Breast Cancer in Men
Sharon H. Giordano, MD; Aman U. Buzdar, MD; and Gabriel N. Hortobagyi, MD

Purpose: Breast cancer in men is uncommon; 1500 new cases are diagnosed in the United States yearly. Optimal management of breast cancer in men is unknown because the rarity of the disease precludes large randomized trials. A review of the literature was undertaken with emphasis on articles published over a 10-year period.

Data Sources: Articles published between 1942 and 2000 on breast cancer in men were identified by using CancerLit, MEDLINE, and study bibliographies.

Study Selection: All retrospective series and studies focusing on the epidemiology, risk factors, genetics, and pathology of breast cancer in men.

Data Extraction: Data on the epidemiology, risk factors, genetics, pathology, molecular markers, prognostic factors, therapy, and outcomes of breast cancer in men.

Data Synthesis: Carcinoma of the male breast accounts for 0.8% of all breast cancers. Risk factors include testicular disease, benign breast conditions, age, Jewish ancestry, family history, and the Klinefelter syndrome. BRCA2 mutations predispose men to breast cancer and may account for 4% to 14% of all cases. Pathology data were reviewed: 81% of tumors were estrogen receptor positive, 74% were progesterone receptor positive, 37% overexpressed c-erbB-2, 30% overexpressed p53, 79% overexpressed Bcl-2, 51% overexpressed cyclin D1, and 39% overexpressed epidermal growth factor receptor. Prognostic factors include tumor size, histologic grade, and lymph node status; survival is similar to that of breast cancer in women when patients are matched for age and stage. Adjuvant hormonal therapy and chemotherapy, using the same guidelines as for women, are recommended for men. Hormonal therapy is the primary therapy for metastatic disease; chemotherapy should be reserved for hormone-refractory disease.

Conclusion: Breast cancer is similar in men and women; however, breast cancer in men is more frequently hormone receptor positive and may be more sensitive to hormonal therapy.

For author affiliations, see end of text.
Table 1. Risk Factors for Breast Cancer in Men

<table>
<thead>
<tr>
<th>Testicular abnormalities</th>
<th>Undescended testes</th>
<th>Congenital inguinal hernia</th>
<th>Orchiectomy</th>
<th>Orchitis</th>
<th>Testicular injury</th>
<th>Infertility</th>
<th>Klinefelter syndrome</th>
<th>Positive family history</th>
<th>Benign breast conditions</th>
<th>Nipple discharge</th>
<th>Breast cysts</th>
<th>Breast trauma</th>
<th>Radiation exposure</th>
<th>Increasing age</th>
<th>Jewish ancestry</th>
</tr>
</thead>
</table>

Table 2. BRCA2 Mutations in Breast Cancer in Men

<table>
<thead>
<tr>
<th>Author, Year (Reference)</th>
<th>Patients Tested</th>
<th>Patients with BRCA2 Mutations</th>
<th>Patients with Positive Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couch et al., 1996 (27)</td>
<td>50</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Thorlacius et al., 1996 (28)</td>
<td>30</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Friedman et al., 1997 (21)</td>
<td>54</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Mavraki et al., 1997 (29)</td>
<td>28</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Haraldsson et al., 1998 (30)</td>
<td>34</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Cskay et al., 1999 (31)</td>
<td>18</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Diez et al., 2000 (32)</td>
<td>17</td>
<td>3</td>
<td>18</td>
</tr>
</tbody>
</table>
breast in that almost 75% of cases are a papillary subtype and almost all cases are low to intermediate grade (37).

In men, the predominant histologic subtypes of invasive carcinoma are infiltrating ductal carcinoma, which accounts for more than 80% of all tumors (38–45), and papillary carcinoma, which makes up about 5% (22, 38, 39, 45–47). Lobular carcinoma is much less common in men than in women and represents only 1% of all cases (15, 22, 44). The rarer subtypes, such as medullary, tubular, mucinous, and squamous carcinomas, have all been reported in men, although they may be slightly more uncommon than in women (34, 43–45). Inflammatory carcinoma and Paget disease are seen with similar frequency in men and women (34, 45, 46).

Carcinomas of the male breast have a higher rate of hormone receptor positivity than do carcinomas of the female breast when matched for tumor stage, grade, and patient age (48–50). Our review of the literature indicates that 81% of breast cancers in men are estrogen receptor positive, and 74% are progesterone receptor positive (Table 3) (11, 15, 22, 34, 41–45, 48, 51–82). In contrast to women, men do not have a higher incidence of estrogen receptor–positive tumors with advancing age (34, 51, 60, 61).

**Molecular Markers**

C-erbB-2, p53, Bcl-2, cyclin D1, and epidermal growth factor receptor (EGFR) are important in the pathogenesis and prognosis of breast cancer in women. Recent literature has evaluated their role in carcinoma of the male breast, and we present a synthesis of these data (Table 3).

<table>
<thead>
<tr>
<th>Pathologic Feature</th>
<th>Total</th>
<th>Tumors</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive or Immunoreactive</td>
<td>Positive or Immunoreactive</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>1301</td>
<td>1053</td>
<td>81</td>
</tr>
<tr>
<td>Progesterone receptor</td>
<td>1040</td>
<td>766</td>
<td>74</td>
</tr>
<tr>
<td>C-erbB-2t</td>
<td>511</td>
<td>190</td>
<td>37</td>
</tr>
<tr>
<td>p53 protein</td>
<td>472</td>
<td>143</td>
<td>30</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>193</td>
<td>153</td>
<td>79</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>117</td>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td>EGFR</td>
<td>61</td>
<td>24</td>
<td>39</td>
</tr>
</tbody>
</table>

* Data pooled from multiple studies; EGFR = epidermal growth factor receptor.
† Tested by immunohistochemistry.
found p53 mutations to be associated with decreased survival (55, 57–60, 87).

Bcl-2 is a protooncogene that inhibits apoptosis and thereby promotes cell growth. In breast cancer in women, expression of Bcl-2 has been associated with favorable prognostic features (97). Several studies have investigated the incidence of Bcl-2 expression in breast cancer in men. Overall, Bcl-2 expression was seen in 153 (79%) of 193 cases (60, 61, 83, 93). Men may have significantly higher rates of Bcl-2 expression than women (60), but Bcl-2 expression has not been shown to have prognostic significance in men (60, 61, 93). The high rates of expression of Bcl-2 in male breast cancer suggest that apoptotic mechanisms may be important in the etiology of breast cancer in men.

Cyclin D1 is involved in cell-cycle regulation and helps control the cell’s entry into S phase. In breast cancer in women, this gene is oncogenic but appears to be associated with a favorable prognosis (95). A total of 117 tumors of the male breast were tested for cyclin D1 overexpression; 60 (51%) were immunoreactive (61, 94). This number is very similar to the 50% rate of overexpression seen in women (95). Rayson and colleagues (61) found that cyclin D1 negativity was associated with significantly decreased progression-free survival, indicating that gene overexpression may be a favorable prognostic factor in men with carcinoma of the breast.

The data on EGFR expression are even more limited. Epidermal growth factor receptor is a transmembrane glycoprotein that is present in low levels in normal breast tissue and is overexpressed in 35% to 60% of breast cancers in women (96). Overexpression of EGFR in women is inversely correlated with estrogen receptor expression and may be a negative prognostic factor. Only two studies have reported the rates of EGFR expression in men. Fox and colleagues (75) found that 16 of 21 cases (76%) expressed EGFR, and Willsher and colleagues (59) reported that 8 of 40 cases (20%) showed EGFR expression. No association was found with either estrogen receptor status or with p53 mutations in breast cancer in men, even after adjustment for tumor stage and axillary lymph node status (45).

Tumor size has also been shown to be a significant prognostic factor in breast cancer in men (16, 19, 22, 41, 98, 99). In a series of 397 patients in France, 5-year crude survival rates by tumor size were 85% for tumors measuring less than 2 cm in diameter, 63% for tumors 2 to 5 cm, and 51% for tumors greater than 5 cm (19). High histologic grade is similarly associated with decreased survival rates (43, 99, 100). Ribeiro and colleagues (43) found a statistically significant difference in 5-year survival based on histologic grade of tumor (grade 1, 76%; grade II, 66%; and grade III, 43%).

Finally, most evidence points to hormonal status in men being a prognostic factor, although the number and size of studies are limited. A study from Princess Margaret Hospital in Toronto, Ontario, Canada, of 229 patients found that estrogen receptor positivity predicted better overall survival in univariate analysis; but after adjustment for patient age, tumor size, lymph node status, and type of therapy, this difference was no longer significant (15). However, a large study of 215 patients from health care institutions in eastern Wisconsin showed that men with hormone receptor–positive tumors had improved overall survival, even after adjustment for tumor stage and axillary lymph node status (45).

Clinical outcome for men with breast cancer is similar to that for women. Five-year overall survival rates for all stages of breast cancer in men have been reported to range from 36% to 66%, and 10-year overall survival rates range from 17% to 52% (100, 101). Disease-specific survival rates are somewhat higher; 52% to 74% of patients are alive at 5 years and 26% to 51% are alive at 10 years (19, 102). Overall and disease-specific survival rates are shown in Table 4. Stage of disease predicts survival rates; overall 5-year survival rates are 55% to 100% for stage I, 41% to 78% for stage II, 16% to 57% for stage III, and 0% to 14% for stage IV disease (11, 38, 39, 41, 43–45, 104).

Although older articles have reported that men with breast cancer have poorer survival rates than women (46, 47), most recent series show that men and women have

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival Rate, %</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>36–66</td>
<td>11, 15, 19, 44, 45, 47, 100–103</td>
</tr>
<tr>
<td>Stage I</td>
<td>55–100</td>
<td>38, 41, 43, 103, 104</td>
</tr>
<tr>
<td>Stage II</td>
<td>41–78</td>
<td>38, 41, 43, 104</td>
</tr>
<tr>
<td>Stage III</td>
<td>16–57</td>
<td>11, 43, 104</td>
</tr>
<tr>
<td>Stage IV</td>
<td>0–14</td>
<td>11, 41, 102, 104</td>
</tr>
<tr>
<td>Node negative</td>
<td>52–100</td>
<td>15, 19, 38, 39, 64, 98, 105, 106</td>
</tr>
<tr>
<td>Node positive</td>
<td>31–60</td>
<td>15, 19, 38, 39, 64, 98, 105, 106</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td>52–74</td>
<td>19, 44, 45, 102, 103</td>
</tr>
</tbody>
</table>

Table 4. Survival Rates for Breast Cancer in Men

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Breast Cancer in Men REVIEW

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Table 5. Presenting Signs and Symptoms

<table>
<thead>
<tr>
<th>Presenting Signs and Symptoms</th>
<th>Frequency, %</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast mass</td>
<td>50-97</td>
<td>15, 16, 19, 43, 44, 103, 104, 107</td>
</tr>
<tr>
<td>Nipple retraction</td>
<td>10-51</td>
<td>15, 19, 44, 104</td>
</tr>
<tr>
<td>Local pain</td>
<td>4-20</td>
<td>15, 44, 104, 107</td>
</tr>
<tr>
<td>Nipple ulceration</td>
<td>4-17</td>
<td>15, 44, 103, 107</td>
</tr>
<tr>
<td>Nipple bleeding</td>
<td>2-9</td>
<td>15, 103, 107</td>
</tr>
<tr>
<td>Nipple discharge</td>
<td>1-12</td>
<td>15, 44, 103, 104, 107</td>
</tr>
<tr>
<td>None</td>
<td>1-2</td>
<td>15, 107</td>
</tr>
</tbody>
</table>

Clinical Features

Approximately 85% of men with breast cancer present with a painless subareolar mass (43). Other common presenting signs and symptoms are nipple retraction, local pain, nipple ulceration, nipple discharge, and nipple bleeding (Table 5). Most patients present with more than one sign or symptom (15, 44). The rate of nipple involvement has been reported to be approximately 40% to 50%, perhaps because of the sparsity of breast tissue and the central location of most tumors (58, 105). The disease has a slight predilection for the left breast (16, 44, 45, 107) with a left-to-right ratio of 1.07:1 (5). Bilateral disease is rare. Men are more likely than women to have a delay between the onset of symptoms and a diagnosis of breast cancer, possibly because of the limited public awareness of breast cancer in men. This delay in diagnosis may contribute to men presenting at later stages than do women.

When a man presents with a breast mass, the primary differential diagnosis is gynecomastia versus carcinoma. Mammography can be useful in distinguishing a benign from malignant condition; carcinoma is often eccentric with irregular, spiculated margins (1). Screening mammography has no role in men because of the rarity of the disease and the small size of the male breast, which allows easy palpation of most masses. As in women, a biopsy of any suspicious mass should be performed. Fine-needle aspiration has been evaluated in male patients and has been found to be very sensitive and specific (108). When malignancy is diagnosed, men should have the same staging evaluation as women. The American Joint Committee on Cancer (AJCC) classification is the most widely used staging system and is based on tumor size, presence of nodal metastases, and presence of distant metastases (TNM) (109).

Local Therapy

For men who present with nonmetastatic disease, the currently recommended surgical therapy is modified radical mastectomy. Historically, most men were treated with radical mastectomy; however, because women have been shown to do as well with a more limited surgical approach, most men are now treated with modified radical mastectomies. Studies that have compared radical with modified radical mastectomy in men have found equivalent local recurrence and survival rates for these two surgical approaches (41, 71, 110). Thus, it seems reasonable to recommend less extensive surgery. Because the male breast has sparse amounts of tissue, segmental mastectomy probably does not have a role in the treatment of carcinoma of the male breast. As in women, axillary dissection is an essential part of surgical therapy (16, 19).

Limited data are available for determining which patients need radiation therapy after modified radical mastectomy. Several studies have found that radiation reduces the risk for local recurrence but does not change overall survival (19, 40, 45, 104). Some authors have suggested that the central location of tumors in the male breast may predispose to internal mammary lymph node metastases. They conclude that radiation to the internal mammary nodes should be considered for all patients and that chest wall radiation should be considered for patients with locally advanced disease (111).

Adjuvant Therapy

Adjuvant hormonal therapy with tamoxifen in women with estrogen receptor–positive breast carcinoma has resulted in significantly improved survival rates. Because men have high rates of hormone receptor positivity, adjuvant hormonal therapy is theoretically very promising. No randomized clinical trials have evaluated the use of adjuvant tamoxifen. Several large studies have retrospectively compared men who were treated with tamoxifen in an adjuvant setting with men who received no hormonal therapy and have found improved survival in patients treated with tamoxifen (15, 43, 63). Ribeiro and Swindell (63) compared 39 patients with stage II and stage III disease who received tamoxifen with historical controls and found a 5-year survival of 61% versus 44%, suggesting a significant benefit from tamoxifen (63). The studies of adjuvant tamoxifen may underestimate its benefit because most men were treated for less than 2 years. The optimal length of therapy in women is 5 years; therefore, a greater benefit in men may be seen with longer duration of therapy. Based on the available data, we recommend that all men with hor-
Breast Cancer in Men

Figure. Treatment recommendations for breast cancer in men.

Breast mass

Perform fine-needle aspiration, core biopsy, or excisional biopsy; consider mammography

Benign

Malignant

Staging: chest radiograph and laboratory evaluation; bone scan and CT scan of the abdomen (depending on stage)

Perform yearly physical examination

Local disease

Surgery

Adjuvant chemotherapy if lymph nodes are involved or if tumor is > 1 cm

Adjuvant tamoxifen for 5 years if tumor is hormone receptor positive

Adjuvant radiation therapy if primary tumor is T3 or T4 or if ≥ 4 lymph nodes are involved

Hormone receptor-negative tumor

Chemotherapy

Hormone receptor-positive tumor

Hormonal therapy with tamoxifen

Disease progression

Second-line hormonal therapy with aminogluthethimide, progestins, antiandrogens, GnRH agonists, steroids, or androgens

Disease progression

Chemotherapy or third-line hormonal therapy (if disease has responded to previous hormonal regimens)

CT = computed tomography; GnRH = gonadotropin-releasing hormone.

mone receptor-positive tumors be treated with tamoxifen for 5 years.

The role for adjuvant chemotherapy in men is less established, but the limited data do suggest a benefit. Given the considerable toxicity of chemotherapy, few men with early-stage disease have received chemotherapy; thus, even retrospective data have been difficult to obtain. The National Cancer Institute studied 24 male patients who were given adjuvant chemotherapy for node-positive stage II breast cancer (69). The 5-year survival rate among treated patients was 80%, which was significantly better than the survival rates among historical controls. The experience with adjuvant anthracycline therapy was reviewed at M.D. Anderson Cancer Center (70). Eleven node-positive patients who were treated with adjuvant chemotherapy (10 with an anthracycline-based regimen) were found to have an estimated 5-year survival rate of greater than 85%, which was substantially better than survival rates of historical controls. Other authors have also found improved outcomes in patients treated with adjuvant chemotherapy (16, 42, 45). With most data supporting a benefit of adjuvant chemotherapy in men and the clear benefit for adjuvant chemotherapy in women, we would offer adjuvant chemotherapy to men who have substantial risk for recurrence. Because there are no data with which to determine exactly which men will benefit from adjuvant chemotherapy, we use the same guidelines in men as in women and offer chemotherapy to men with node-positive disease or primary tumors that are larger than 1 cm.

THERAPY FOR METASTATIC DISEASE

Hormonal therapy has been the mainstay of treatment for metastatic carcinoma of the male breast for the past 5
Breast Cancer in Men

decades. Initial hormonal therapies were ablative orchietomy, adrenalectomy, and hypophysectomy. Farrow and Adair (112) described the first response to orchietomy in 1942, and orchietomy became the standard of care for treatment of metastatic disease. Jaiyesimi and colleagues reviewed ablative therapies in 447 patients and found response rates of 55% for orchietomy, 80% for adrenalectomy, and 56% for hypophysectomy (1). Patients who responded to orchietomy were more likely to respond to second-line ablative therapies, and responding patients had improved survival (113).

Additive hormonal therapy has also been shown to have substantial response rates in metastatic breast carcinoma in men. It is an appealing alternative to ablative therapies because such therapy is reversible, avoids surgical morbidity and mortality, and is psychologically more acceptable to most men than orchietomy. Overall rates of response to the various additive therapies have been reported as 75% for androgens, 57% for antiandrogens, 50% for steroids, 32% for estrogens, 50% for progestins, 40% for aminoglutethimide, and 49% for tamoxifen (1). These numbers may be optimistic because responders are more likely to have been reported in the literature. Estrogen receptor positivity appears to predict response to hormonal therapy. Jaiyesimi and colleagues found that 69% of 35 men with estrogen receptor–positive tumors responded to hormonal manipulation compared with 0% of 8 men with estrogen receptor–negative tumors (1). We recommend tamoxifen as first-line hormonal therapy because of its established efficacy in men and limited toxicity. In addition, most oncologists have considerable experience with this drug in women.

Systemic chemotherapy, which is another option for men with metastatic breast cancer, is usually reserved for second-line therapy because most men will respond to hormonal manipulation. One study directly compared chemotherapy with hormonal therapy and found superior response rates in patients treated with hormonal therapy (114). Chemotherapy, however, can offer significant palliation to men in whom hormonal therapy has failed or those with hormone receptor–negative disease. Response rates reported in the literature are 67% for 5-fluorouracil, doxorubicin, and cyclophosphamide; 55% for doxorubicin and vincristine; 53% for cyclophosphamide; 33% for cyclophosphamide, methotrexate, and 5-fluorouracil; and 13% for 5-fluorouracil (1). For all other regimens or single agents, fewer than five cases have been reported in the literature. For all chemotherapy regimens, the overall response rate was 40% (1).

**Conclusions**

Carcinoma of the male breast has many similarities to breast cancer in women, but the diseases have different genetic and pathologic features. Both *BRCA1* and *BRCA2* mutations can cause breast cancer in women, but only *BRCA2* mutations confer a significant risk to men. Non-invasive carcinomas in men are all low- to intermediate-grade ductal carcinoma in situ; pure lobular carcinoma in situ is extremely rare. Most invasive carcinomas are infiltrating ductal, with lobular carcinoma representing only about 1% of invasive disease. Men have higher rates of estrogen and progesterone positivity than do women but similar percentages of c-erbB-2, p53, cyclin D1, and EGFR overexpression. Men may be more likely to have tumors that overexpress bcl-2, but the clinical significance of this finding is not clear.

The diagnostic evaluation and staging of breast cancer in men is similar to that in women. For localized disease, modified radical mastectomy is the preferred surgical approach. There is no evidence that adjuvant radiation therapy after mastectomy improves survival, although men may have a higher risk for internal mammary lymph node metastases and in theory could benefit from internal mammary radiation therapy. Although the evidence is limited, most studies point to a benefit from both adjuvant tamoxifen and chemotherapy. Given the known benefit of adjuvant therapy in women, we recommend that men also be offered adjuvant therapy using the same guidelines that are the standard of care for women. Metastatic disease can be treated with either hormonal therapy or chemotherapy. Because men have high rates of response to additive hormonal therapy, this approach is recommended for first-line treatment in hormone receptor–positive disease. Tamoxifen is the most accepted front-line additive therapy. Selective aromatase inhibitors (anastrozole and letrozole) have been approved for first-line treatment of metastatic breast cancer in women, but there are no published reports of responses in men. Chemotherapy can be of use for hormone-refractory disease.

Areas for future investigation are plentiful. Larger studies of pathologic markers would be helpful to define which genetic abnormalities play a role in breast cancer in men and to determine which markers are important prognostic factors. The role of adjuvant hormonal and chemotherapy deserves further study, especially to determine which subgroups of men will benefit. New hormonal and chemotherapeutic agents, such as selective aromatase inhibitors and taxanes, deserve investigation for the therapy of carcinoma of the male breast. Finally, men should be strongly encouraged to participate in clinical trials so that prospectively gathered information will be available and more can be learned about breast cancer in men.

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References
Breast Cancer in Men
