ORIGINAL RESEARCH • BREAST IMAGING

Radiology

Breast Cancer Screening in High-Risk Men: A 12-year Longitudinal Observational Study of Male Breast Imaging Utilization and Outcomes

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Conflicts of interest are listed at the end of this article.

Radiology 2019; 293:282–291 • https://doi.org/10.1148/radiol.2019190971 • Content code: BR

Background: Male breast cancer incidence is rising. There may be a potential role in selective screening in men at elevated risk for breast cancer, but the effectiveness of such screening remains unexplored.

Purpose: To evaluate patterns of male breast imaging utilization, to determine high-risk screening outcomes, and to delineate risk factors associated with cancer diagnosis.

Materials and Methods: This retrospective study reviewed consecutive male breast imaging examinations over a 12-year period (between 2005–2017). Examination indications, biopsy recommendations, and pathologic results were correlated with patient characteristics. Fisher exact test, Mann-Whitney test, Spearman correlation, and logistic regression were used for statistical analysis.

Results: A total of 1869 men (median age, 55 years; range, 18–96 years) underwent 2052 examinations yielding 2304 breast lesions and resulting in 149 (6.5%) biopsies in 133 men; 41 (27.5%) were malignant and 108 (72.5%) were benign. There were 1781 (86.8%) diagnostic and 271 (13.2%) screening examinations. All men undergoing screening had personal or family history of breast cancer and/or genetic mutations. There was a significant increase in the number of examinations in men relative to the number of examinations in women over time (Spearman correlation, $r = 0.85$; $P < .001$). Five node-negative cancers resulted from screening mammography, yielding a cancer detection rate of 18 per 1000 examinations (95% confidence interval [CI]: 7, 41), with cancers diagnosed on average after 4 person-years of screening (range, 1–10 person-years). Mammographic screening sensitivity, specificity, and positive predictive value of biopsy were 100% (95% CI: 50%, 100%), 95.0% (95% CI: 93.1%, 98%), and 50% (95% CI: 22.2%, 77.8%). Older age ($P < .001$), Ashkenazi descent ($P < .001$), genetic mutations ($P = .006$), personal history ($P < .001$), and first-degree family history ($P = .03$) were associated with breast cancer. Non–first-degree family history was not associated with cancer ($P = .09$).

Conclusion: There is potential benefit in screening men at high risk for developing breast cancer. Such screening may have increased over time.

Male breast cancer is primarily diagnosed after clinical presentation, as screening is not routinely performed. For this reason, breast imaging plays a limited role in detection of male breast cancer, and data on this topic are sparse. The American Cancer Society projects that 2670 new cases of invasive breast cancer will be diagnosed in men in 2019, compared with only 900 cases diagnosed in 1991 (1). Furthermore, there is persistent evidence of disparity between male and female breast cancer survival due to delayed diagnosis and less tailored therapy in men (median survivals, 7 years for men vs 9.8 years for women; $P < .005$), with the greatest survival disparity seen in stage I or II and node-negative disease (median survivals, 6.1 years for men vs 14.6 years for women; $P < .005$), underscoring the need for early and timely diagnosis in men (2,3).

Although general screening has no role in male breast cancer detection due to an overall low prevalence of disease in men, the utility of selective screening in those with identifiable risk factors is unknown. Despite often sporadic and inconsistent screening practices in men with high risk for breast cancer in the absence of guidelines (4,5), there is anecdotal evidence of individual benefits in case reports (6–8). For example, *BRCA*2 male breast cancers are known to be associated with a younger age at diagnosis (mean age, 50s to 60s), positive axillary nodal status, and a typically nontriple-negative molecular profile (most commonly estrogen receptor–positive, progesterone receptor–positive, and human epidermal growth factor receptor 2–negative), all of which might support screening (9–11). Mammography and sonography perform well in men in the diagnostic setting, both with sensitivities and negative predictive values approaching 100% (12–14), and have the potential to provide early breast cancer detection in select patients and to improve individual outcomes. Yet, although men at risk may be increasingly identified in recent years given the wider availability of genetic testing and counseling and also through family members diagnosed with certain genetic mutations, it is currently unknown how and to what

Abbreviations

BI-RADS = Breast Imaging Reporting and Data System, CDR = cancer detection rate, CI = confidence interval, PPV = positive predictive value

Summary

Selective mammography screening in men at elevated risk for breast cancer is beneficial and depicts clinically occult malignancy at a cancer detection rate higher than that of screening among women with average risk.

Key Results

- Mammography screening in men with high risk allowed early cancer diagnosis and yielded a cancer detection rate of 18 per 1000 examinations, which is higher than cancer yield among women with average risk of 3–5 per 1000 examinations.
- Mammographic screening depicted clinically occult breast malignancies in men with high risk, all of which were stage 0–1 and node negative, improving prognosis.
- Risk factors associated with male breast cancer included a personal history of breast cancer (odds ratio, 84), Ashkenazi ancestry (odds ratio, 13), genetic mutations (odds ratio, 7), and first-degree family history of breast cancer (odds ratio, 3).
- The number of breast imaging examinations in men increased relative to the number of examinations in women over the 12-year period, suggesting a need for guidance.

extent breast imaging is used in this population (15,16). To our best knowledge, there is no prior study evaluating male breast imaging utilization patterns and screening outcomes in men. We hypothesized that risk-based screening will provide early cancer detection in men, and that such screening may have increased in recent years.

The purpose of this study was, therefore, to evaluate the pattern of male breast imaging utilization, to determine high-risk screening outcomes, and to delineate risk factors associated with cancer diagnosis.

Materials and Methods

Study Population

This institutional review board–approved Health Insurance Portability and Accountability Act–compliant retrospective study was performed with a waiver of written informed consent. An observational study design was used to capture multiple imaging examinations performed in the same patient over time. The study cohort comprised consecutive adult men (both symptomatic and asymptomatic) who underwent breast imaging examinations (mammography with or without US) at a tertiary academic medical center between January 2005 and April 2017 for all clinical indications, with at least 1 year of clinical and/or imaging follow up. Men younger than 18 years (n = 7) were excluded, given extremely low likelihood of malignancy. Those who presented for care from outside institutions with missing imaging reports, pathologic results, or lack of documentation of patient characteristics of interest were excluded (n = 29). Transgender patients (n = 12) were excluded. Details of inclusion and exclusion are displayed in a flow chart (Fig 1).

Examination Considerations

Screening examinations were defined as examinations performed either for surveillance due to a personal history of breast cancer, or for screening due to elevated risks predisposing to breast cancer. Mammography was the only modality used for screening in men. Diagnostic examinations were defined as examinations performed for evaluation of male breast symptoms, or for follow-up of probably benign findings. Mammography and/or sonography were both used in diagnostic evaluations. Diagnostic studies performed at a single visit aimed at answering the same clinical question were considered a single event or examination. For example, a single diagnostic examination might include a mammogram only, or might include both a mammogram and an US. For the purpose of this study, therefore, the number of examinations was defined as the number of single-event breast imaging evaluations. The number of examinations performed in men was compared to the total number of examinations and the number of examinations performed in women in each year. During the study period, mammograms were obtained by using full-field digital mammography (between 2005–2016) or digital breast tomosynthesis (between 2016–2017) (Hologic, Bedford, Mass). US was performed by using 7–12-MHz linear array transducers (Philips, Bothell, Wash; or GE, Wauwatosa, Wis) (between 2005–2006) and 14-MHz transducers (Siemens, Mountain View, Calif) (between 2006–2017).

Data Collection

Imaging and pathologic archives and electronic medical records were reviewed (Y.G., breast imaging fellowship–trained with 6 years of experience; J.E.G., 1st-year resident; and T.K.Y., 4th-year medical student). Examination indications, imaging findings, biopsy recommendations, and pathologic results were correlated with patient characteristics including age, personal and/or family history of breast cancer, any known genetic mutation, and Ashkenazi descent. Men with any or a combination of known risk factors predisposing to breast cancer such as personal and family history of breast cancer, breast cancer related–genetic mutations, or Ashkenazi descent who presented for screening were considered high risk, as in, higher-than-average risk. Finer delineation of breast cancer risk in men is not currently possible due to a lack of data or guidelines (8,17). Examinations were categorized as either diagnostic or screening in indication, as defined previously. Imaging examinations and reports were reviewed to identify clinical presentation and the number, type, and location of all described breast lesions, as well as Breast Imaging Reporting and Data System (BI-RADS) classification. Presence of gynecomastia was recorded. Pathologic results were reviewed for percutaneous biopsies and for surgical excisions whenever appropriate. Clinical and imaging features of all malignant lesions were analyzed, documenting whether clinically evident or occult, lesion type, size, grade, receptor status, axillary nodal status, and first imaging modality of detection. For the screening group, screen interval and whether regular annual screening or sporadic screening was undertaken was recorded. Patient characteristics of those who underwent regular versus sporadic screening were reviewed. Number of person-years screened to achieve cancer diagnosis

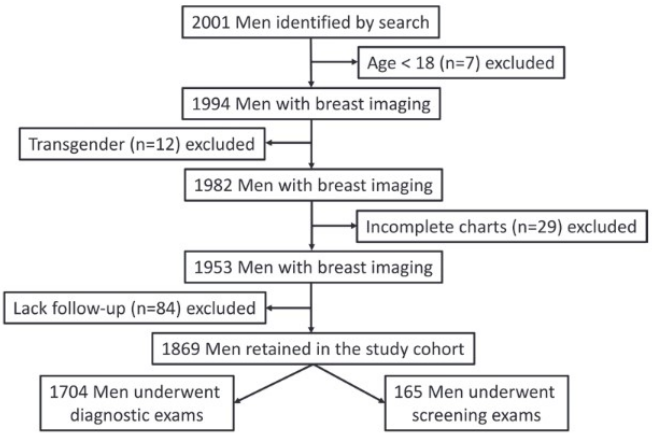

Figure 1: Flowchart demonstrates study cohort inclusion and exclusion criteria.

Table 1: Characteristics of Men Who Underwent Breast Imaging Examinations between 2005–2017 (*n* = 1869)

Patient Characteristic	Value (%)
Family history of breast cancer	20.2 (378/1869)
First-degree family history of breast cancer	12.9 (242/1869)
Genetic mutation	2.4 (45/1869)
Ashkenazi descent	1.2 (22/1869)
Personal history of breast cancer	2.5 (47/1869)

Note.—Data in parentheses are numerators and denominators. Median age was 55 years (range, 18–96 years) and mean age ± standard deviation was 54 years ± 19.

was recorded in all men with screen-detected cancers (with or without personal history of prior breast cancer). Interval cancers—defined as any cancer presenting within 12 months of a preceding screening mammogram that was negative for breast cancer—were recorded, as was any presentation of clinical concern or diagnostic imaging presenting within 12 months of a screening examination.

Screening and Diagnostic Outcomes

Subanalysis was performed to acquire screening and diagnostic outcomes. There are no established breast cancer screening metrics among men. Screening mammography benchmarks in women based on the fifth edition of American College of Radiology BI-RADS definitions were used to assess outcomes in our screening group. For those with multiple screening mammograms, annual screening was defined as returning to screen within 9–18 months of the preceding mammogram (18). Cancer detection rate (CDR), sensitivity, specificity, positive predictive value (PPV), and negative predictive value were calculated as applicable. PPV1 was defined as probability of cancer among all positive screening mammograms (BI-RADS 0, 3, 4, or 5). PPV2 was defined as probability of cancer among all lesions recommended for biopsy (BI-RADS 4 or 5). PPV3 was defined as probability of cancer among all biopsied lesions (BI-RADS 4 or 5) (19). For all measures except PPV2 and PPV3, a positive mammogram was defined as one with initial assessment of BI-RADS 0, 3, 4 or 5. For PPV2 and PPV3, a positive mammogram was defined as one with final assessment of BI-RADS 4 or 5. Interval cancer rate was assessed as described above (20). Diagnostic mammography outcomes of cancer yield, sensitivity, specificity, PPV2, and PPV3 were also calculated (21).

Statistical Analysis

Statistical analysis was performed by using the Mann-Whitney test for age comparison of men with and without breast cancer diagnosis. The Fisher exact test was performed to allow comparison of prevalence of risk factors such as family history of breast cancer, personal history of breast cancer, known genetic mutation, or Ashkenazi Jewish ancestry among men with and without breast cancer diagnosis. The Fisher exact test was also performed for comparison of imaging features of breast malignancies detected at screening versus diagnostic examinations. The Spearman correlation was used to assess whether the number of examinations in men tended to increase or decrease relative to the number of examinations in women over time, and whether the proportion of examinations with a given indication tended to increase or decrease over time. Time was binned by year of study, with time represented for each patient with multiple examinations as the year of study in which the patient underwent their first examination. Temporal trends in the proportion of examinations with each indication were assessed by using logistic regression. The logistic analysis used the individual patient as the unit of observation and time was represented as the actual date of the examination of each patient. The strength of any temporal change in the probability of examinations with a given indication was characterized in terms of the odds ratio, with increased odds expressed as odds ratio greater than 1 or decreased odds if odds ratio was less than 1, with 95% confidence interval (CI) provided.

To account for the fact that some men underwent multiple examinations and that multiple results for the same person cannot be assumed to be statistically independent, generalized estimating equations were used to incorporate an anonymized identifier into the analysis, allowing results to be analyzed as symmetrically correlated when associated with the same person, and as independent when associated with different people. The generalized estimating equations–based logistic regression for correlated data were also used to assess whether each risk factor influenced the likelihood of a biopsy recommendation, and whether each risk factor was predictive of a positive biopsy for malignancy. All statistical tests were conducted with the two-sided significance level of 5% by using SAS (version 9.3; SAS Institute, Cary, NC).

Results

Study Population and Breast Imaging Utilization

There were 1781 (86.8%) diagnostic and 271 (13.2%) screening studies for a total of 2052 examinations in 1869 men

Table 2: Distribution of Screening and Diagnostic Examinations Performed in Men and Women over the 12-Year Period

	Screening Examinations					Diagnostic Examinations				
Year	No. Men	No. Women	No. Total	Men (%)	M/W (%)	No. Men	No. Women	No. Total	Men (%)	M/W (%)
1	9	6385	6394	0.141	0.141	54	4843	4897	1.10	1.12
2	7	6199	6206	0.113	0.113	24	5008	5032	0.48	0.48
3	3	6875	6878	0.044	0.044	29	5609	5638	0.51	0.52
4	3	7017	7020	0.043	0.043	22	6259	6281	0.35	0.35
5	15	6974	6989	0.215	0.215	60	6597	6657	0.90	0.91
6	13	7266	7279	0.179	0.179	57	7499	7556	0.75	0.76
7	13	8577	8590	0.151	0.152	81	8546	8627	0.94	0.95
8	19	9673	9692	0.196	0.196	135	8765	8900	1.52	1.54
9	24	11627	11651	0.206	0.206	141	8959	9100	1.55	1.57
10	33	12963	12996	0.254	0.255	247	8999	9246	2.67	2.74
11	56	14581	14637	0.383	0.384	340	8711	9051	3.76	3.90
12	61	15992	16053	0.380	0.381	466	8803	9269	5.03	5.29

Note.—Data are the total number of examinations performed each year, the number of these examinations that were for men and woman and the percentage of examinations during each year that were performed in men, as well as the ratio of the number of examinations performed each year for men (M) to the number of examinations in that year performed for women (W). Study period was 2005–2017 and examination modality was mammography. Spearman correlation between year of study and the percentage of examinations each year that were performed in men was $r = 0.85$ for screening examinations and $r = 0.83$ for diagnostic examinations, with both correlations significant at $P < .001$.

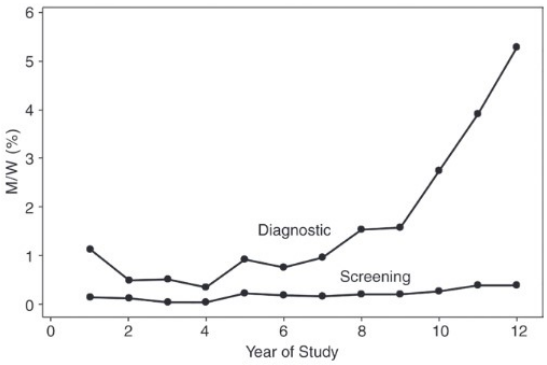

Figure 2: Graph shows ratio of number of screening and diagnostic examinations performed each year in men (M) to number of examinations in that year performed in women (W), expressed as a percentage. Spearman correlation between year of study and ratio of M/W was $r = 0.85$ for screening examinations ($P < .001$) and $r = 0.83$ for diagnostic examinations ($P < .001$).

Table 3: Histopathologic Analysis of Biopsied Breast Lesions ($n = 149$)

Biopsy Yield and Pathologic Finding	No. of Biopsied Lesions	Percentage
Malignant		
Invasive ductal carcinoma with ductal carcinoma in situ	38	25.5
Ductal carcinoma in situ	3	2.0
Benign		
Apocrine metaplasia	7	4.7
Angiolipoma	6	4.0
Abscess/Phlegmon	5	3.4
Lipoma	10	6.7
Fat necrosis	13	8.7
Fibroadenoma	1	0.7
Hematoma	3	2.0
Gynecomastia	39	26.2
Granulomatous reaction	9	6.0
Lymphoid hyperplasia	7	4.7
Nodular fibrosis	4	2.7
Myofibroblastoma	1	0.7
Cavernous hemangioma	1	0.7
Steatocytoma	1	0.7
Benign, not otherwise specified	1	0.7

(median age, 55 years; range, 18–96 years) between 2005–2017 (Table 1). All 2052 examinations included mammography and 1004 (48.9%) also included sonography. The use of digital breast tomosynthesis was limited to only 46 studies (2.2%, 46 of 2052). The age groups undergoing diagnostic examinations (median age, 54 years; range, 18–96 years) and screening examinations (median age, 61 years; range, 21–92 years) were similar. All men who underwent screening had at least 2 years of clinical follow-up. Men who underwent diagnostic examinations had at least 1 year of clinical follow-up. For both screening and diagnostic examinations, the number of examinations in men significantly increased relative to the number of examinations in women over time (Spearman correlation, $r = 0.85$ for screening examinations; $P < .001$ and Spearman correlation, $r = 0.83$ for diagnostic examinations; $P < .001$) (Table 2) (Fig 2). The proportion of examinations in men with screening indications, however, did not fluctuate with the year of study (Spearman correlation, $r = -0.42$; $P = .16$). All men undergoing screening had personal or family history of breast cancer and/or genetic mutations ($n = 165$). This included men with genetic mutations in *BRCA*2 ($n = 29$), *BRCA*1 ($n = 12$), *BARD*1 ($n = 1$), *BRCA*2

Table 4: Risk Factors Associated with Malignancy

Feature	Feature Absent	Feature Present	Odds Ratio			
			Estimate	Lower	Upper	*P* Value
Ashkenazi	22.2 (30/135)	78.6 (11/14)	13	3	49	<.001
Family history*	24.1 (28/116)	39.4 (13/33)	2	1	5	.09
First-degree relative†	24.0 (30/125)	45.8 (11/24)	3	1	7	.03
Mutation	24.5 (34/139)	70.0 (7/10)	7	2	29	.006
Personal history	17.7 (23/130)	94.7 (18/19)	84	11	659	<.001

Note.—Unless otherwise specified, data are percentages, with numerators and denominators in parentheses. The percentage of biopsies with a positive result for malignancy in men with and without each risk factor and the lower and upper limits of a 95% confidence interval for the odds ratio of each risk factor as a predictor of a positive biopsy. Each *P* value is from the generalized estimating equations analysis to test whether the risk factor influences the probability of a positive biopsy.

* Indicates family history of breast cancer not otherwise specified. When specified as in first-degree relative(s), they are categorized separately under "first-degree relative" and not included under the general "family history" designation.

† Indicates family history of breast cancer in first-degree relative(s).

variant of uncertain significance (n = 1), *NBN* variant of uncertain significance (n = 1), *MLH*1 (Lynch syndrome) (n = 1), and men with Klinefelter syndrome (n = 2). While some men underwent regular annual screening, others underwent sporadic screening without consistent intervals. Men with personal history of prior breast cancer comprised the majority of the annual screening group (56.4%, 22 of 39). Of a total of 165 men, 18 (10.9%) underwent at least three screening examinations (up to 11 examinations), 21 (12.7%) underwent two screening examinations, and 126 (76.4%) underwent one screening examination. Among the 126 men who underwent one screening examination, 16 (12.7%) presented for surveillance due to personal history of prior breast cancer and 110 (87.3%) for high-risk screening related to other risk factors.

Patients and Histologic Analysis

In total, there were 149 (6.4%) biopsies in 133 men. Of these lesions, 41 (27.5%) were malignant and 108 (72.5%) were benign. Malignant lesions included 38 invasive ductal carcinomas with or without ductal carcinoma in situ, and three ductal carcinomas in situ. Benign lesions yielded a wide variety of concordant histopathologic results, as detailed in Table 3. Logistic regression detected a significant tendency for the likelihood of a positive biopsy to increase with age ($P < .001$) with an odds ratio of 1.06 (95% CI: 1.03, 1.08). The men diagnosed with breast cancer were significantly older than were those without breast cancer according to a Mann-Whitney test (median age, 64 years vs 50 years) (mean age ± standard deviation, 65.2 years ± 14.1 vs 51.4 years ± 16.7) ($P < .001$). Patients with a personal history of breast cancer or patients of Ashkenazi descent were more likely than those without these risk factors to be recommended for a biopsy. Older age, Ashkenazi descent, genetic mutations, personal history, and first-degree family history were associated with breast cancer. Non–first-degree family history was not significantly associated with cancer (Table 4). Among the 1869 men, 1084 (58%) had imaging findings of gynecomastia, the vast majority of which (95.2%, 1032 of 1084) were not associated with biopsy. Gynecomastia was present in eight men diagnosed with cancer (two at screening and six at diagnostic examinations), in none of the cases negatively impacting diagnosis.

Cancer Yield: Screening versus Diagnostic

A total of 41 breast cancers were diagnosed, five at screening and 36 at diagnostic examinations. Five node-negative cancers resulted from screening (four in men with personal history, one in a man with strong family history and genetic mutation) (Fig 3, Table 5), yielding a CDR of 18 per 1000 examinations (five of 271; 95% CI: 7, 41), with cancer diagnosed on average after 4 person-years of screening (range, 1–10 person-years) (Table 5). Among those with personal history, contralateral second cancers were diagnosed on average after 5.5 person-years of screening (range, 1–10 person-years). In comparison, 36 cancers resulted from 1781 diagnostic evaluations in symptomatic men, with a CDR of 20 per 1000 examinations (36 of 1781; 95% CI: 14.2, 27.8). Of these 36 cancers, nine were remote diagnoses without lesion type and size available, and three were without nodal status due to diagnosis in men advanced in age who did not undergo sentinel node dissection at surgery, leaving 24 cancers with complete profile for direct comparison with screen-detected cancers (Table 5). All cancers detected at diagnostic examinations (100%, 24 of 24) were masses (two of which were associated with calcifications) and were on average 2.1 cm in size (range, 1–3.8 cm) (Table 6). Most cancers (58.3%, 14 of 24) had axillary nodal metastasis. Concurrent with axillary nodal metastases, two tumors also had further lymphovascular invasion and distant metastases (Table 5). One tumor detected at diagnostic examination had direct dermal lymphatic invasion without axillary nodal spread (size, 2.3 cm) (Fig 4). The first imaging modality of detection for all cancers detected at diagnostic examination was mammography. All cancers detected at diagnostic examination were also visible at US. False-positive biopsy rate of US was 9.8% (98 of 1004). Of cancers detected at screening examinations, 40% (two of five) were masses and 60% (three of five) were calcifications only. The screen-detected masses averaged 1.2 cm in size (range, 0.8–1.5 cm). None of the screen-detected breast cancers had axillary nodal spread or other signs of local invasion. The first imaging modality of detection for all screen-detected cancers was mammography. Only two of the five screen-detected cancers were visible at US. In comparison to cancers detected at diagnostic examinations, screen-detected cancers were less likely to be mass lesions (40%, two of five vs 100%, 24 of 24) (P = .003) and more likely to be calcifications only (60%, three of five vs 0%, zero of 24) (P = .003); were more likely to be in situ as opposed to invasive disease (60%, three of five vs 0%, zero of 24) (P = .003); and were less

Table 5: Profiles of Male Breast Cancers Detected at Screening and Diagnostic Examinations (*n* = 29)

Lesion	Cancer Type	Patient Age (y)	Detection	Lesion Characteristics	Tumor Grade	Axillary Node	Years Screened
Profile of screen-detected male breast cancers (*n* = 5)							
1	IDC with DCIS	82	Mammogram and US	1.5-cm mass/calcifications	Grade 2	Negative	10
2	DCIS	73	Mammogram only	Calcifications	Grade 2	Negative	4
3	IDC	68	Mammogram and US	0.8-cm mass	Grade 3	Negative	7
4*	IDC with DCIS	53	Mammogram only	Calcifications	Grade 2	Negative	1
5*	DCIS	54	Mammogram only	Calcifications	Grade 2	Negative	1
Profile of diagnostic-detected male breast cancers (*n* = 24)							
6	IDC with DCIS	61	Mammogram and US	1-cm mass	Grade 2	Negative	…
7	IDC with DCIS	53	Mammogram and US	2.3-cm mass/calcifications	Grade 2	Negative	…
8	IDC with DCIS	52	Mammogram and US	2.2-cm mass/calcifications	Grade 3	Positive	…
9	IDC with DCIS	90	Mammogram and US	2.5-cm mass	Grade 2	Positive	…
10	IDC with DCIS	74	Mammogram and US	1.8-cm mass	Grade 3	Negative	…
11	IDC with DCIS	69	Mammogram and US	2.3-cm mass	Grade 3	Negative	…
12	IDC with DCIS	50	Mammogram and US	2-cm mass	Grade 3	Positive	…
13	IDC with DCIS	80	Mammogram and US	2.8-cm mass	Grade 3	Positive	…
14	IDC	37	Mammogram and US	1-cm mass	Grade 3	Positive	…
15	IDC with DCIS	68	Mammogram and US	2.7-cm mass	Grade 3	Negative	…
16	IDC with DCIS	64	Mammogram and US	1.5-cm mass	Grade 2	Negative	…
17	DCIS	57	Mammogram and US	1.7-cm mass	Grade 2	Negative	…
18	IDC	59	Mammogram and US	1.5-cm mass	Grade 2	Negative	…
19	IDC	86	Mammogram and US	1.7-cm mass	Grade 2	Positive	…
20	IDC with DCIS	81	Mammogram and US	2.7-cm mass	Grade 2	Positive	…
21	IDC with DCIS	83	Mammogram and US	2-cm mass	Grade 3	Positive	…
22	IDC with DCIS	83	Mammogram and US	2.3-cm mass	Grade 2	Positive	…
23	IDC with DCIS	61	Mammogram and US	2 cm mass	Grade 2	Positive	…
24	IDC with DCIS	74	Mammogram and US	3.8-cm mass	Grade 2	Positive	…
25	IDC with DCIS	38	Mammogram and US	3-cm mass	Grade 3	Positive	…
26	IDC with DCIS	74	Mammogram and US	1.8-cm mass	Grade 2	Negative	…
27	IDC with DCIS	66	Mammogram and US	1.9-cm mass	Grade 3	Positive	…

(Table 5 continues)

Table 5 (*continued*): Profiles of Male Breast Cancers Detected at Screening and Diagnostic Examinations (*n* = 29)

Lesion	Cancer Type	Patient Age (y)	Detection	Lesion Characteristics	Tumor Grade	Axillary Node	Years Screened
Profile of diagnostic-detected male breast cancers (*n* = 24)							
28	IDC with DCIS	64	Mammogram and US	2.5-cm mass	Grade 3	Positive	…
29	IDC with DCIS	57	Mammogram and US	2-cm mass	Grade 3	Positive	…

Note.—All invasive ductal carcinomas (IDCs) except lesion 13 were estrogen receptor (ER)–positive, progesterone receptor (PR)–positive, and human epidermal growth factor receptor 2 (HER2)–negative (lesion 13 was ER-positive, PR-positive, and HER2-positive); all ductal carcinomas in situ (DCIS) were ER-positive and PR-positive.

* Lesions 4 and 5 were detected in the same individual (see Fig 3). Lesions 7 and 27 were associated with lymphovascular invasion and lymphangitic spread to the lung, respectively.

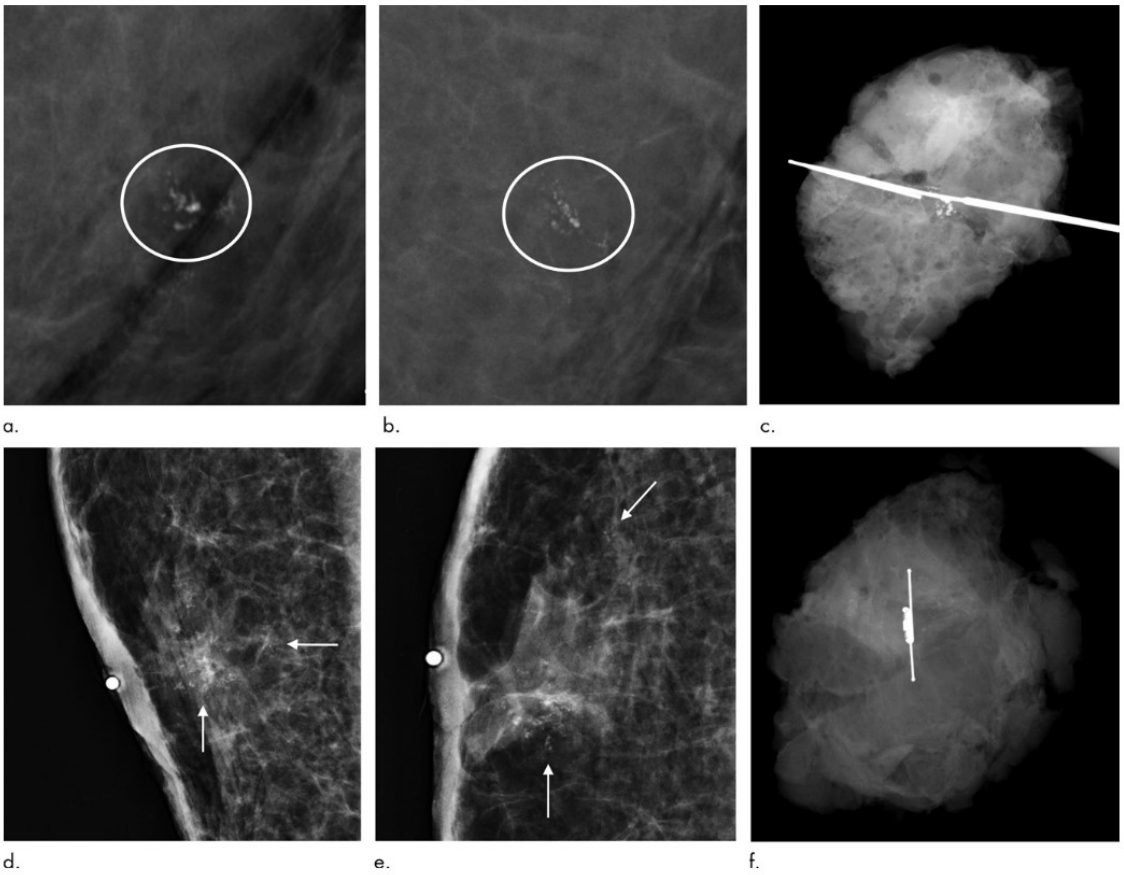

Figure 3: Images in a 53-year-old man with Ashkenazi Jewish ancestry with *BARD1* genetic mutation and strong family history of breast cancer including male breast cancer in father and premenopausal breast cancer in multiple sisters. Patient was found to have left breast cancer on **(a–c)** baseline screening mammogram and contralateral right breast cancer on **(d–f)** subsequent-year screening mammogram. Grouped coarse heterogeneous calcifications in left breast on baseline screening mammogram as shown on magnification views in (**a**) mediolateral and (**b**) craniocaudal projections (circles) underwent excisional biopsy, with surgical specimens showing (**c**) inclusion of targeted calcifications. Pathologic result yielded estrogen receptor (ER)–positive, progesterone receptor (PR)–positive, and human epidermal growth factor receptor 2 (HER2)–negative grade 2 invasive and in situ carcinoma, ultimately treated with mastectomy. One year later, grouped and scattered calcifications were seen on right breast screening mammogram as shown on magnification views in (**d**) mediolateral and (**e**) craniocaudal projections (arrows), which underwent SAVI Scout (Cianna Medical, Aliso Viejo, Calif) radar-localized excisional biopsy with surgical specimens showing (**f**) inclusion of targeted calcifications. Pathologic result yielded ER-positive and PR-positive grade 2 ductal carcinoma in situ, which subsequently underwent mastectomy.

Table 6: Feature Comparison of Diagnostic- versus Screen-detected Male Breast Cancers

Features	Diagnostic-detected (n = 24)	Screen-detected (n = 5)	P Value
Lesion type (%)			
Mass*	100	40	.003
Calcification only	0	60	.003
Average lesion size†			
Mass (cm)	2.1 (1–3.8)	1.2 (0.8–1.5)	.003
Calcification (mm)	N/A	9 (4–18)	.003
Nodal status			
Axillary node positive (%)	58.3	0	.004

Note.—N/A = does not apply.

* The masses were sometimes associated with calcifications.

† Data in parentheses are ranges.

likely to be node positive (0%, zero of five vs 58.3%, 14 of 24) (P = .004). Screen-detected invasive cancers were also smaller in size compared with those found at diagnostic examinations (average size, 1.2 cm vs 2.1 cm) (Table 5).

Screening and Diagnostic Outcomes

For men who presented for screening, mammographic sensitivity, specificity, PPV1, PPV2, PPV3, and negative predictive value for breast cancer detection were 100% (five of five; 95% CI: 50.0%, 100%), 95.0% (266 of 280; 95% CI: 93.1%, 98.0%), 26.3% (five of 19; 95% CI: 11.0%, 50.0%), 45.5% (five of 11; 95% CI: 19.9%, 75.1%), 50% (five of 10; 95% CI: 22.2%, 77.8%), and 100% (266 of 266; 95% CI: 98.7%, 100%), respectively. The CDR was 18 per 1000 examinations (five of 271; 95% CI: 7, 41). Among the screening group, 13 patients presented with clinical concerns within 12 months of a negative mammogram, five of whom were deemed within normal limits at clinical examination and eight of whom required further diagnostic imaging evaluation. Six of the eight diagnostic imaging examinations were negative for cancer (either BI-RADS 1 or 2), and the other two resulted in benign biopsies (yielding a hematoma and gynecomastia, respectively). The interval cancer rate was 0% (zero per 1000 screening examinations).

For men who presented for diagnostic evaluation, mammographic sensitivity, specificity, PPV2, PPV3, and negative predictive value for breast cancer detection were 94.7% (36 of 38; 95% CI: 82.5%, 99.1%), 92.4% (1745 of 1888; 95% CI: 93.3%, 95.4%), 24.0% (36 of 150; 95% CI: 17.4%, 31.5%), 25.9% (36 of 139; 95% CI: 18.9%, 33.6%), 99.9% (1745 of 1747; 95% CI: 99.6%, 99.9%), respectively. The CDR was 20 per 1000 examinations (36 of 1781; 95% CI: 14.2, 27.8).

Discussion

There are no prior data describing screening outcomes for men at high risk along with evaluation of utilization. Our study shows that although such screening takes place to a limited extent (13.2% examinations, 271 of 2052), it has the potential to depict clinically occult early-stage malignancy in this population, with a cancer detection profile highly comparable and superior to screening outcomes seen in women with average risk. We found a cancer detection rate (CDR) of 18 per 1000 examinations, yielding small invasive cancers (average size, 1.2 cm) and a high proportion of in situ cancers (60%, three of five), which compares favorably to reported CDRs of 3.4–5.1 per 1000 examinations in women with average risk who undergo screening, yielding similar-sized invasive cancers (average size, 1.3–1.6 cm) and in situ cancers (21.6%–31.4%) (19,22,23) and contrasts with the clinically detected male breast cancers in our cohort—all of which were invasive tumors of larger sizes (average size, 2.1 cm). The CDR of 18 per 1000 examinations also compares favorably to reported CDRs of 7.2–7.5 per 1000 examinations in women with high risk who undergo mammographic screening (24,25). Axillary nodal involvement is the strongest predictor of both local recurrence and metastatic risk for breast cancer, and it was present in 58.3% (14 of 24) of male breast cancers detected at diagnostic evaluation in our cohort, comparable to findings in the literature (26). This is in stark contrast to the screen-detected male breast cancers in our study, none of which had nodal involvement, suggesting a possible mortality benefit from screening.

Mammographic sensitivity for cancer is excellent in men due to a relative lack of breast fibroglandular tissue. In our study, the first imaging modality of detection was mammography for all cancers, both at diagnostic and screen examinations. Although clinical breast examination is thought to be highly sensitive and negatively predictive, and currently serves as the norm of male breast cancer detection even among the high-risk population (4,27), our study yielded five clinically occult breast cancers at screening, three of which presented as calcifications alone. This potential for early disease detection in men is supported by the fact that 90% of male breast cancers are ductal in origin, and up to 98% of precursors to invasive male breast cancers are ductal carcinoma in situ, typically seen as calcifications at mammography (28,29). Preclinical detection also mitigates the greater propensity of male breast cancer for early dermal lymphatic spread and regional metastasis compared with female breast cancer due to anatomic differences (30–33). In our study, mammographic sensitivity, specificity, positive predictive value (PPV) 3, and negative predictive value in the screening setting (100%, 95.0%, 50%, and 100%) (five of five, 266 of 280, five of 10, and 266 of 266) were comparable if not superior to results in the diagnostic setting both in our cohort (94.7%, 92.4%, 25.9%, 99.9%) (36 of 38, 1745 of 1888, 36 of 139, 1745 of 1747) and in the literature (92%–100%, 90%–91.4%, 32%–55%, 99%–100%) (13,34), validating its clinical utility. The high sensitivity and negative predictive value of mammography suggests screening with additional modalities would likely not be justified. Of note, the difference in cancer yield between screening and diagnostic settings in men (18 vs 20 per 1000 examinations) appears to be smaller than that reported in women (3–5 vs 25–34 per 1000

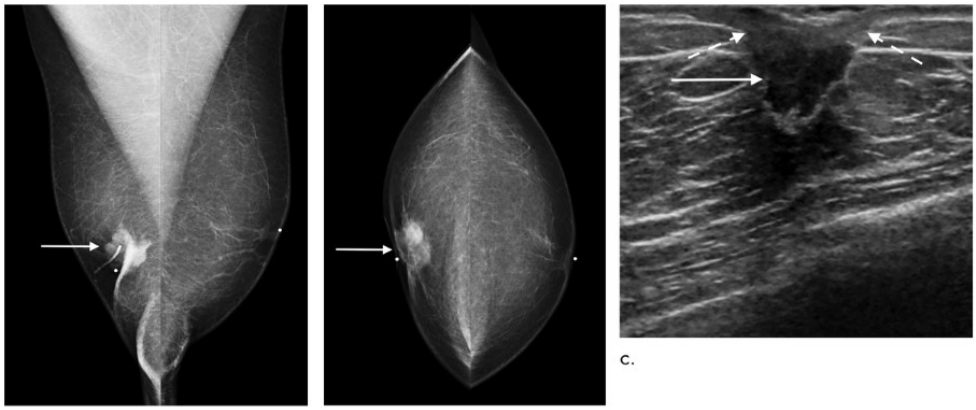

Figure 4: Images in a 74-year-old man who presented for diagnostic evaluation of palpable right breast mass. **(a, b)** Mammogram in mediolateral and craniocaudal projections (arrows) illustrates subareolar mass in right breast with associated nipple retraction. **(c)** US shows correlating centrally located irregular mass (solid arrow) with direct invasion of nipple areolar complex causing retraction (dashed arrows), but no evidence of axillary nodal spread (not shown). Dermal lymphatic tumor extension was confirmed at pathologic analysis.

examinations) (21,35). This may be related to an overall low cancer prevalence in men with average risk who largely comprised the diagnostic group compared with that in men who were screened due to a high risk. Finally, we found an interval cancer rate of zero, likely due to a combination of high mammographic sensitivity and less aggressive tumor molecular profile in men (28,36,37).

Selective screening appears beneficial in our study, particularly in men with a personal history of breast cancer, who represent the largest group in this cohort to undergo regular annual screening (56.4%, 22 of 39). Of the four cancers found in this group, except for one cancer identified at baseline screening following prior cancer treatment, the remaining three cancers were found following multiple years of screening. These contralateral second cancers were identified on average after 5.5 person-years of screening (range, 1–10 person-years), which is consistent with the time frame of male breast cancer recurrence reported in prior data (38), suggesting routine screening may be of value in this group. This may be particularly relevant given poorer 5-year survival following breast cancer diagnosis in men than in women based on a recent 2018 Surveillance, Epidemiology, and End Results data analysis (with 43% greater risk of death in men than in women during follow-up; hazard ratio, 1.43; 95% confidence interval: 1.26, 1.61) (3). However, many men in our screening cohort underwent one-time screening (n = 126), the majority of whom had genetic mutations and/or family history of breast cancer (110 of 126, 87.3%). This suggests a "single baseline examination" approach by clinicians to rule out abnormality before embarking on annual clinical breast examinations rather than poor adherence. While current 2019 National Comprehensive Cancer Network, or NCCN, guidelines for men with high risk (including those with *BRCA*2 and *BRCA*1 mutations) advocate annual clinical breast examination starting at age 35 years and do not recommend mammography, prior 2012 NCCN guidelines had suggested consideration of baseline mammograms on an individual basis, which is in line with the more recent 2017 American Society of Clinical Oncology recommendations (4,26,39). Although the effectiveness of such baseline examinations is unknown, the high sensitivity and negative predictive value (both 100%) of mammography seen in our study may support such use. However, current breast cancer risk stratification in men is highly limited. Particularly given a known wide distribution in absolute cancer risks observed at the extremes of common genetic variants, a more nuanced understanding of risk may help better direct targeted screening among men with high risk (40,41). Finally, the number of breast imaging examinations in men (both screening and diagnostic examinations) significantly increased relative to the number of examinations in women in our study over time, consistent with increased utilization of breast imaging in men, suggesting a need for guidance. While the number of screening examinations in men also significantly increased relative to the number of screening examinations in women over the 12-year period, this may reflect to a greater extent a decline in screening adherence in women in recent years than concurrent increase in screening in men, given the proportion of examinations with screening indications in men did not fluctuate significantly over time (42,43).

Our study was limited by its retrospective design. The study was also limited by our single-institution experience where all studies were interpreted by subspecialized physicians, which may not be generalizable to all practice types. Selection bias may be present given that patient referral for screening was largely determined by surgical or medical oncologists, as well as in part driven by patients, due to the lack of guidelines and consensus. Results may also be subject to verification bias, given limited long-term follow-up in men, although unavoidable given the retrospective nature of the data. In addition, report of family history of breast cancer was patient dependent and may be incomplete. Although our longitudinal design

allowed observation of temporal changes in practice pattern, it is difficult to attribute these changes to any specific factors, such as alterations in established management guidelines over time.

In conclusion, selective screening in men at elevated risk for breast cancer was beneficial in our study, and mammography was able to depict clinically occult malignancy at a cancer detection rate higher than that of screening among women with average risk. Breast imaging utilization in men has increased over time, suggesting a need for guidance. Further and larger studies are needed to validate results and provide more definitive recommendations as to whether and how best to screen men at high risk.

Author contributions: Guarantors of integrity of entire study, Y.G., L.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, Y.G., J.E.G., T.K.Y., L.M., S.L.H.; clinical studies, Y.G., J.E.G., T.K.Y., L.M., S.L.H.; statistical analysis, J.S.B., L.M.; and manuscript editing, Y.G., J.E.G., J.S.B., L.M., S.L.H.

Disclosures of Conflicts of Interest: Y.G. disclosed no relevant relationships. **J.E.G.** disclosed no relevant relationships. **T.K.Y.** disclosed no relevant relationships. **J.S.B.** disclosed no relevant relationships. **L.M.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for iCAD; has grants/grants pending with Siemens; holds stock/stock options in Lunit. Other relationships: is on the editorial board of *Radiology*. **S.L.H.** disclosed no relevant relationships.

References

1. American Cancer Society. Key statistics for breast cancer in men. https://www.cancer.org/cancer/breast-cancer-in-men/about/key-statistics.html. Published 2019. Accessed February 10, 2019.
2. Nahleh ZA, Srikantiah R, Safa M, Jazieh AR, Muhleman A, Komrokji R. Male breast cancer in the veterans affairs population: a comparative analysis. Cancer 2007;109(8):1471–1477.
3. Liu N, Johnson KJ, Ma CX. Male Breast Cancer: An Updated Surveillance, Epidemiology, and End Results Data Analysis. Clin Breast Cancer 2018;18(5):e997–e1002.
4. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 3.2019. https://www.nccn.org/professionals/physician_gls/default.aspx#genetics_screening. Updated January 18, 2019. Accessed March 4, 2019.
5. Expert Panel on Breast Imaging, Niell BL, Lourenco AP, et al. ACR Appropriateness Criteria® Evaluation of the Symptomatic Male Breast. J Am Coll Radiol 2018;15(11S):S313–S320.
6. Brenner RJ, Weitzel JN, Hansen N, Boasberg P. Screening-detected breast cancer in a man with BRCA2 mutation: case report. Radiology 2004;230(2):553–555.
7. Freedman BC, Keto J, Rosenbaum Smith SM. Screening mammography in men with BRCA mutations: is there a role? Breast J 2012;18(1):73–75.
8. Gao Y, Heller SL, Moy L. Male breast cancer in the age of genetic testing: an opportunity for early detection, tailored therapy, and surveillance. RadioGraphics 2018;38(5):1289–1311.
9. Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2007;99(23):1811–1814.
10. Ibrahim M, Yadav S, Ogunleye F, Zakalik D. Male BRCA mutation carriers: clinical characteristics and cancer spectrum. BMC Cancer 2018;18(1):179.
11. Silvestri V, Barrowdale D, Mulligan AM, et al. Male breast cancer in BRCA1 and BRCA2 mutation carriers: pathology data from the Consortium of Investigators of Modifiers of BRCA1/2. Breast Cancer Res 2016;18(1):15.
12. Muñoz Carrasco R, Alvarez Benito M, Muñoz Gomariz E, Raya Povedano JL, Martínez Paredes M. Mammography and ultrasound in the evaluation of male breast disease. Eur Radiol 2010;20(12):2797–2805.
13. Patterson SK, Helvie MA, Aziz K, Nees AV. Outcome of men presenting with clinical breast problems: the role of mammography and ultrasound. Breast J 2006;12(5):418–423.
14. Rong X, Zhu Q, Jia W, et al. Ultrasonographic assessment of male breast diseases. Breast J 2018;24(4):599–605.
15. Rosenthal ET, Evans B, Kidd J, et al. Increased Identification of Candidates for High-Risk Breast Cancer Screening Through Expanded Genetic Testing. J Am Coll Radiol 2017;14(4):561–568.
16. Kurian AW, Ward KC, Hamilton AS, et al. Uptake, Results, and Outcomes of Germline Multiple-Gene Sequencing After Diagnosis of Breast Cancer. JAMA Oncol 2018;4(8):1066–1072.
17. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet 2006;367(9510):595–604.
18. American College of Radiology. American College of Radiology Breast Imaging Reporting and Data System Atlas (BI-RADS Atlas). Reston, Va: American College of Radiology, 2013.
19. Lehman CD, Arao RF, Sprague BL, et al. National performance benchmarks for modern screening digital mammography: Update from the Breast Cancer Surveillance Consortium. Radiology 2017;283(1):49–58.
20. Noroozian M, Carlson LW, Savage JL, et al. Use of Screening Mammography to Detect Occult Malignancy in Autologous Breast Reconstructions: A 15-year Experience. Radiology 2018;289(1):39–48.
21. Sprague BL, Arao RF, Miglioretti DL, et al. National performance benchmarks for modern diagnostic digital mammography: Update from the Breast Cancer Surveillance Consortium. Radiology 2017;283(1):59–69.
22. Rosenberg RD, Yankaskas BC, Abraham LA, et al. Performance benchmarks for screening mammography. Radiology 2006;241(1):55–66.
23. Lee CS, Bhargavan-Chatfield M, Burnside ES, Nagy P, Sickles EA. The National Mammography Database: Preliminary Data. AJR Am J Roentgenol 2016;206(4):883–890.
24. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 2012;307(13):1394–1404.
25. Lo G, Scaranelo AM, Aboras H, et al. Evaluation of the utility of screening mammography for high-risk women undergoing screening breast MR imaging. Radiology 2017;285(1):36–43.
26. Korde LA, Zujewski JA, Kamin L, et al. Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010;28(12):2114–2122.
27. Chau A, Jafarian N, Rosa M. Male Breast: Clinical and Imaging Evaluations of Benign and Malignant Entities with Histologic Correlation. Am J Med 2016;129(8):776–791.
28. Cardoso F, Bartlett JMS, Slaets L, et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol 2018;29(2):405–417.
29. Doebar SC, Slaets L, Cardoso F, et al. Male breast cancer precursor lesions: analysis of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Mod Pathol 2017;30(4):509–518.
30. Joshi MG, Lee AK, Loda M, et al. Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. Cancer 1996;77(3):490–498.
31. Laronga C, Kemp B, Johnston D, Robb GL, Singletary SE. The incidence of occult nipple-areola complex involvement in breast cancer patients receiving a skin-sparing mastectomy. Ann Surg Oncol 1999;6(6):609–613.
32. Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of nipple/areolar involvement with mastectomy: can the areola be preserved? Ann Surg Oncol 2002;9(2):165–168.
33. Foerster R, Schroeder L, Foerster F, et al. Metastatic male breast cancer: a retrospective cohort analysis. Breast Care (Basel) 2014;9(4):267–271.
34. Evans GF, Anthony T, Turnage RH, et al. The diagnostic accuracy of mammography in the evaluation of male breast disease. Am J Surg 2001;181(2):96–100.
35. Sickles EA, Miglioretti DL, Ballard-Barbash R, et al. Performance benchmarks for diagnostic mammography. Radiology 2005;235(3):775–790.
36. Anderson WF, Jatoi I, Tse J, Rosenberg PS. Male breast cancer: a population-based comparison with female breast cancer. J Clin Oncol 2010;28(2):232–239.
37. Houssami N, Hunter K. The epidemiology, radiology and biological characteristics of interval breast cancers in population mammography screening. NPJ Breast Cancer 2017;3:12.
38. Dong C, Hemminki K. Second primary breast cancer in men. Breast Cancer Res Treat 2001;66(2):171–172.
39. American Society of Clinical Oncology (ASCO). Hereditary Breast and Ovarian Cancer (ASCO Guidelines): Screening for men with a BRCA1 or BRCA2 gene mutation. 7/2017. https://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer. Published 2017. Accessed March 14, 2019.
40. Pich A, Margaria E, Chiusa L. Oncogenes and male breast carcinoma: c-erbB-2 and p53 coexpression predicts a poor survival. J Clin Oncol 2000;18(16):2948–2956.
41. Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. J Clin Oncol 2017;35(20):2240–2250.
42. Boroumand G, Teberian I, Parker L, Rao VM, Levin DC. Screening mammography and digital breast tomosynthesis: Utilization updates. AJR Am J Roentgenol 2018;210(5):1092–1096.
43. Sprague BL, Bolton KC, Mace JL, et al. Registry-based study of trends in breast cancer screening mammography before and after the 2009 U.S. Preventive Services Task Force recommendations. Radiology 2014;270(2):354–361.