REVIEW ARTICLE

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Breast Cancer in Men

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Breast cancer in men is a rare and understudied disease. Few prospective studies focusing on breast cancer in men have been conducted, and clinical trials of breast cancer treatments have routinely excluded men. Most of the published data have been collected from small cohorts of patients treated at single institutions, and treatment recommendations have been extrapolated from the results of clinical trials that enrolled only women. Over the past decade, substantial efforts have been made to gain a better understanding of the biologic features, most effective treatments, and outcomes of breast cancer in men and to identify clinically relevant differences in the disease according to sex.[1] Although breast cancer in men and in women is similar in some ways, breast cancer in men has distinct features, which are summarized in Table 1. In this article, I review current data on the epidemiology of breast cancer in men, its pathological and clinical characteristics, and prognosis and treatment, with a focus on recent advances in our understanding of this disease.

Epidemiology and Risk Factors

Breast cancer in men accounts for approximately 1% of all breast cancers. In the United States in 2018, an estimated 2500 incident breast cancers will be diagnosed in men, and approximately 500 men are expected to die from this disease.[12] Data from the Surveillance, Epidemiology, and End Results (SEER) program indicate that the age-adjusted incidence rate has increased from 0.85 cases per 100,000 men in the general population in 1975 to a high of 1.43 cases per 100,000 in 2011.[13] The lifetime risk of breast cancer for a man is approximately 1:1000, as compared with 1:8 for a woman.[2] As is the case with many cancers, breast cancer in men is an age-related disease, with incidence rates rising steadily with age. The average age at diagnosis is approximately 5 years older for men than for women (67 years vs. 62 years).[5] Black men appear to be at greater risk than non-Hispanic white men.[13,14] The risk of breast cancer is doubled for men who have a first-degree relative with the disease.[15] Risk factors for breast cancer in men are shown in Table 2.

Mutations in *BRCA* are among the most clearly established risk factors for breast cancer in men. *BRCA1* and *BRCA2* are tumor-suppressor genes involved in DNA repair; mutations in these genes are found in 5 to 10% of women with breast cancer and confer a 45 to 65% risk of breast cancer by the age of 70 years.[3] Population-based studies have shown that 0 to 4% of men with breast cancer have *BRCA1* mutations, and 4 to 16% have *BRCA2* mutations.[16-19] In populations with founder mutations, *BRCA* mutations account for a higher percentage of cases; for instance, in Iceland, a *BRCA2* founder mutation is implicated in 40% of cases of breast cancer in men.[20] The risk of breast cancer is substantially lower among healthy men with *BRCA* mutations than among healthy women with *BRCA* mutations. Using data

Table 1. Key Differences between Breast Cancer in Men and in Women.*

Factor	Men	Women
Risk of breast cancer (%)		
General population[2]	<1	12
Carrier of *BRCA1* mutation[3,4]	1	65
Carrier of *BRCA2* mutation[3,4]	7	45
Clinical presentation		
Median age at diagnosis (yr)[5]	67	62
Median tumor diameter (mm)[6]	20	15
Nodal involvement (% of patients)[6]	42	33
Pathological characteristics (%)		
Invasive lobular subtype[5]	1	12
Estrogen-receptor–positive[2,7]	99	83
HER2-positive[2,7]	9	17
Androgen-receptor–positive[7,8]	97	61
Somatic mutations[9]	Mutations in DNA-repair genes more likely in men	Loss of 16q and mutations in *PIK3CA* and *TP53* more likely in women
Subtypes (%)[2,7]		
HR-positive, HER2-negative	90	71
HR-positive, HER2-positive	9	12
HR-negative, HER2-positive	<1	5
HR-negative, HER2-negative	<1	12
5-Yr overall survival (%)[6]		
Stage I	87	90
Stage II	74	82
Stage III	57	57
Stage IV	16	19
Treatment		
Genetic counseling[10]	All patients	Selected patients
Adjuvant endocrine therapy[11]	Tamoxifen	Tamoxifen, aromatase inhibitor, ovarian suppression (premenopausal)

* HER2 denotes human epidermal growth factor receptor 2, and HR hormone receptor.

Table 2. Risk Factors for Breast Cancer in Men.

Demographic
Increasing age
Black race
Family history of breast cancer
Genetic
BRCA2
BRCA1
CHEK2
PALB2
Environmental
Radiation exposure
Hormonal
Increased serum estradiol
Klinefelter's syndrome
Gynecomastia
Liver disease
Obesity
Testicular abnormalities

from 1939 families in the National Cancer Institute's Cancer Genetics Network, Tai and colleagues evaluated the risk of breast cancer among male carriers of *BRCA* mutations. In 70-year-old men, the estimated cumulative risk of breast cancer was 1.2% for *BRCA1* mutation carriers and 6.8% for *BRCA2* mutation carriers.[4] Data are inconsistent on the question of whether the presence of a *BRCA* mutation affects the age at diagnosis or the prognosis.[21,22] The National Comprehensive Cancer Network (NCCN) guidelines recommend that men with *BRCA* mutations receive breast self-examination training and education and undergo yearly clinical breast examination, starting at the age of 35 years, with prostate cancer screening considered (for *BRCA1* mutation carriers) or recommended (for *BRCA2* mutation carriers) starting at the age of 45 years. The guidelines note that data in support of breast imaging in men are limited, and the guidelines do not include recommendations to screen male *BRCA* mutation carriers with mammography or magnetic resonance imaging.[10]

Several genes have also been identified that confer a moderate risk of breast cancer for men, as well as for women. *CHEK2* encodes a cell-cycle checkpoint kinase involved in DNA-repair pathways. According to a report from the CHEK2–Breast Cancer Consortium, a truncating mutation (*CHEK2**1100delC) in men confers a risk of breast cancer that is increased by a factor of 10, as compared with the risk among men who do not have the mutation.[23] However, other case series studies have had inconsistent results, and taken as a whole, these studies suggest that the *CHEK2* variant may modestly increase the risk but

is unlikely to account for a substantial fraction of cases of breast cancer in men.[24-27] *PALB2* (partner and localizer of BRCA2), which encodes a BRCA2-interacting protein, has been shown to confer a susceptibility to breast cancer in women.[28] Mutations in *PALB2* have also been reported in men with breast cancer and in families with cases of breast cancer in men, but the prevalence of *PALB2* mutations in men with breast cancer is reported to be only 1 to 2%.[19,29-32] Single-nucleotide polymorphisms in *CYP17*, *RAD51B*, and chromosomes 2q35, 5p12, 6q25.1, 10q26.13, and 16q12.1 have been reported to increase the risk of breast cancer in men.[33-35] Mutations in *PTEN* (resulting in Cowden's disease) and the androgen receptor have also been reported in men with breast cancer.[36,37]

Radiation exposure has been reported as a risk factor for breast cancer in men.[38] The most compelling evidence comes from studies of atomic bomb survivors.[39,40] A cohort of 45,880 Japanese men was followed from 1958 through 1998, and rates of cancer were reported. The rate of breast cancer in men increased during that period, with a dose–response relationship between the estimated radiation dose to the breast and the incidence of breast cancer, providing convincing evidence of the link between radiation and breast cancer in men.

Elevated levels of estrogen are thought to predispose men to breast cancer. The Male Breast Cancer Pooling Project conducted a nested case–control study of estrogen and androgen levels in relation to the risk of breast cancer in men. Although androgen levels were not associated with the risk of breast cancer, circulating estradiol levels were. For men in the highest quartile of estradiol levels as compared with those in the lowest quartile, the odds ratio for breast cancer was 2.47 (95% confidence level, 1.10 to 5.58).[41] Other conditions that are associated with elevated estrogen levels are also linked to breast cancer in men, including gynecomastia, liver disease, testicular abnormalities, and obesity.[42-44] Klinefelter's syndrome, or the 47,XXY karyotype, is characterized by hypogonadism and low testosterone levels and has been associated with an increased risk of breast cancer in men. In a study from the Swedish Cancer Registry, the estimated risk of breast cancer among men with Klinefelter's syndrome was increased by a factor of 50, as compared with the risk among men without the syndrome.[45] A cohort study in Britain involving 3518 men with Klinefelter's syndrome showed that the cumulative risk of breast cancer was 0.9% by the age of 75 years.[46] The increased risk may be related to a high ratio of estrogen to androgen.

CLINICAL PRESENTATION AND EVALUATION

Most men with breast cancer present with a painless, retroareolar mass.[47] Other signs can include nipple retraction, bleeding from the nipple, skin ulceration, and palpable axillary adenopathy. The most common differential diagnosis is gynecomastia, which is a highly prevalent condition.[48] If there is concern about the possibility of cancer, breast imaging should be performed. The American College of Radiology has published criteria for evaluation of the male breast and recommends ultrasonography as the initial test for men younger than 25 years of age who have an indeterminate palpable mass.[49] For men 25 years of age or older or those with questionable findings on physical examination, mammography is recommended as the initial diagnostic test, with ultrasonography recommended if the mammographic findings are inconclusive or suggestive of cancer.[49] On mammograms, breast cancers in men often appear as eccentric, retroareolar masses with irregular, spiculated edges.[50,51] Men with suggestive lesions should undergo core biopsy to confirm the diagnosis. As a consequence of low public awareness and the absence of screening programs, men are likely to present with larger tumors than women and are more likely than women to present with regional nodal metastases.[6] Staging for breast cancer in men is the same as for women, and there are no sex-specific recommendations for the use of systemic staging studies.[11] Because breast cancer in men is associated with an increased risk of germline *BRCA* mutations, as compared with the risk among women with breast cancer, practitioners should consider referral of all men with breast cancer to a specialist in cancer genetics for discussion of genetic testing.[10]

PATHOLOGICAL CHARACTERISTICS

Since mammographic screening is not recommended for the general male population, and

since ductal carcinoma in situ is rarely manifested as a palpable mass, only approximately 10% of men with breast cancer present with ductal carcinoma in situ.[5,52,53] Lobular carcinoma in situ is very rare, since terminal lobules are typically not present in the male breast. Most cases of breast cancer in men are invasive carcinomas, with invasive ductal carcinoma by far the most prevalent histologic type. Less common histologic subtypes in men include papillary cancers (in 2 to 3% of cases) and mucinous cancers (in 1 to 2% of cases).[5,54] Although lobular carcinomas account for approximately 12% of invasive cancers in women, this subtype is much less prevalent among men, accounting for only 1 to 2% of cases.[5,54]

Overall, breast cancers in men are more likely to be positive for estrogen receptor and negative for human epidermal growth factor receptor 2 (HER2) than breast cancers in women, although the incidence of these markers is similar to that in older, postmenopausal women.[5,55,56] In the International Male Breast Cancer Program, a central pathological review of tumor samples from 1483 men with breast cancer was performed.[56] In this large series, 99% of the tumors were positive for estrogen receptor, 82% were positive for progesterone receptor, and 97% were positive for androgen receptor. Only 9% of the tumors were HER2-positive. With the use of immunochemical surrogates, the study also evaluated breast cancer subtypes: 42% of the tumors were luminal A–like, 49% were luminal B–like and HER2-negative, 9% were HER2-positive, and less than 1% were triple-negative (estrogen-receptor–negative, progesterone-receptor–negative, and HER2-negative). Other studies with genomic profiling of breast cancers from men have also shown that most cases are either luminal A–like or luminal B–like.[9] Although some of the somatic mutations found in breast tumors in men were similar to those found in estrogen-receptor–positive breast tumors in women, the frequency of such mutations differed, with tumors from men less likely to have 16q losses, *PIK3CA* mutations, and *TP53* mutations.[9] In addition, the breast cancers in men were more likely to have somatic mutations affecting genes related to DNA repair and were less likely to have mutations in genes affecting the phosphatidylinositol 3-kinase (PI3K)–AKT–mTOR (mammalian target of rapamycin) pathway.[9] A gene-expression study using unsupervised clustering showed two unique subgroups of breast cancer in men, M1 and M2, which differed from the intrinsic subtypes seen in breast cancer in women.[57,58] These findings show that there are biologic differences in breast cancers in men and women that have the potential to be clinically meaningful.

PROGNOSIS

Several studies have evaluated outcomes in men with breast cancer.[6,59-61] In general, men with breast cancer have lower unadjusted rates of overall survival than do women with breast cancer. However, much of this difference can be explained by a more advanced stage of disease and an older age at diagnosis, as well as a shorter life expectancy in general, for men than for women.[6,59-61] In a study of men with breast cancer in Europe and Asia, men had lower 5-year survival rates than women in the unadjusted analysis but had higher survival rates than women after adjustment for demographic characteristics, disease stage, and treatment.[61] Black men with breast cancer have worse outcomes than white men with breast cancer, although the differences are diminished after adjustment for insurance coverage and income level.[62,63] Men who are older at diagnosis, have more advanced disease, and have triple-negative breast cancer have lower survival rates than younger men, those with less advanced disease, and those with a subtype other than triple-negative disease.[64] Survival rates have improved over time for both men and women with breast cancer, but unfortunately, the improvement for men has lagged behind that for women.[59]

Like women with breast cancer, men with breast cancer are at increased risk for second primary cancers as compared with their unaffected counterparts. The absolute risk of a second breast cancer in men is just under 2%.[65,66] Affected men also have an increased risk of melanoma and cancers of the small intestine, rectum, pancreas, prostate, and lymphohematopoietic system.[66,67] It is not clear whether these increases in risk are due to underlying mutations such as those in *BRCA2*, increased detection as a result of more careful attention to general medical care, or other factors.

TREATMENT

Since no randomized trials of local therapy have focused on men with breast cancer, treatment approaches are extrapolated from studies of treatment for women with breast cancer. Women with newly diagnosed breast cancer often undergo breast-conserving therapy (i.e., lumpectomy and whole-breast irradiation), but most men undergo mastectomy with either axillary lymph-node dissection or sentinel-node biopsy.[56] Even in men with early-stage disease, breast conservation is not common, despite the absence of any medical contraindication. An analysis of data from the SEER registries showed that only 18% of men with T1N0 tumors, according to the tumor–node–metastasis (TNM) staging system, underwent breast-conserving surgery.[68] Although not commonly used, breast-conserving therapy has been associated with survival rates equivalent to those associated with mastectomy in observational studies, suggesting that data from trials of surgery in women may be safely applied to men.[68-71] In addition, breast-conserving therapy may offer improved cosmetic and functional outcomes.[72] Sentinel-node biopsy is the standard approach for women with a clinically negative axilla, and this approach seems to be both feasible and accurate in men with breast cancer.[73,74]

Adjuvant radiotherapy should also be offered according to guidelines developed for women with breast cancer.[1] In practice, radiotherapy is often underused in men with breast cancer.[56,68] Data from SEER (for the 1988–2012 period) indicate that only 42% of men with stage I breast cancer received radiotherapy after breast-conserving surgery.[68] Internationally, the trend seems to be similar: for the 1990–2010 period, almost half of men who were treated with breast-conserving surgery did not receive radiotherapy.[56] No randomized trials have evaluated the role of radiotherapy after mastectomy in men, but population-based observational studies have suggested a benefit in men with node-positive breast cancer.[75-77]

In accordance with national treatment guidelines developed for women with breast cancer, adjuvant or neoadjuvant chemotherapy and HER2-targeted therapy should be offered to men with breast cancer who are at substantial risk for recurrence and death.[11] However, as is the case with local therapies, no randomized trials of chemotherapy have enrolled men with breast cancer. Between 1974 and 1988, a single prospective trial was conducted to evaluate adjuvant chemotherapy in men with breast cancer.[78] This National Cancer Institute study enrolled 31 men who had stage II breast cancer with lymph-node involvement. All the men were treated with mastectomy and 12 cycles of cyclophosphamide, methotrexate, and fluorouracil. This cohort has been followed for more than 20 years, and survival rates have been better than historical rates, with an 80% survival rate at 5 years, 65% at 10 years, and 42% at 20 years. Observational cohort studies have suggested improved survival among men who received adjuvant chemotherapy.[79-81] In examining the risks and potential benefits of chemotherapy, it is important for clinicians to consider that men tend to be older at diagnosis and that they have a shorter life expectancy than women.[5]

Genomic tests, such as Oncotype DX, a 21-gene assay that yields a recurrence score, and MammaPrint, are increasingly being used to determine the prognosis for women with breast cancer and the likelihood that chemotherapy will be beneficial. The results of Oncotype DX testing and outcomes in men with breast cancer have been reported (Table 3).[82-84] The mean quantitative gene expression was greater in men than in women for genes related to estrogen receptor, proliferation, and invasion. Overall, the mean recurrence score (which ranges from 0 to 100, with higher scores indicating a greater likelihood of recurrence) was similar in men and women. However, significantly more men than women had a recurrence score of 31 or higher (12% vs. 7%), indicating a high risk of recurrence, or a score of less than 11 (34% vs. 22%), indicating a low risk of recurrence. Outcome data for 322 men in the SEER registry who underwent recurrence-score testing support the prognostic value of such testing in men.[82] The 5-year breast cancer–specific survival rates among men were 99.0% for those with a recurrence score of less than 18, 95.9% for those with a recurrence score of 18 to 30, and 81.0% for those with a recurrence score of 31 or higher. Among women, the survival rates were 99.5%, 98.6%, and 94.9% respectively. These data suggest that men with high recurrence scores have worse outcomes than women

Table 3. Distribution of 21-Gene Recurrence Scores and Associated 5-Year Survival among Men with Breast Cancer.*

Score Distribution and Survival	No. of Patients Tested	Recurrence Score†		
		<18	18–30	≥31
		% of patients		
Score distribution				
SEER, men[82]	3806	58.0	29.6	12.4
SEER, women[82]	571,115	58.2	34.4	7.4
Israeli men[83]	65	44.6	41.5	13.9
NCDB, men[84]	1478	59.3	27.4	13.3
5-Year BCSS				
SEER, men[82]	322	99.0	95.9	81.0
SEER, women[82]	55,842	99.5	98.6	94.9

* BCSS denotes breast cancer–specific survival, NCDB National Cancer Data Base, and SEER Surveillance, Epidemiology, and End Results.
† The recurrence score ranges from 0 to 100, with higher scores indicating a greater likelihood of recurrence. A recurrence score of 31 or higher indicates a high risk of recurrence, and a score of less than 18 indicates a low risk of recurrence.

with high scores, but the small number of men in this group (42) must be taken into account.

Since most breast cancers in men are hormone-receptor–positive (positive for estrogen receptor, progesterone receptor, or both), endocrine therapy is an important component of cancer management. It is also the treatment that is most likely to differ in efficacy between men and women because of underlying differences in hormone production. The standard adjuvant endocrine therapy for men with hormone-receptor–positive breast cancer is 5 to 10 years of treatment with tamoxifen. Decisions about the duration of therapy may be individualized, as they are for women, on the basis of the risk of recurrence and side effects.[11] Tamoxifen has established efficacy in patients with metastatic cancer, and observational studies of adjuvant treatment with tamoxifen have also suggested a survival benefit.[47,85] The side effects of tamoxifen in men may include venous thrombosis, cataracts, sexual dysfunction, mood changes, hot flashes, and leg cramps. Few published studies have specifically evaluated differences in side effects between men and women.[86]

The efficacy of aromatase inhibitors in men is not clear and may be lower in men than in women. Population-based series have shown inferior survival rates when men were treated with adjuvant aromatase inhibitors as compared with tamoxifen.[87,88] The hormonal effects of aromatase inhibitors in men without breast cancer have been evaluated in several studies.[89,90] These studies indicated that treatment of healthy men with anastrozole results in a decrease in estradiol levels by approximately 50%, a 60% increase in testosterone levels, and increases in luteinizing hormone and follicle-stimulating hormone levels.[89] After treatment with anastrozole, estradiol in healthy men was suppressed to a level of 14.1 pg per milliliter (52 pmol per liter).[90] In contrast, postmenopausal women treated with anastrozole had estradiol levels that were suppressed to a level of less than 1 pg per milliliter (3.7 pmol per liter).[91] The lack of complete estradiol suppression in men treated with aromatase inhibitors is thought to be due to feedback loops to the hypothalamus and pituitary glands, which can be overcome with the addition of a gonadotropin-releasing hormone (GnRH) analogue. For men who are not good candidates for tamoxifen, such as those with a prior thrombosis, a GnRH analogue can be used as adjuvant therapy, with or without an aromatase inhibitor. However, treatment with single-agent aromatase inhibitors is not be considered to be a standard adjuvant approach.

The management of metastatic breast cancer in men generally mirrors treatment approaches used in women, although fewer data are available regarding the efficacy of specific hormonal therapies. Some of the earliest studies showed responses to surgical approaches, including orchiectomy, adrenalectomy, and hypophysectomy.[92] However, these approaches result in substantial morbidity and are no longer routinely in use.

Current approaches to endocrine therapy in men with metastatic breast cancer include the same medications that are indicated for the treatment of metastatic breast cancer in women, including tamoxifen, aromatase inhibitors, and fulvestrant. Case reports and case series have documented clinical responses to both single-agent aromatase inhibitors and aromatase inhibitors plus GnRH analogues, but the latter may be

the preferred approach.[93-97] Fulvestrant, a selective estrogen-receptor down-regulator, also has activity in hormone-receptor–positive metastatic breast cancer in men. A pooled analysis of data for 23 men treated with fulvestrant (without a GnRH analogue) showed that 26% of the men had a partial response and 48% had stable disease, response rates that are similar to those reported for women.[98] No data are available from studies comparing the efficacy of fulvestrant alone with fulvestrant given in combination with a GnRH analogue, although the pooled analysis suggests the efficacy of fulvestrant as a single agent. Cyclin-dependent kinase (CDK) inhibitors or mTOR inhibitors used in combination with endocrine therapy, as compared with endocrine therapy alone, have been reported to result in significantly improved outcomes in women with breast cancer.[99,100] Unfortunately, data on such treatment in men with breast cancer are lacking. However, NCCN guidelines recommend that men be treated with the same approach as that used in postmenopausal women, with the caveat that aromatase inhibitors used alone may not be as effective as aromatase inhibitors used with a GnRH analogue.[11] Therefore, the use of CDK inhibitors or mTOR inhibitors as part of combination endocrine therapy is a reasonable approach for men with metastatic breast cancer.

FOLLOW-UP AFTER TREATMENT

In general, follow-up care for men with breast cancer should be similar to the care provided for women with breast cancer. However, the usefulness of screening mammography has not been established, and imaging may not be necessary, given the low incidence of second primary tumors and the absence of a recommendation for imaging in male *BRCA* mutation carriers. Men who are treated with GnRH analogues are at increased risk for bone loss, and an NCCN task force recommends that such patients undergo assessment of bone mineral density at baseline and every 2 years.[101] Hot flashes are a common side effect of both GnRH analogues and tamoxifen. To help relieve hot flashes in men undergoing treatment for breast cancer, treatment with venlafaxine, which was shown to be effective in reducing hot flashes in men with prostate cancer who were receiving GnRH analogues,[102] can be considered.

FUTURE DIRECTIONS

Many gaps remain in our knowledge about breast cancer in men. Efforts are needed that will focus on preventing the undertreatment of men with breast cancer. In addition, a better understanding of the biology of the disease is critical, particularly in order to identify differences between breast cancer in men and breast cancer in women and to determine whether identified differences have therapeutic implications. The International Male Breast Cancer Program has collected samples from more than 1400 men with breast cancer, and further analyses, including RNA sequencing studies, are ongoing.[7] This program has recently completed a prospective study enrolling more than 500 men with breast cancer and collecting samples and quality-of-life data.[103] The overall goal of this international effort will be to launch therapeutic clinical trials focusing on breast cancer in men.

Other clinical trials are currently under way, including a study of the safety and efficacy of seviteronel, an oral selective CYP17 lyase inhibitor and androgen-receptor blocker, in men with breast cancer (ClinicalTrials.gov number, NCT02580448). The German Breast Group has enrolled 55 men in a phase 2 clinical trial comparing tamoxifen, tamoxifen plus a GnRH analogue, and an aromatase inhibitor with a GnRH analogue (NCT01638247).[104]

Finally, although most treatment trials were previously limited to women with breast cancer, many trials are now enrolling both men and women.[105-108] Whenever feasible, studies of treatment for breast cancer should be open to both men and women with breast cancer in order to build an evidence base that supports future treatment recommendations. These recent efforts provide evidence that clinical trials of treatment for breast cancer in men are feasible, and a continued commitment to such studies will be essential to improve the standard of care for men with breast cancer.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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