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

Yiming Gao, MD • Julia E. Goldberg, MD, MBA • Trevor K. Young, BSc • James S. Babb, PhD • Linda Moy, MD • Samantha L. Heller, MD, PhD

From the Department of Radiology, New York University Langone Medical Center, 160 E 34th St, New York, NY 10016 (Y.G., J.S.B., L.M., S.L.H.); New York University School of Medicine, New York, NY (J.E.G., T.K.Y.); and Center for Advanced Imaging Innovation and Research, New York University School of Medicine, New York, NY (J.S.B., L.M.). Received April 28, 2019; revision requested June 12; final revision received July 3; accepted July 19. Address correspondence to Y.G. (e-mail: Yiming.Gao@nyulangone.org).

Brianna Frame, MS4
Journal Club RADY Curriculum July 14, 2020
Learning Objectives

By the end of this journal club, participants will be able to:

• Understand basic anatomy of female and male breast
• Understand male breast cancer epidemiology, risk factors, presentation, pathology, and diagnostic work up
• Understand BIRADS assessment categories
• Understand DDx of a mass in a male breast
• Understand potential need of guidelines for screening mammograms in high-risk males
Module Outline

I. **Case**
II. Background
III. Article Overview
IV. Clinical Questions
V. Key Points
Case Presentation

74-year-old male who presents with left breast mass

PMHx: ESRD s/p kidney transplant (2017), recurrent bacteremia and UTIs, CAD, T2DM, HFpEF, Afib s/p watchman, vascular dementia, prostate cancer s/p prostatectomy (2013) and newly diagnosed RCC in right native kidney

HPI:
- Presented with complicated MDR Klebsiella UTI in the setting of sepsis and acute encephalopathy
- Concern for possible unidentified source of infection due to recurrent bacteremia
Case Presentation

Interval Events:
- Underwent a PET CT for possible unidentified nidus of infection
- Findings: FDG avid microabscess of left obturator muscle AND FDG avid lesion underlying left nipple on PET CT

Follow-up:
- Patient reports no breast changes (size, pain, redness, breast mass, nipple retraction, swelling, nipple discharge)
- No previous breast biopsies or abnormal mammograms
- Known bilateral gynecomastia noted on previous imaging
- Family history of sister with breast cancer
- Referred to breast radiology for further imaging
Case Questions

• What imaging studies would you perform for this patient?
• What is the most common breast finding in a male?
Case Imaging

LT BREAST RETROAREOLAR TRANS MH CK

LT BREAST RETROAREOLAR LONG MH CK
Case Pathology Report

Procedure: Ultrasound-guided Core Needle Biopsy
Diagnosis: Invasive ductal carcinoma, histologic grade 1
  ER positive 100%
  PR positive 70%
  HER 2 negative
Case Questions to Consider

• What histologic subtypes of breast cancer are found in men?
• What are the imaging study recommendations for the diagnostic evaluation of a male breast mass?
• Should high-risk males undergo screening mammography?
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Anatomy of the Breast
Male Breast Cancer

• Accounts for about 0.5-1% of breast cancers annually\(^1\)

• Risk Factors:
  • Breast cancer in a first degree relative, mutations: BRCA1/2, PTEN tumor suppressor gene (Cowden Syndrome), tumor protein p53 (Li-Fraumeni Syndrome), mismatch repair genes (Lynch Syndrome)
  • Alterations in the estrogen to androgen ratio: hormonal therapies, hepatic dysfunction, obesity, marijuana use, thyroid disease, or an inherited condition (Klinefelter syndrome)
  • Primary testicular conditions: orchitis, cryptorchidism, and testicular injury
Male Breast Cancer

- **Presentation**: painless, firm mass; retroareolar; nipple retraction
- **Pathology**: About 85-90% are invasive ductal carcinomas, rarely lobular carcinomas\(^2\)
- **Subtype**: hormone-receptor positive, luminal A or luminal B\(^2,3\)
- **Diagnostic Evaluation\(^4\):**
  - < 25 years old: US
  - ≥ 25 years old: mammography
  - Can use mammography initially for any age if highly suspicious of breast cancer
BI-RADS Assessment Categories
Breast Imaging Reporting and Data Systems

- **Category 0**: INCOMPLETE - NEED ADDITIONAL IMAGING EVALUATION AND/OR PRIOR MAMMOGRAMS FOR COMPARISON
  
  Recall for additional imaging and/or comparison with prior examinations

- **Category 1**: NEGATIVE (0% risk)
  
  Routine mammography screening

- **Category 2**: BENIGN (0% risk)
  
  Routine mammography screening

- **Category 3**: PROBABLY BENIGN (<2% risk)
  
  Short interval 6 month follow-up OR continued surveillance

- **Category 4**: SUSPICIOUS (2-95% risk)
  
  Biopsy should be performed in the absence of clinical contraindications

- **Category 5**: HIGHLY SUGGESTIVE OF MALIGNANCY (>95% risk)
  
  Biopsy should be performed in the absence of clinical contraindications

- **Category 6**: KNOWN BIOPSY-PROVEN MALIGNANCY (100% risk)
  
  Surgical excision when clinically appropriate
Differential of Breast Mass in Male

- Gynecomastia
  - Benign proliferation of ductal and stromal tissue elements
  - Most commonly bilateral, but can be unilateral
  - Soft tender mass, mobile, central to nipple
  - Common etiology: medications

Mammogram: Flame or fan shape
Differential of Breast Mass in Male

• Breast Cancer
Differential of Breast Mass in Male

• Lymph Node

• Others: psuedogynecomastia, infections, lipoma, fibromatosis, granular cell tumor, pseudoangiomatous stromal hyperplasia and more!
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Article Nuts and Bolts

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

**Journal:** Radiology, November 2019

**Study Type:** Retrospective study reviewed consecutive male breast imaging examinations over a 12-year period (2005-2017)

**Number of Cases:** 1869 men who underwent 2052 examinations

**Data:** Examination indications, mammogram findings, biopsy/pathology results, patient characteristics, number of person years to achieve a diagnosis
Study Cohort

- Adult men (both symptomatic and asymptomatic) who underwent breast imaging examinations (mammography ± 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.

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

• **Screening Examinations:** 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 used
  - Recorded whether annual or sporadic screening was undertaken

• **Diagnostic Examinations:** examinations performed for evaluation of male breast symptoms, or for follow-up of probably benign findings.
  - Mammography and/or US used

• The number of examinations was defined as the number of single-event breast imaging evaluations.
  - Compared to the total number of exams performed in women each year
Material and Methods Continued

• Examination indications, imaging findings, biopsy recommendations, and pathologic results were correlated with patient characteristics (age, personal and/or family history of breast cancer, any known genetic mutation, and Ashkenazi descent)

• **High-Risk**: men with any known risk factors predisposing to breast cancer such as personal and family history of breast cancer, breast cancer related–genetic mutations, or Ashkenazi descent

• Number of person years screened to achieve a cancer diagnosis was recorded in men with screen detected cancers
### Table 1: Characteristics of Men Who Underwent Breast Imaging Examinations between 2005–2017 (n = 1869)

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

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.
Results

• **2052 examinations**: 1781 diagnostic (86.8%) and 271 screening (13.2%)
  - All included mammography, 1004 included US
  - All men undergoing screening had personal or family history of breast cancer and/or genetic mutations (BRCA2 being the most common).
  - Screening: 10.9% underwent at least 3 screens, 12.7% underwent 2, and 76.5% underwent 1

• **Yielded**: 2304 breast lesions

• **149 biopsies in 133 men**: 41 (27.5%) were malignant, 108 (72.5%) were benign
<table>
<thead>
<tr>
<th>Biopsy Yield and Pathologic Finding</th>
<th>No. of Biopsied Lesions</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma with ductal carcinoma in situ</td>
<td>38</td>
<td>25.5</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apocrine metaplasia</td>
<td>7</td>
<td>4.7</td>
</tr>
<tr>
<td>Angiolipoma</td>
<td>6</td>
<td>4.0</td>
</tr>
<tr>
<td>Abscess/Phlegmon</td>
<td>5</td>
<td>3.4</td>
</tr>
<tr>
<td>Lipoma</td>
<td>10</td>
<td>6.7</td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>13</td>
<td>8.7</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Hematoma</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>39</td>
<td>26.2</td>
</tr>
<tr>
<td>Granulomatous reaction</td>
<td>9</td>
<td>6.0</td>
</tr>
<tr>
<td>Lymphoid hyperplasia</td>
<td>7</td>
<td>4.7</td>
</tr>
<tr>
<td>Nodular fibrosis</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Myofibroblastoma</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Cavernous hemangioma</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Steatocytoma</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Benign, not otherwise specified</td>
<td>1</td>
<td>0.7</td>
</tr>
</tbody>
</table>
### Table 6: Feature Comparison of Diagnostic- versus Screen-detected Male Breast Cancers

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

Note.—N/A = does not apply.
* The masses were sometimes associated with calcifications.
† Data in parentheses are ranges.
Results continued

• **Screening**: cancer detection rate (CDR) of 18 per 1000 examinations (95% CI: 7, 41), with cancers diagnosed on average after 4 person-years of screening.

• **Diagnostic**: CDR of 20 per 1000 examinations (95% CI: 14.2, 27.8)

Older age, Ashkenazi descent, genetic mutations, personal history, and first-degree family history were associated with breast cancer.
Table 4: Risk Factors Associated with Malignancy

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

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).
Discussion

• Screening is not common in men, but has the potential to detect clinically occult, early stage breast cancers
• Cancer detection rate are comparable (possibly better) in screening for male breast cancer than female breast cancer\textsuperscript{5,6}
• Screening has a possible mortality benefit in men
• Selective screening for male breast cancer appears to be beneficial, especially in high-risk males
  • No screening guidelines in place for high-risk males
Study Limitations

• Retrospective design

• Single institution with imaging studies interpreted by subspecialized physicians, so may not be generalizable to all practice types

• Selection bias: referral for screening was determined by surgical or medical oncologists and driven by patients due to lack of guidelines

• Family history of breast cancer was patient reported, so may be incomplete

• Lack of baseline patient characteristics, unclear if generalizable
Module Outline

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Clinical Questions

• Should males with a first-degree relative diagnosed with breast cancer undergo screening? Should those with other high-risk features?
• Should we create guidelines for screening in males in order to have a consensus?
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Key Points

• Although less common than gynecomastia, male breast cancer DOES occur – keep it in your differential diagnosis!

• Due to male breast anatomy, most male breast cancers are invasive ductal carcinoma, with hormone positive receptors.

• Mammography screening in high-risk men can detect clinically occult and smaller breast cancers.

• High-risk men (older age, Ashkenazi descent, genetic mutations, personal history, and first-degree family history) are more likely to get breast cancer.

• No current guidelines exist for male breast cancer screening.
References


