapy. These are discussed below.

Radiation therapy — In the absence of high-quality data, the indications for RT for men with breast cancer mirror those for women. These include patients (see "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer"):

- Who underwent breast-conserving surgery. Such patients are typically treated with whole-breast radiation and may also receive a boost to the tumor bed and, if axillary nodes are involved, axillary radiation.
- Who underwent a mastectomy for T4 or T3 disease (especially if associated with positive surgical margins or pathologic node involvement).
- Who had four or more involved lymph nodes.
- In addition to the above indications, we also suggest postmastectomy radiation for men with one to three involved nodes, although this approach is the subject of some debate, both in men and women. This recommendation is extrapolated from the data in women with the same extent of nodal disease, where trials indicate that RT reduces the risk of recurrence and potentially improves disease-specific survival. However, as in women, the modest locoregional and potential survival benefit from treatment must be weighed against the risk of treatment-related toxicities. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer".)

There are limited data regarding the indications for postmastectomy RT in men treated for breast cancer. In retrospective series, postmastectomy RT appears to reduce locoregional recurrence in men with breast cancer, but the influence on survival is not clear [12,54,78-81]. In the absence of high-quality data, these recommendations are extrapolated from the management of women with breast cancer.

Systemic therapy

Chemotherapy — Prospective trials evaluating the benefits of adjuvant chemotherapy specifically for men with newly diagnosed breast cancer have not been performed. Therefore, the same guidelines for adjuvant systemic therapy in women with early-stage breast cancer are generally followed for men who have breast cancer [82].

- (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer".)

- (See "Adjuvant systemic therapy for HER2-positive breast cancer".)

Extrapolating from data in women, we use the 21-gene Recurrence Score (RS) to guide decisions regarding adjuvant chemotherapy for men with hormone receptor-positive, HER2-negative breast cancer and either no or limited lymph node involvement. (See "Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer", section on 'Recurrence Score'.)

Limited data in men suggest the RS may identify men with hormone receptor-positive breast cancer at sufficiently low risk for recurrence that adjuvant chemotherapy is unlikely to be of benefit. In a retrospective study of 38 male breast cancer patients with estrogen receptor (ER)-positive/HER2-negative breast cancer, all of whom were treated with total mastectomy (and one of whom received adjuvant radiotherapy), and 90 percent of whom received adjuvant endocrine therapy, RS was low (≤17) in 26 cases (68 percent), intermediate (18 to 30) in 9 cases (24 percent), and high (≥31) in 3 cases (13 percent) [83]. Chemotherapy was administered to no patients with low RS, 3 patients (67 percent) with intermediate RS, and 1 patient (33 percent) with a high RS. In the entire group, there was 1 recurrence, which occurred in a patient with intermediate RS and lymph node-positive disease who had received adjuvant endocrine therapy and chemotherapy.

Toxicities of standard chemotherapy regimens for breast cancer are also poorly studied in men, so prophylactic and treatment strategies (eg, for nausea and neutropenia) are extrapolated from women. Cardiac toxicity rates during and after anthracycline and HER2-directed therapies are particularly deserving of additional research in men.

Endocrine therapy — For men with hormone receptor-positive breast cancer, we recommend endocrine therapy following surgery rather than observation, given benefits observed in trials enrolling women with hormone receptor-positive breast cancer as well as retrospective evidence in male breast cancer. The data on endocrine therapy in women with newly diagnosed, hormone receptor-positive breast cancer are discussed separately. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer".)

Among the available agents, we prefer tamoxifen rather than an AI (in the absence of contraindications to tamoxifen [eg, hypercoagulable state]), consistent with guidelines from ASCO [84], although an AI with GnRHa is an acceptable alternative. Toxicities of treatment are discussed elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal

women with hormone receptor-positive breast cancer", section on 'Side effects' and "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Side effects'.)

Retrospective evidence suggests improvements in overall survival for men with hormone receptor-positive disease treated with adjuvant tamoxifen. For example, in a registry study including 392 male patients with hormone receptor-positive breast cancer (84 percent of whom had non-metastatic disease), adjuvant treatment with tamoxifen was associated with improved survival (hazard ratio [HR] 0.4, 95% CI 0.1-0.99) [85]. Similarly, in a retrospective study including 135 male patients with non-metastatic breast cancer, 115 of whom had ER-positive disease, and 38 of whom received adjuvant endocrine therapy, receipt of endocrine therapy was associated with improvement in overall survival (HR 0.45, 95% CI 0.25-0.84) [86]. Thirty-five of the 38 men receiving adjuvant endocrine therapy were treated with tamoxifen.

An explanation for the differential activity of AIs in men versus postmenopausal women is that testicular production of estrogen is not inhibited by an AI. Use of GnRHa may suppress this production and improve outcomes when used with AIs in men. The Male-GBG54 trial is a 50-patient prospective randomized phase II study evaluating tamoxifen with or without GnRHa versus an AI with GnRHa in male breast cancer patients [87]. In preliminary results, AI plus GnRHa therapy was associated with a 64 percent suppression in estradiol levels (compared with 35 percent with AI alone based on historical literature). Although there was no AI-alone arm in this study, it does provide some support for the use of GnRHa, if AI is going to be used in this setting.

On the basis of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial in women, which supported administration of 10 rather than 5 years of tamoxifen, men with higher-risk breast cancer based on tumor characteristics (eg, higher tumor grade, pathologic node involvement, and larger tumor size) and those who are tolerating treatment are appropriate candidates for extended tamoxifen treatment. For all others, a decision on whether to continue treatment beyond five years should be based on an individual consideration of their side effects (eg, hot flashes, sexual dysfunction). The results of the ATLAS trial are discussed separately. (See 'Breast cancer subtype' above.)

Despite the potential survival benefits of tamoxifen, several studies indicate that a large proportion of men discontinue treatment before five years, which may be associated with worse outcomes [88,89]. In a study of 116 men, persistence rates fell from 65 percent at year 1 to 18 percent by year 5 [89]. Compared with men who were persistent with tamoxifen, low persistence was associated with a significantly lower ten-year rate of disease-free survival (DFS;

42 versus 73 percent, respectively; p = 0.007) and overall survival (50 versus 80 percent; p = 0.008). Factors associated with low persistence included:

- Age ≤60 years (HR 1.10, 95% CI 1.01-1.21)
- Lack of social support (HR 2.45, 95% CI 1.32-4.55)
- Onset of adverse effects (HR 2.19, 95% CI 1.57-3.04), including fatigue (21 percent), anxiety (20 percent), sleep disorders (19 percent), decreased libido (11 percent), and weight gain (10 percent)

Based upon these results, interventions are needed to improve the persistence of men with breast cancer to complete the full treatment course of tamoxifen.

Targeted agents in those with high-risk disease — The adjuvant use of targeted agents such as inhibitors of cyclin-dependent kinase (CDK) 4/6 and poly(ADP-ribose) polymerase (PARP) in men with breast cancer follows the same principles as in women.

- Select patients with high-risk, node-positive, ER-positive, HER2-negative breast cancer are candidates for adjuvant treatment with the CDK 4/6 inhibitor abemaciclib. Patient selection is discussed elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Incorporation of targeted therapies for select patients'.)
- For select patients with breast cancer susceptibility gene 1/2 (*BRCA1/2*) mutations and high-risk early, HER2-negative breast cancer, adjuvant treatment with olaparib, an inhibitor of PARP, has been shown to improve disease-free survival outcomes. This is discussed in detail elsewhere. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'BRCA carriers with high-risk disease'.)

Bisphosphonates — Men with early-stage disease should not be treated with bone-modifying agents to prevent recurrence, but could still receive these agents to prevent or treat osteoporosis, according to guidelines from ASCO [84].

Although DFS benefits of bone-modifying agents have been observed in women, particularly in postmenopausal women receiving AIs, absolute improvements have been small and somewhat inconsistent, and trials have never been conducted in men. (See "Use of osteoclast inhibitors in early breast cancer".)

Prognosis — Studies have evaluated survival in male breast cancer patients [4,15,49,73,90-94]:

- In the worldwide consortium analysis of 1500 male breast cancer patients discussed above, at a median follow-up of 8.2 years, the five-year breast cancer-specific mortality improved steadily in five-year increments from 15.1 (1990 to 1995) to 7.6 percent (2006 to 2010) [46]. Additionally, for patients with luminal A-like breast cancer, the median overall survival was 9.5 compared with 8.8 years in those with luminal B-like/HER2-negative breast cancer and 10 years for those with luminal B-like/HER2-positive breast cancer.

- In an analysis from the SEER database of male breast cancer patients diagnosed between 2005 and 2009, male breast cancer patients experienced a worse prognosis compared with women, with a risk of death that was 41 percent higher than females during the same period [95]. Similarly, the 5- and 10-year survival rates of male patients (85 and 73 percent, respectively) were lower than female patients (90 and 85 percent, respectively). These findings were similar across race and stage subgroups. Other analyses have also suggested worsened breast cancer-specific and overall survival in men compared with women with breast cancer [96,97]. As in women, tumor size and the presence as well as number of involved nodes are the most important prognostic factors for breast cancers in men [12,15,54,91,98-104].

- In a cohort study including 2836 men with stage I to III hormone receptor-positive breast cancer, the 20-year risk of breast cancer-specific mortality was 12.4 percent for stage I disease, 26 percent for stage II disease, and 46 percent for stage III disease [105]. There was an increase in late recurrences as nodal involvement increased, such that a bimodal distribution of recurrences was present for those with N3 and stage III disease, peaking at 4 and 11 years. Higher stage, grade, and age were all associated with higher risks.

RS is prognostic for men with hormone receptor-positive, HER2-negative breast cancer, as it is for women. In a retrospective analysis including 3800 men with hormone receptor-positive breast cancer, five-year breast cancer-specific survival was 99 percent for men with RS ≤17, 96 percent for men with RS 18 to 30, and 81 percent for men RS ≥31 [96].

Racial disparities — As is the case in women, Black men with breast cancer have a worse prognosis than do White men [10,106].

This was illustrated in a report of 510 men aged 65 years or older (456 White Americans, 34 Black Americans) with stage I to III breast cancer derived from the linked Medicare/SEER database [106]. Treatment consisted of mastectomy, chemotherapy, and RT in 94, 28, and 29 percent of men, respectively.

Compared with White men, Black men were significantly more likely to have advanced-stage disease (eg, 24 versus 9 percent with stage III) and larger tumor size. In addition, there was a

nonsignificant trend for Black men to have more node-positive disease (45 versus 34 percent) and poorly differentiated tumors (44 versus 32 percent), fewer hormone receptor-positive tumors (56 versus 72 percent), and comorbidity scores greater than 0 (53 versus 38 percent). Black men were approximately 50 percent less likely to be referred to a medical oncologist and to receive chemotherapy, but these differences were also not statistically significant. After adjusting for known clinical, demographic, and treatment-related factors, Black men had a greater than threefold increased risk of dying as a result of their breast cancer compared with White men. Five-year survival rates were 66 and 90 percent, respectively.

Survivorship issues

Post-treatment surveillance — In general, men treated for breast cancer should undergo similar post-treatment surveillance as women. However, whether or not there is a role for mammography is not known. While limited data suggest these patients are at an increased risk of a contralateral breast cancer [107,108], the absolute risk appears to be low [17]. Our approach to screening, consistent with ASCO guidelines, is as follows [84]:

- Ipsilateral annual mammogram should be offered to men with a history of breast cancer treated with lumpectomy, regardless of genetic predisposition.
- Contralateral annual mammogram may be offered to men with a history of breast cancer and a genetic predisposing mutation. Although we do not suggest it for patients lacking a genetic mutation, we acknowledge that experts are divided in this regard [84]. More research is needed on the risk of contralateral breast cancers in men without cancer-predisposing genetic mutations.
- Breast magnetic resonance imaging is not recommended routinely.

However, the role of screening in men with a history of breast cancer is uncertain, and decision-making should take into account men's preferences and values.

As in women, these patients are also at risk for secondary malignancies [109,110]. This was shown in one study that included data from over 10,000 male breast cancer survivors, in which the standardized incidence ratio (SIR) of a second primary cancer, relative to healthy male controls, was 1.3; specifically, there were increased colorectal (SIR 1.3), pancreatic (SIR 1.6) and thyroid (SIR 5.6) cancer risks [109]. Male breast cancer survivors should engage in cancer screening according to guidelines according to age, personal and family history, and genetic risk factors (if present), as discussed elsewhere. (See "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp" and "Familial risk factors for pancreatic cancer and screening of high-risk patients" and "Cancer risks in BRCA1/2 carriers".)

Physical and psychologic side effects — Small studies suggest that toxicities are common in men on tamoxifen, and that this is one of the major reasons for the high rate of endocrine therapy discontinuation in men [88,111,112].

Optimal management of endocrine therapy side effects such as hot flashes and sexual dysfunction is unknown in men, so strategies are usually extrapolated from those proven effective in female breast cancer survivors (for hot flashes) and the general population of men (for sexual dysfunction).

- Options for management of hot flashes include the same nonhormonal options that are offered to women with a history of breast cancer, such as selective serotonin reuptake inhibitors that do not interfere with metabolism of tamoxifen (eg, venlafaxine). (See "Menopausal hot flashes", section on 'Women with breast cancer'.)

- In general, sexual dysfunction in male breast cancer patients is treated similarly as in men without breast cancer, although we avoid the use of testosterone, as it has been suggested that metabolism of testosterone to estrogen derivatives can stimulate breast tissue [113]. Phosphodiesterase-5 inhibitors may be used for men with erectile dysfunction. (See "Treatment of male sexual dysfunction".)

Little is known about the experience of men after breast cancer. However, issues related to emasculation and psychologic distress appear to be common themes [114-117]. In one study that included over 160 men with breast cancer who were a median of 2.9 years out from diagnosis, psychologic distress consisted of [117]:

- Significant depression and anxiety (measured with the Hospitalized Anxiety and Depression Scale) were present in 1 and 6 percent of participants, respectively.

- Psychologic distress was significantly higher among men who underwent a mastectomy, those experiencing comorbid symptoms, and those who were not married.

- Cancer-related distress was significantly correlated with younger age, altered body image, more frequent use of engagement and avoidance coping, and greater perceived stressfulness due to reduced physical ability, pain, fear, and uncertainty about the future.

A more general discussion on survivorship care is covered separately. (See "Overview of cancer survivorship care for primary care and oncology providers" and "Assuring quality of care for cancer survivors: The survivorship care plan".)

METASTATIC DISEASE

Approach — The approach to men with metastatic or advanced breast cancer is similar to that of women with metastatic breast cancer.

- Chemotherapy is administered to men in a similar fashion as for women, for appropriate candidates. (See "Overview of the approach to metastatic breast cancer".)
- For men with human epidermal growth factor receptor 2 (HER2)-positive disease, incorporation of HER2-directed agents into the treatment strategy is recommended, as for women. (See "Systemic treatment for HER2-positive metastatic breast cancer".)
- For those with metastatic, hormone receptor-positive, HER2-negative disease, endocrine therapies are often employed. However, in the setting of rapidly progressive or extensive visceral disease, chemotherapy is an alternative.
- Although data are mixed regarding survival benefits for local treatments in metastatic breast cancer, they may be appropriate for some men, in clinical scenarios analogous to women. (See "The role of local therapies in metastatic breast cancer".)

Special considerations for hormone receptor-positive, HER2-negative disease — For men with hormone receptor-positive, advanced breast cancer, the approach to choice of therapy is largely extrapolated from data in women with hormone receptor-positive breast cancer and is discussed below. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

- For men who present with de novo, metastatic, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, we suggest the combination of either tamoxifen or an aromatase inhibitor (AI)/gonadotropin-releasing hormone agonist (GnRHa) with a cyclin-dependent kinase (CDK) 4/6 inhibitor [84]. Palbociclib and ribociclib have been approved by the US Food and Drug Administration (FDA) for men with metastatic, hormone receptor-positive breast cancer, in combination with either an AI or fulvestrant [118,119], but abemaciclib is an appropriate off-label substitute. A choice between AI/GnRHa versus tamoxifen, among those who are also receiving a CDK 4/6 inhibitor, should be driven by patient preferences in regard to toxicity and scheduling, given lack of comparative data regarding efficacy.
- For men who have previously been treated with adjuvant tamoxifen, or who have progressed on tamoxifen in the metastatic setting, we suggest an AI/GnRHa plus a CDK 4/6 inhibitor.

In either of the above cases, an acceptable alternative is to omit the CDK 4/6 inhibitor and administer endocrine therapy alone, especially for those with lower burden of disease or comorbidities, or due to patient preferences.

- We typically opt for fulvestrant as part of subsequent-line therapy after progression on an AI/GnRHa. If palbociclib has not yet been administered, we combine it with fulvestrant (with or without a GnRHa, depending on previous tolerance). For those whose tumors harbor mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) or in the PI3K pathway and who have progressed on endocrine therapy, the addition of alpelisib or capivasertib to fulvestrant is another option.

- An AI/GnRHa/everolimus is an option for later-line therapy, which we typically reserve for use after progression on the above agents.

Below are the limited available data in men regarding endocrine therapy.

- **AIs with GnRHa** – Because AIs do not reduce testicular production of estrogens, we administer GnRHa concurrently with AI. Case studies of response to AI plus GnRHa have been reported, one of which was in a patient whose metastatic disease had progressed on both single-agent AI and single-agent GnRHa prior to responding to the combination [120]. Another pooled report of AI therapy alone or in combination with GnRHa in 23 men showed a partial response in 26.1 percent and stable disease in 56.5 percent.

  Responses to single-agent AIs have also been documented [121-124], though we prefer to avoid AI monotherapy for reasons mentioned above. (See 'Endocrine therapy' above.)

- **Tamoxifen** – Small, older, observational studies suggest that approximately 40 percent of men with hormone receptor-positive disease respond to tamoxifen, though many patients in these older studies had prior orchiectomies, and the true response rate in male breast cancer may be higher [11,125-128]. Men with hormone receptor-negative breast cancer do not appear to derive benefit from treatment. Tamoxifen is associated with hot flashes, sexual dysfunction, changes in mood, cataracts, leg cramps, and venous thromboembolism (VTE), with one study suggesting VTEs occurring in approximately 10 percent of men within the first 18 months of treatment [129]. (See "Managing the side effects of tamoxifen and aromatase inhibitors".)

- **Addition of CDK 4/6 inhibitors** – Inhibitors of CDK 4/6 have demonstrated activity in women when combined with endocrine therapy, but their use in men is not well-studied. A case report on fourth-line letrozole plus palbociclib in a man with metastatic estrogen

receptor (ER)-positive, HER2-negative breast cancer reported stable disease at four months on treatment [130].

- **Addition of a PI3K inhibitor** – The addition of alpelisib to fulvestrant improved progression-free survival for those with tumor *PIK3CA* mutations in the phase III SOLAR-1 trial. The trial mostly consisted of postmenopausal women, although one male patient was included. Full details of this trial are discussed elsewhere.

- **Addition of mechanistic target of rapamycin (mTOR) inhibitors** – Two case reports of heavily pretreated male patients receiving everolimus with either tamoxifen or exemestane reported favorable responses to therapy, although one patient had to stop treatment after four months due to stomatitis [131,132].

- **Fulvestrant** – Data regarding the role of fulvestrant are limited. Two case reports totaling seven men documented a partial response in two and stable disease (in one case lasting 22 months) in three others. A pooled analysis of 23 male patients receiving fulvestrant as first-, second-, or third-line treatment of metastatic disease reported a partial response rate of 26 percent, and an additional 48 percent had stable disease [133].

- **Later-line hormonal treatments** – Men responding to one form of hormonal treatment have a greater likelihood of responding to subsequent hormonal manipulations [128]. Other endocrine therapies (megestrol acetate, androgens, antiandrogens, corticosteroids, cyproterone acetate, estrogens) are associated with 50 to 70 percent response rates in ER-positive breast cancer [127,134-136]. However, side effect profiles tend to be less favorable than with tamoxifen, and most have been poorly studied in men. Hence, they are reserved for subsequent-line therapy. Although bilateral orchiectomy yields response rates of 32 and 67 percent [11,126,137-139], we prefer medical options given the psychologic and physical impact of bilateral orchiectomy.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary breast and ovarian cancer" and "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Breast cancer (The Basics)")
- Beyond the Basics topics (see "Patient education: Treatment of metastatic breast cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Breast cancer is much less common in men than in women. Men tend to present at an older age than women. Men with breast cancer should be referred for genetic counseling and testing. (See 'Epidemiology and risk factors' above and "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes", section on 'Concerning personal or family history'.)
- Biopsy is required to confirm the diagnosis and assay for hormone receptors and human epidermal growth factor receptor 2 (HER2) expression, both of which may influence the selection of treatment. (See 'Diagnostic evaluation and staging' above.)
- Most men with early-stage breast cancer are treated with mastectomy rather than lumpectomy due to limited breast tissue. However, for men with sufficient breast tissue to be candidates for breast conservation, either mastectomy or breast-conserving therapy are appropriate options. For men who pursue breast-conserving surgery, we recommend adjuvant radiation therapy (RT) (**Grade 1B**). (See 'Early-stage disease' above and 'Radiation therapy' above.)

●As in women, surgical evaluation of the axillary lymph nodes is required. (See 'Management of the regional nodes' above.)

- For men with a clinically positive axilla, as in women, we recommend axillary lymph node dissection (**Grade 1B**). (See "Overview of management of the regional lymph nodes in breast cancer" and "Overview of management of the regional lymph nodes in breast cancer", section on 'Axillary evaluation'.)

- For patients with a clinically uninvolved axilla, we suggest a sentinel lymph node biopsy (SLNB) instead of full axillary node dissection (**Grade 2B**).

  - Men with a negative SLNB do not require further surgery. However, the role of a complete axillary node dissection for men with a positive SLNB is controversial. Given the lack of data to inform this issue, the approach to patients with a positive SLNB mirrors that for women. (See "Overview of sentinel lymph node biopsy in breast cancer".)

- As in women, for men with locally advanced breast cancer (ie, T3 or T4 disease) and/or four or more involved axillary nodes, we recommend postoperative chest wall and regional lymph node irradiation following surgery (**Grade 1B**). For those with one to three involved lymph nodes or high-risk primary tumors, we also suggest regional nodal RT (**Grade 2B**), as in women. (See 'Radiation therapy' above and "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer".)

- The approach to adjuvant systemic therapy (ie, chemotherapy and/or HER2-directed therapy) for men with newly diagnosed breast cancer mirrors that for women. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer" and "Adjuvant systemic therapy for HER2-positive breast cancer".)

- For those with hormone receptor-positive disease,

  - If **early stage**, we suggest adjuvant tamoxifen rather than an aromatase inhibitor (AI) (**Grade 2C**), given insufficient evidence to support AI monotherapy for men. We also suggest adjuvant tamoxifen over an AI with gonadotropin-releasing hormone agonists (GnRHa) (**Grade 2C**), given better tolerability. However, for those with contraindications to tamoxifen (eg, hypercoagulable state), an AI with GnRHa is an acceptable alternative. (See 'Endocrine therapy' above.)

  - If **metastatic**, we suggest the addition of a cyclin-dependent kinase (CDK) 4/6 inhibitor to either tamoxifen or an AI/GnRHa, rather than these therapies alone (**Grade 2B**). However, data in this area are extremely limited, and it is an acceptable alternative to omit the CDK 4/6 inhibitor and administer endocrine therapy alone, especially for those with lower burden of disease or comorbidities, or due to patient preferences. When

using an AI, we suggest addition of a GnRHa, given possible ongoing testicular production of estrogen when an AI is used as monotherapy in men.

- Although evidence for CDK 4/6 inhibitors fulvestrant, alpelisib, and everolimus is limited in men, we incorporate these agents into metastatic disease treatment using a similar approach as in women. When using an AI (with or without a targeted therapy), we use a GnRHa to suppress testicular production of estrogen. (See 'Metastatic disease' above.)

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GRAPHICS

BRCA2 mutations in male breast cancer

Author; year	Men tested	Men with *BRCA2* mutations	% of men with *BRCA2* mutations	% of men with positive family history
Couch, FJ; 1996	50	7	14	80
Thorlacius, S; 1996	30	12	40	25
Friedman, LS; 1997	54	2	4	17
Mavraki, E; 1997	28	3	11	36
Haraldsson, K; 1998	34	7	21	13
Csokay, B; 1999	18	6	33	0
Diez, O; 2000	17	3	18	53
Sverdlov, R; 2000	31	1	3	35
Kwiatkowska, E; 2001	37	4	11	13
Basham, V; 2002	94	3	8	20
Frank, TS; 2002	76	14	18	36
Ottini, L; 2003	25	4	16	28
Ding, Y; 2011	115	18	16	22

Graphic 80912 Version 4.0

Prognosis for stage I and II male breast cancer*

Surgery	Radiation	Stage I (%)	Stage II (%)
BCS	No RT	96	91.8
	RT (BCT)	100¶	100
SM	No RT	97.4	91.2
	RT	100	73.2
MRM	No RT	97.3	91.2
	RT	100¶	93.6

Data presented as n (95% CI).

BCS: breast-conserving surgery; RT: radiation therapy; BCT: breast conservation therapy; SM: simple mastectomy; MRM: modified radical mastectomy; CI: confidence interval.

* Five-year cancer-specific survival rates.

¶ 95% CI unable to be calculated.

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