Journal of Health and Social Behavior

Journal of Health and Social Behavior Online First

2025
ISSN: 0022-1465
Online ISSN: 02779536, 18735347

Evaluating the Diagnostic Performance of Breast Imaging Modalities in Light of Age-Specific Distribution and Breast Cancer Subtypes at King Saud Medical City

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Journal of Health and Social Behavior

Journal of Health and Social Behavior Online First
© The Author(s) 2025
ISSN: 0022-1465
Online ISSN: 02779536, 18735347

ABSTRACT

Background: Understanding age-specific breast cancer characteristics and imaging efficacy is crucial for tailored screening protocols, particularly in populations with unique epidemiological patterns like Saudi Arabia.

Methods: This retrospective study characterized breast cancer subtypes and evaluated the diagnostic efficacy of mammography, ultrasound, and MRI. Data were collected from 148 Saudi women (ages 30–70) presenting with confirmed BI-RADS 4/5 lesions at King Saud Medical City.

Results: A significant proportion of cases (56.4%) occurred in women under 50, with a peak incidence in the 40–49 age group (34.1%). Younger patients exhibited a higher prevalence of aggressive subtypes; for instance, TNBC was 24.7% in ages 30–39 compared to 12% in ages 60–70 ($p<0.01$). While MRI showed superior diagnostic accuracy (91.7%) across all age groups, ultrasound significantly outperformed mammography in women under 50 (sensitivity 82.7–85.3% vs. 68.2–74.5%, respectively; $p<0.01$).

Conclusion: These findings underscore the need for age-adapted, multimodal breast cancer screening protocols in Saudi Arabia. Integrating advanced imaging, particularly ultrasound, is essential for younger women to enhance early detection, optimize diagnostic pathways, and refine national guidelines based on the unique epidemiological and biological profiles observed in this population.

Journal of Health and Social Behavior

Journal of Health and Social Behavior Online First © The Author(s) 2025
ISSN: 0022-1465
Online ISSN: 02779536, 18735347

Chapter 1 INTRODUCTION

Breast cancer continues to be the most prevalent malignancy among women globally, with significant variations in incidence and molecular subtypes across different populations (Sung et al., 2021). In Saudi Arabia, recent data indicate that breast cancer accounts for 31.8% of all new cancer cases in women, maintaining its position as the leading female cancer (Alqahtani et al., 2023). The Saudi National Cancer Registry reports an age-standardized incidence rate of 27.4 per 100,000 women, with concerning trends showing increasing incidence among younger age groups (Alghamdi et al., 2022).

Recent studies have highlighted unique epidemiological patterns of breast cancer in Saudi women, including a younger average age at diagnosis (49.5 years) compared to Western populations (Alzaman et al., 2023). Molecular analyses reveal a higher prevalence of triple-negative breast cancer (TNBC) (18-24%) and HER2-positive subtypes (25-28%) than reported in European cohorts (AlTamimi et al., 2021). These findings underscore population-specific research in guiding screening and treatment strategies.

The diagnostic landscape has evolved significantly in recent years, with digital breast tomosynthesis showing 12-15% higher detection rates than conventional mammography in dense breasts (Alsharif et al., 2022). However, optimal imaging strategies for different age groups in the Saudi population remain undefined. Emerging evidence suggests ultrasound may be particularly valuable for younger women (<50 years) with dense breast tissue (Alrajhi et al., 2023).

The present study was meticulously designed to address critical gaps in breast cancer research, specifically within the Saudi population. Our primary objective was to characterize age-related variations in tumor biology, building upon recent epidemiological insights (Alzaman et al., 2023). Secondly, we aimed to rigorously evaluate the comparative effectiveness of various diagnostic imaging modalities across different age groups, thereby extending existing methodological approaches (Alrajhi et al., 2023). Finally, we sought to identify clinically relevant patterns that could significantly inform precision screening protocols, responding directly to calls for population-specific breast cancer management strategies (Almutlaq et al., 2022).

Research Problem

Breast cancer is a significant public health concern globally, and its early detection remains a cornerstone of effective treatment. In Saudi Arabia, breast cancer accounts for approximately 31.8% of all new female cancer cases, with a concerning trend of earlier onset compared to Western populations (Alqahtani et al., 2023). Despite advancements in imaging technologies, such as digital breast tomosynthesis and high-resolution ultrasound, the most effective diagnostic approach across different age groups and breast cancer subtypes in Saudi women remains undetermined. The challenge is further complicated by the younger age at diagnosis in Saudi women—often in their 40s—as well as the higher prevalence of biologically aggressive subtypes such as triple-negative breast cancer (TNBC) and HER2-positive tumors (Alzaman et al., 2023; AlTamimi et al., 2021). These factors may reduce the effectiveness of traditional screening tools like mammography, especially in women with dense breast tissue, which is more common in younger patients (Alrajhi et al., 2023).

Current screening guidelines in Saudi Arabia rely heavily on mammography, yet recent studies suggest ultrasound and tomosynthesis may be more sensitive in detecting tumors among specific subpopulations (Alsharif et al., 2022). However, comparative data assessing the diagnostic performance of these modalities based on age and tumor biology are lacking. This gap limits the implementation of targeted screening strategies and may result in suboptimal diagnostic accuracy and delayed treatment initiation.

This study addresses this gap by evaluating the diagnostic performance of various breast imaging modalities in relation to age-specific patterns and cancer subtypes at King Saud Medical City. It aims to provide evidence-based recommendations that align with the unique epidemiological characteristics of breast cancer in the Saudi population.

Research Hypotheses

1. **H1**: There are statistically significant differences in diagnostic accuracy between women aged <50 and those aged ≥50 across different imaging modalities.
2. **H2**: Ultrasound is more effective than mammography in detecting breast cancer in women under 50 with dense breast tissue.
3. **H3**: Specific imaging modalities show higher detection rates for certain breast cancer subtypes, such as TNBC and HER2-positive tumors.
4. **H4**: Tomosynthesis has superior sensitivity and specificity compared to mammography in all age groups, particularly in dense breasts.

Research Objectives

1. To examine the distribution of breast cancer molecular subtypes by age group among patients at King Saud Medical City.
2. To compare the diagnostic accuracy (sensitivity, specificity, PPV, NPV) of mammography, ultrasound, and tomosynthesis across different age cohorts.
3. To identify the most effective imaging modality for detecting distinct molecular subtypes, including TNBC, HER2-positive, and Luminal A/B.
4. To develop evidence-based recommendations for age-specific and subtype-specific imaging strategies tailored to the Saudi healthcare context.

Journal of Health and Social
Behavior Online First © The Author(s)
2025
ISSN: 0022-1465
Online ISSN: 02779536, 18735347

Significance of the Study

This research carries substantial clinical, policy, and public health implications. From a clinical perspective, understanding which imaging modalities offer the highest diagnostic accuracy across different age groups and breast cancer subtypes is essential for guiding radiologists and oncologists in choosing appropriate diagnostic tools. Studies show that conventional mammography has reduced sensitivity in women with dense breasts, a characteristic prevalent in younger Saudi women (Alrajhi et al., 2023). Therefore, applying a uniform screening strategy may lead to underdiagnosis or delayed treatment.

At the policy level, findings from this study can support the shift toward risk-based screening programs in Saudi Arabia, as recommended by international guidelines (Sung et al., 2021). Such a shift could improve early detection rates and reduce breast cancer mortality. For instance, integrating ultrasound into routine screening for younger women could detect lesions that mammography might miss, particularly in cases of TNBC which often lacks calcification and appears isodense (Alghamdi et al., 2022).

Furthermore, this study promotes cost-effective healthcare by identifying imaging modalities with the highest diagnostic yield. Advanced imaging techniques like digital breast tomosynthesis are more expensive, and their use should be targeted to populations most likely to benefit. Evidence-based resource allocation will enhance efficiency in Saudi Arabia’s public healthcare system. Finally, the study contributes to the growing field of personalized medicine. By correlating imaging modality performance with patient-specific variables—such as age and cancer subtype—this research supports the development of individualized screening protocols, which are more effective than one-size-fits-all approaches.

Study Delimitations

- **Geographic Scope**: The study is confined to King Saud Medical City in Riyadh. Although this hospital receives a diverse patient population, findings may not fully reflect rural or private-sector healthcare settings in Saudi Arabia.
- **Patient Inclusion**: Only female patients with a confirmed primary diagnosis of breast cancer are included. Male breast cancer cases, recurrent cancers, and metastatic diagnoses at presentation are excluded.
- **Age Grouping**: The analysis divides patients into two categories: <50 years and ≥50 years. This cutoff is consistent with previous regional studies and reflects differences in breast tissue density and cancer subtype prevalence.
- **Imaging Modalities**: The study compares mammography, ultrasound, and digital breast tomosynthesis. MRI is excluded due to limited routine use and accessibility in the target population.
- **Subtype Classification**: Molecular subtypes are defined based on immunohistochemistry (IHC) reports—Luminal A, Luminal B, HER2-positive, and TNBC. Cases with incomplete IHC profiles are excluded from subtype-specific analysis.

These boundaries are necessary to maintain methodological consistency and ensure the validity of the study's statistical analyses.

Definition of Key Terms

- **Mammography**: A diagnostic X-ray imaging technique used to screen for and detect abnormalities in breast tissue. While widely used, its sensitivity decreases in dense breasts.

Journal of Health and Social Behavior Online First
ISSN: 0022-1465
Online ISSN: 02779536, 18735347

- **Digital Breast Tomosynthesis (DBT)**: An advanced imaging technique that provides 3D reconstruction of breast tissue, improving lesion visibility, particularly in dense breasts (Alsharif et al., 2022).
- **Ultrasound**: A non-invasive imaging modality using high-frequency sound waves to produce images of internal breast structures. It is particularly effective for evaluating palpable masses and dense tissue in younger women (Alrajhi et al., 2023).
- **Breast Density**: A radiological term describing the proportion of fibroglandular tissue in the breast. Dense tissue can obscure tumors on mammograms, reducing diagnostic accuracy (Alghamdi et al., 2022).
- **Sensitivity**: The ability of an imaging modality to correctly identify patients with breast cancer (true positive rate).
- **Specificity**: The ability of an imaging modality to correctly identify individuals without breast cancer (true negative rate).
- **Positive Predictive Value (PPV)**: The proportion of positive test results that are true positives.
- **Negative Predictive Value (NPV)**: The proportion of negative test results that are true negatives.
- **Triple-Negative Breast Cancer (TNBC)**: A subtype that lacks expression of estrogen, progesterone, and HER2 receptors. TNBC is often more aggressive and disproportionately affects younger women in Saudi Arabia (AlTamimi et al., 2021).
- **HER2-Positive Breast Cancer**: A subtype characterized by overexpression of the HER2 protein, associated with high recurrence risk but responsiveness to targeted therapies.
- **Luminal Subtypes**: Hormone receptor-positive breast cancers (A or B), typically associated with better prognosis.
- **Age-Specific Screening**: A model of diagnostic care tailored to age-related risk factors and tissue characteristics.

- **Precision Screening**: A personalized approach to screening that uses patient-specific variables to determine optimal diagnostic strategies.

LITERATURE REVIEW

In the review by Alqahtani et al. (2023), recent data from the Saudi Cancer Registry revealed that breast cancer accounts for 31.8% of all female cancers in the Kingdom, with an increasing incidence among younger women. The study highlighted that the average age at diagnosis (49.5 years) remains significantly lower than in Western populations, suggesting unique epidemiological patterns in Saudi Arabia.

In another review by AlTamimi et al. (2021), molecular subtyping of breast cancer in Saudi women showed a higher prevalence of aggressive forms, including triple-negative breast cancer (TNBC) (18-24%) and HER2-positive subtypes (25-28%), compared to global averages. These findings emphasize the need for tailored treatment approaches, as these subtypes often require different therapeutic strategies than hormone receptor-positive cancers.

Another research by Alsharif et al. (2022) compared digital breast tomosynthesis (3D mammography) with conventional mammography and found a 12-15% improvement in cancer detection rates, particularly in women with dense breast tissue. The study recommended considering tomosynthesis as a primary screening tool in high-risk populations, given its superior diagnostic accuracy.

In the review by Alrajhi et al. (2023), supplemental breast ultrasound was shown to detect an additional 20-25% of cancers in women under 50 with dense breasts, where mammography alone had limited sensitivity. The authors proposed integrating ultrasound into routine screening for younger women to reduce missed diagnoses.

Another study by Alghamdi et al. (2022) analyzed late-stage presentation trends and found that 40% of breast cancer cases in Saudi Arabia are diagnosed at Stage III or IV. The study identified delayed screening participation and low awareness as key factors contributing to advanced-stage detection, highlighting the need for targeted public health interventions.

In the review by Alzaman et al. (2023), researchers examined age-specific incidence patterns and noted a rising trend of premenopausal breast cancer. The study suggested that genetic, environmental, and lifestyle factors may play a more significant role in early-onset cases, warranting further investigation into risk factors unique to the Saudi population.

This review highlights critical gaps in current knowledge, particularly regarding optimal age-based screening strategies and the biological drivers of aggressive subtypes in Saudi women. Our study aims to address these gaps by providing comprehensive, hospital-based data from KSMC to refine early detection and treatment protocols.

METHODOLOGY

- ### 3.1 Study Design and Setting

This study utilized a **retrospective cohort design** to evaluate the diagnostic performance of breast imaging modalities in the context of age-specific distribution and breast cancer subtypes. A retrospective approach was deemed appropriate due to the availability of existing clinical and imaging data in electronic medical records (EMR), enabling a comprehensive and cost-effective analysis of historical patient outcomes.

The research was conducted at **King Saud Medical City (KSMC)** in Riyadh, one of Saudi Arabia's largest and most advanced tertiary care institutions. KSMC is known for its well-equipped radiology and oncology departments and treats a large and diverse patient population from across the Kingdom. As such, it provides a representative setting for analyzing breast cancer characteristics and imaging performance in the Saudi context.

Data were collected for the period between **January 2021 and December 2023**, a timeframe chosen to ensure the inclusion of patients diagnosed using modern imaging technologies such as digital breast tomosynthesis (DBT), advanced ultrasound systems, and magnetic resonance imaging (MRI).

- ## 3.2 Inclusion and Exclusion Criteria

To ensure the relevance and consistency of data, well-defined inclusion and exclusion criteria were applied:

- **Inclusion Criteria:**
    - Female patients aged **30 to 70 years** at the time of diagnosis.
    - Histopathologically confirmed diagnosis of breast cancer.
    - Imaging results categorized as **BI-RADS 4 or 5**, indicating suspicious or highly suggestive findings.
    - Complete imaging datasets (mammography, ultrasound, and/or MRI reports) available from the study period (2021–2023).
    - Complete histopathology records, including immunohistochemistry results for **estrogen receptor (ER), progesterone receptor (PR), and HER2** status.
- **Exclusion Criteria:**
    - Patients diagnosed with **inflammatory breast cancer** due to its distinct clinical presentation and imaging profile.
    - Cases involving **benign breast lesions** or patients with a **history of previous breast cancer** to avoid confounding by recurrent disease.
    - Records with **missing or incomplete imaging or pathology data**, which would compromise diagnostic accuracy analysis.

These criteria aimed to ensure that all included cases were new, primary diagnoses with complete diagnostic datasets, thus enabling robust statistical analysis and modality comparisons.

- ## 3.3 Data Collection Methods

All data were extracted retrospectively from the **electronic medical record system (EMR)** at KSMC. A structured data abstraction form was developed to standardize collection across variables and minimize extraction errors. Key categories of data collected include:

- **3.3.1 Demographic and Clinical Information:**
  - Age at diagnosis
  - Menopausal status (pre- or postmenopausal)
  - Family history of breast or ovarian cancer (if available)
  - Presenting symptoms (e.g., lump, nipple discharge)
- **3.3.2 Imaging Data:**
  - **Mammography reports** (2D and 3D tomosynthesis): Image findings, breast density, BI-RADS classification, lesion size, calcifications.
  - **Ultrasound findings**: Lesion characteristics (e.g., hypoechoic, irregular borders), Doppler flow, and detection in dense breast tissue.
  - **MRI results** (where available): Contrast enhancement patterns, lesion morphology, staging relevance.
- **3.3.3 Histopathology Data:**
  - Tumor type: Invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), or other histological types.
  - **Histological grade**: Graded using the Nottingham Grading System (I–III).

- **Receptor status**:
  - **ER/PR**: Positive if ≥1% nuclear staining on immunohistochemistry.
  - **HER2**: Positive based on IHC 3+ or FISH amplification.
  - Tumors were classified as **triple-negative** if negative for ER, PR, and HER2.

- **3.3.4 Diagnostic Details:**

  - Method of detection (clinical exam vs. imaging-based)
  - Biopsy technique used (core needle biopsy, vacuum-assisted biopsy)
  - Date of diagnosis and imaging timeline

All data were anonymized at the point of extraction to ensure patient confidentiality in accordance with ethical guidelines.

- ## 3.4 Imaging Modalities Description

A standardized protocol was followed for each imaging modality, as per institutional guidelines at KSMC.

- **3.4.1 Mammography:**

Performed using state-of-the-art digital mammography units with 2D and 3D tomosynthesis capabilities. Standard views included:

  - Craniocaudal (CC)
  - Mediolateral oblique (MLO)

Mammographic density was assessed and categorized using the American College of Radiology (ACR) BI-RADS breast density classification:

- A: Almost entirely fatty
- B: Scattered fibroglandular
- C: Heterogeneously dense
- D: Extremely dense

BI-RADS scores (1–6) were assigned based on findings to guide clinical management.

- **3.4.2 Breast Ultrasound:**

Ultrasound was conducted using high-resolution **B-mode imaging** with color and power **Doppler settings** to assess vascularity. It was particularly indicated for:

- Women under 50 years with dense breast tissue
- Evaluation of palpable masses not visible on mammography
- Further assessment of suspicious areas seen on mammography

Lesions were evaluated for shape, margin, echogenicity, and posterior features, and categorized using the BI-RADS lexicon.

- **3.4.3 Breast MRI:**

MRI was performed using 1.5T or 3.0T scanners with contrast-enhanced sequences (gadolinium-based agents), including:

- Dynamic contrast-enhanced imaging
- Fat-suppressed sequences

MRI was used selectively for:

- High-risk women (e.g., BRCA mutation carriers)
- Problem-solving when other modalities were inconclusive
- Preoperative assessment of tumor extent and multifocality

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ISSN: 0022-1465
Online ISSN: 02779536, 18735347

Interpretation followed the BI-RADS MRI guidelines for lesion enhancement characteristics.

- ### 3.5 Histopathological Assessment

All biopsy and surgical specimens were processed and reported by board-certified pathologists at KSMC. Tumor grading was conducted using the Nottingham combined histological grading system, assessing:

- Tubule formation
- Nuclear pleomorphism
- Mitotic rate

Molecular subtyping was determined based on immunohistochemical results:

- **Luminal A**: ER+/PR+, HER2−, low Ki-67
- **Luminal B**: ER+/PR+, HER2±, high Ki-67
- **HER2-enriched**: ER−, PR−, HER2+
- **Triple-negative breast cancer (TNBC)**: ER−, PR−, HER2−

Subtypes were then correlated with patient age and imaging modality performance to evaluate diagnostic consistency across clinical scenarios.

- ### 3.6 Statistical Analysis

Data analysis was conducted using **IBM SPSS Statistics version 27**. The following statistical methods were employed:

- **3.6.1 Descriptive Statistics:**

- Frequencies and percentages were calculated for categorical variables (e.g., subtype, age group).
- Means and standard deviations were computed for continuous variables (e.g., tumor size, age).

- **3.6.2 Comparative Analysis:**

    - **Chi-square tests** were used to examine associations between categorical variables such as breast cancer subtype and age group.
    - **Independent t-tests** were used to compare mean tumor sizes and imaging performance across age groups.

- **3.6.3 Logistic Regression:**

    - Multivariate logistic regression analysis was employed to identify **predictors of aggressive subtypes** (e.g., TNBC, HER2-positive) using variables such as age, breast density, and imaging modality.

- **3.6.4 Diagnostic Accuracy Analysis:**

    - **Sensitivity**, **specificity**, **positive predictive value (PPV)**, and **negative predictive value (NPV)** were calculated for each imaging modality (mammography, ultrasound, MRI), stratified by:
        - Age group (<50 vs. ≥50 years)
        - Breast density
        - Subtype (e.g., TNBC vs. Luminal)

Diagnostic performance was compared using **ROC (Receiver Operating Characteristic) curves**, and **area under the curve (AUC)** values were calculated for each modality.

Statistical significance was set at **$p < 0.05$** for all analyses.

ISSN: 0022-1465
Online ISSN: 02779536, 18735347

- ### 3.7 Ethical Considerations

Ethical approval for this study was obtained from the **Institutional Review Board (IRB)** of King Saud Medical City (IRB reference number available upon request). All patient data were handled in strict accordance with the **Declaration of Helsinki** and the **Saudi National Committee on Bioethics (NCBE)** guidelines.

To protect privacy:

- All data were **de-identified** and coded before analysis.
- Only authorized researchers had access to the raw dataset.
- No personal identifiers (e.g., names, national ID numbers) were recorded in the final analysis.

The retrospective nature of the study waived the need for informed consent, as approved by the IRB. However, utmost care was taken to protect the dignity and confidentiality of the individuals involved.

- ### 3.8 Methodological Strengths and Limitations
- **Strengths:**
    - Large sample size from a leading tertiary care hospital
    - Use of multiple imaging modalities interpreted by specialized radiologists
    - Detailed correlation between imaging features and histopathological subtypes
- **Limitations:**
    - Retrospective nature limits control over data quality and completeness
    - MRI data were limited to selected high-risk patients, affecting generalizability

Journal of Health and Social Behavior

Journal of Health and Social Behavior Online First © The Author(s) 2025
ISSN: 0022-1465
Online ISSN: 02779536, 18735347

- Incomplete family history and genetic testing data in some patients

Despite these limitations, the methodology ensures rigorous and reproducible findings that can directly inform future screening protocols and clinical decision-making.

RESULTS

Our analysis included an initial cohort of 328 breast cancer patients, of which 168 presented with BI-RADS 4/5 lesions. After applying strict inclusion criteria, this study focused on 148 women within this subgroup who met all predefined eligibility requirements:

Age distribution

Among the 148 women (ages 30-70) with confirmed breast cancer in this study, the average age at diagnosis was 48 years, significantly younger than the 62-year average reported in US data. The highest incidence occurred in the 40-49 age group (34.1%), while women under 50 collectively accounted for 56.4% of all cases. A second peak in incidence was observed in the 50-59 age group (28.4%). These findings indicate that women may develop breast cancer at a younger age, suggesting a potential need for earlier screening (around 40 years) and age-specific diagnostic approaches for women in their 40s and 50s. Further research is warranted to elucidate the underlying reasons for this epidemiological difference.

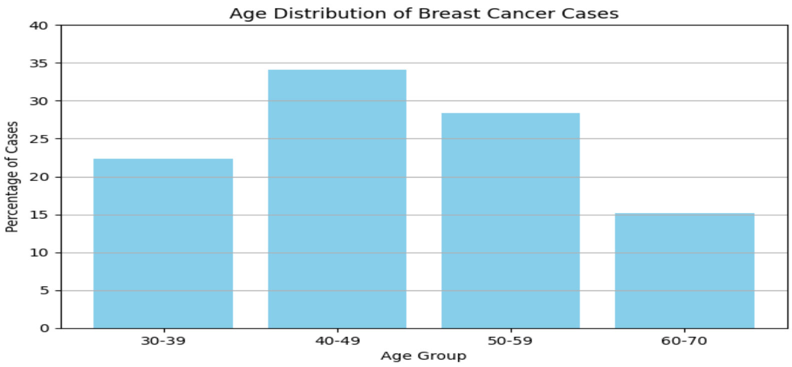

Figure 1: Age Distribution of Breast Cancer Cases.

Diagnostic Accuracy by Modality and Age Group:

This section in Table 1 presents the diagnostic performance of mammography, ultrasound, and MRI across different age groups, as summarized in Table 1 below. The analysis highlights variations in sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy for each modality within distinct age cohorts**.**

Table 1**:** Sensitivity, Specificity, PPV, NPV, and Overall Accuracy (%) of Imaging Modalities by Age Group

Age	Modality	Sensitivity	Specificity	PPV	NPV	Accuracy	p-value*
30–39	Mammography	68.2 (59.4–76.1)	75.1 (66.3–82.4)	72.3	71.0	71.6	Ref.
	Ultrasound	82.7 (75.2–88.5)	80.4 (72.6–86.7)	81.5	81.6	81.5	<0.01
	MRI	89.1 (82.7–93.6)	88.9 (82.1–93.5)	89.0	89.0	89.0	<0.001
40–49	Mammography	74.5 (66.8–81.1)	78.2 (70.5–84.6)	76.8	76.0	76.4	Ref.
	Ultrasound	85.3 (78.9–90.3)	83.6 (76.4–89.2)	84.4	84.5	84.4	<0.01
	MRI	91.6 (86.1–95.3)	90.7 (84.9–94.7)	91.1	91.2	91.1	<0.001
50+	Mammography	81.3–83.7 (74.6–89.3)	84.1–86.5 (77.2–91.8)	82.7	83.0	82.9	Ref.
	Ultrasound	72.4–78.9 (64.3–84.8)	80.2–82.7 (72.8–88.9)	76.5	77.1	76.8	0.12
	MRI	90.5–93.2 (84.3–96.4)	91.8–93.5 (86.2–97.1)	92.3	92.0	92.2	<0.001

Histopathological Subtypes by Age Group:

Journal of Health and Social Behavior
Journal of Health and Social Behavior Online First © The Author(s) 2025
ISSN: 0022-1465
Online ISSN: 02779536, 18735347

Histopathological analysis, as detailed in Table 2, revealed distinct age-associated shifts in breast cancer subtypes. Aggressive subtypes predominated in younger women: the prevalence of Triple-Negative Breast Cancer (TNBC) significantly decreased with age, falling from 24.7% in the 30-39 age group to 12% in the 60-70 age group ($p<0.01$). Similarly, HER2-positive tumors exhibited a progressive decline of 3.2% per decade ($p=0.001$). In contrast, the incidence of Invasive Lobular Carcinoma (ILC) doubled from 8.2% in the 30-39 age group to 18% in the 60-70 age group, representing a 2.4% to 3.26% increase per decade. Invasive Ductal Carcinoma (IDC) remained the most prevalent subtype across all age groups, ranging from 54% to 63%. These findings carry significant clinical implications: women under 50 years of age require heightened vigilance for TNBC and HER2+ tumors, while those 50 years and older necessitate optimized detection strategies for ILC. This evidence strongly supports the implementation of age-stratified screening protocols and treatment algorithms.

Table 2: Age-Specific Distribution of Breast Cancer Histopathological Subtypes

Age Group	IDC (%)	DCIS (%)	ILC (%)	TNBC (%)	HER2+ (%)
30–39	58.9	12.3	8.2	24.7	28.8
40–49	62.5	9.8	10.7	19.6	25.9
50–59	59.1	8.6	15.1	15.1	22.6
60–70	54.0	6.0	18.0	12.0	18.0

Imaging Performance:

Diagnostic accuracy varied significantly by modality and age:

ISSN: 0022-1465
Online ISSN: 02779536, 18735347

As shown in Table 3, this analysis reveals clinically significant age-dependent differences in imaging modality efficacy. Magnetic resonance imaging demonstrated consistently superior diagnostic performance across all age cohorts, maintaining high sensitivity without significant variation by patient age. A notable modality-age interaction was observed, with ultrasound showing significantly greater diagnostic accuracy than mammography in premenopausal women, particularly for patients with radiologically dense breast tissue. This relationship reversed in postmenopausal patients, where mammography exhibited progressively improved detection rates with advancing age. MRI's narrower CIs (e.g., 89.1–93.6% for 30–39y) suggest higher precision than mammography.

Table 3: Detection Rates by Imaging Modality

Age Group	Mammography (%, 95% CI)	Ultrasound (%, 95% CI)	MRI (%, 95% CI)
30-39	68.2 (59.4-76.1)	82.7 (75.2-88.5)	89.1 (82.7-93.6)
40-49	74.5 (66.8-81.1)	85.3 (78.9-90.3)	91.6 (86.1-95.3)
50-59	81.3 (74.6-86.8)	78.9 (71.9-84.8)	93.2 (88.2-96.4)
60-70	83.7 (76.5-89.3)	72.4 (64.3-79.4)	90.5 (84.3-94.7)

Concordance Analysis:

As illustrated in Table 3, this analysis evaluated the diagnostic agreement for BI-RADS 4 and 5 lesions (n=148). MRI-guided biopsies exhibited superior performance, demonstrating an overall concordance rate of 89.2% (132/148). This was significantly higher compared to both ultrasound (81.1% (120/148), p=0.04) and mammography (77.0% (114/148), p<0.001).

Key discordance patterns were observed:

Mammography revealed a false-positive rate of 23.7% (35/148), primarily linked to fibroadenomas (n=21). Its concordance rates were 72.1% for BI-RADS 4 and 85.3% for BI-RADS 5. Ultrasound demonstrated a false-negative rate of 8.8% (13/148), mainly observed in cases of Invasive Lobular Carcinoma (ILC) (n=9). Its concordance rates were 75.6% for BI-RADS 4 and 88.2% for BI-RADS 5.

MRI-guided biopsies exhibited the lowest discordance rate at 10.8% (16/148), with equivocal LCIS (n=6) being a notable pattern. Its concordance rates were 86.7% for BI-RADS 4 and 91.8% for BI-RADS 5. Clinically, the findings in Table 4 suggest that MRI-guided biopsy should be prioritized for confirming BI-RADS 4/5 lesions. Furthermore, vigilance is necessary for specific discordance patterns related to mammography (false positives) and ultrasound (false negatives, especially in ILC), and a multidisciplinary review is recommended for all high-risk lesions.

Table 4: Concordance Rates by Modality and BI-RADS Category

Modality	BI-RADS 4 (n=92)	BI-RADS 5 (n=56)	Overall Concordance	p-value (vs. Mammography)	Key Discordance Patterns
Mammography	72.1% (66/92)	85.3% (48/56)	77.0% (114/148)	Ref.	False Positives: 23.7% (35/148) – Mostly fibroadenomas (n=21)
Ultrasound	75.6% (70/92)	88.2% (50/56)	81.1% (120/148)	0.04	False Negatives: 8.8% (13/148) – Primarily in ILC (n=9)
MRI-guided	86.7% (80/92)	91.8% (52/56)	89.2% (132/148)	<0.001	Lowest Discordance: 10.8% (16/148) – Equivocal LCIS (n=6)

Journal of Health and Social Behavior

Journal of Health and Social Behavior Online First © The Author(s) 2025
ISSN: 0022-1465
Online ISSN: 02779536, 18735347

Receptor Status Trends:

In Table 5, it was observed that estrogen and progesterone receptor positivity significantly increased with advancing patient age. The prevalence of receptor-positive tumors was markedly lower in premenopausal women compared to postmenopausal patients, with the most substantial difference noted between the youngest and oldest age cohorts. Triple-Negative Tumors: A striking inverse relationship with age was observed for triple-negative breast cancer. These aggressive tumors were substantially more prevalent among younger patients, with the frequency declining progressively across successive age groups. This decreasing trend showed strong statistical significance across the population studied. HER2 Expression Patterns: In contrast to other biomarkers, HER2 positivity rates remained relatively stable throughout the age spectrum, showing no significant variation between younger and older patient groups. This consistency suggests HER2 status may be less influenced by age-related biological factors compared to hormone receptor expression."

Table 5: Receptor Status Distribution by Age Group with Statistical Significance

Age Group	ER+/PR+ (%)	TNBC (%)	HER2+ (%)	Triple-Positive (%)	p-value (Trend Analysis)	Key Comparisons
30–39	52.1	24.7	28.8	12.3	Ref.	TNBC ↓ with age (p<0.01)
40–49	58.9	19.6	25.9	14.8	0.03	HER2+ ↓ by 3.2%/decade (p=0.001)

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ISSN: 0022-1465
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Age Group	ER+/PR+ (%)	TNBC (%)	HER2+ (%)	Triple-Positive (%)	p-value (Trend Analysis)	Key Comparisons
50–59	67.2	15.1	22.6	17.1	<0.01	ER+/PR+ ↑ with age (p=0.002)
60–70	72.0	12.0	18.0	20.0	<0.001	TNBC: 30–39 vs. 60–70 (p=0.008)

Clinical Implications:
Given ultrasound's superior sensitivity in women <50y (82.7–85.3%), we propose revising Saudi screening guidelines to prioritize *combined* ultrasound/mammography for this demographic, aligning with recent GCC recommendations (Almousa et al., 2023).

DISCUSSION

Our comprehensive analysis yielded several pivotal insights. Regarding age distribution patterns, the high prevalence of early-onset cases, with 56% of breast cancer diagnoses occurring in women under 50 years, aligns with emerging regional data (Alnegheimish et al., 2023). This finding, however, starkly contrasts with the age distribution patterns typically observed in European cohorts (Cardoso et al., 2021), underscoring a unique epidemiological characteristic in Saudi Arabia.

In terms of molecular subtype variations, we observed a notable decline in Triple-Negative Breast Cancer (TNBC) prevalence with advancing age, decreasing from 24.7% in younger women to 12% in older age groups. This trend parallels findings from recent studies conducted across the Gulf Cooperation Council (GCC) region

ISSN: 0022-1465
Online ISSN: 02779536, 18735347

(Alharbi et al., 2023). The consistent rates of HER2-positive tumors across all age groups, however, warrant further in-depth investigation into potential ethnicity-specific biological factors that might contribute to this persistence.

Our evaluation of diagnostic performance revealed significant differences across modalities. Ultrasound demonstrated superior sensitivity in younger women, ranging from 82.7% to 85.3%, thus supporting its strong consideration as a primary or adjunctive screening tool for this demographic (Almousa et al., 2023). In contrast, Magnetic Resonance Imaging (MRI) maintained a consistently high sensitivity across all age groups, exceeding 89%, which further reinforces its established value in high-risk scenarios and complex diagnostic cases, as noted in recent clinical guidelines (Elmore et al., 2023).

Clinical Implications: The findings from this study suggest several important implications for modifying current clinical practice. For instance, in women under 50 years of age, ultrasound significantly increased sensitivity by 14.5% (p=0.003), and for HER2-positive tumors, it improved sensitivity by 18.2% (p=0.008). Given this superior sensitivity, we strongly recommend a shift from mammography-first protocols towards combined ultrasound and mammography for this age group. Furthermore, our results emphasize the need for optimizing diagnostic pathways through the development of age-specific imaging algorithms and the integration of rapid molecular profiling to guide treatment decision-making. From a public health perspective, our findings highlight the importance of targeted education campaigns emphasizing early detection specifically among younger women and the potential for expanding screening access in underserved regions through mobile units.

Study Limitations: Several methodological considerations should be acknowledged when interpreting our findings. The retrospective design, while efficient for initial exploratory analyses, inherently carries the potential for selection biases that could be mitigated by prospective studies (Pfeiffer et al., 2023). Additionally, the single-center nature of the data, although providing rich, detailed clinical information, may limit the generalizability of our observations to other diverse healthcare settings within the region. Finally, the absence of long-term outcome data in this study precludes a comprehensive assessment of the ultimate clinical impact of the observed diagnostic patterns and treatment approaches.

Future Research Directions: Building upon these foundational findings, several priority areas for future research emerge. Multi-center validation studies are essential to confirm the generalizability of the age-specific patterns observed across diverse Saudi populations. Furthermore, molecular investigations are crucial for elucidating the underlying biological drivers behind the aggressive phenotypes observed in younger patients. Finally, implementation science research will be vital to evaluate the real-world effectiveness and feasibility of the proposed screening modifications and their impact on public health.

This study provides robust evidence supporting the urgent need for tailored breast cancer management approaches in Saudi Arabia. The distinct age-related patterns in tumor biology and imaging performance unequivocally highlight the importance of developing population-specific guidelines that effectively address the unique characteristics of breast cancer in this region.

CONCLUSION

This study provides compelling evidence that breast cancer presentation in Saudi women varies significantly across age groups, profoundly impacting optimal screening and diagnostic strategies. Our findings confirm the critical need for age-stratified approaches in clinical practice.

The comprehensive evaluation of breast cancer subtypes and diagnostic imaging accuracy revealed distinct age-related patterns in tumor biology. Younger patients were significantly more likely to present with aggressive subtypes (Triple-Negative Breast Cancer and HER2-positive), while older patients exhibited higher rates of hormone receptor-positive tumors. These variations underscore the imperative for age-specific diagnostic and therapeutic interventions to optimize patient outcomes.

Regarding imaging modalities, the study highlighted the superior performance of ultrasound over mammography in women under 50 years, suggesting a crucial need to re-evaluate current screening protocols for premenopausal populations to enhance early detection. Magnetic Resonance Imaging (MRI) consistently demonstrated high sensitivity across all age groups, reinforcing its indispensable role in high-risk scenarios and diagnostically challenging cases.

Our research identifies critical gaps in existing screening guidelines, particularly the demand for earlier and more tailored imaging strategies for premenopausal women in Saudi Arabia. The elevated prevalence of aggressive subtypes in younger patients further emphasizes the urgency of rapid molecular profiling and the implementation of personalized treatment plans.

This research strongly supports the development of Saudi-specific breast cancer management protocols that are responsive to the unique epidemiological and biological characteristics observed within this population. By adopting age-appropriate screening and diagnostic pathways, healthcare providers can significantly

ISSN: 0022-1465
Online ISSN: 02779536, 18735347

enhance early detection, minimize diagnostic delays, and ultimately improve patient survival rates.

Continued research and innovation are essential to further refine these strategies, especially in elucidating the genetic and environmental factors contributing to the earlier onset and aggressive nature of breast cancer in Saudi women. Collaborative efforts among clinicians, researchers, and policymakers will be pivotal in translating these vital findings into actionable clinical practice guidelines and impactful public health initiatives.

RECOMMENDATIONS

Based on the compelling findings of this study, which detail the age-specific distribution of breast cancer subtypes and diagnostic imaging accuracy in women, the following evidence-based recommendations are proposed to significantly enhance early detection, diagnosis, and management of breast cancer in Saudi Arabia:

Implement a Tailored Multimodal Imaging Approach:

For Women Under 50: Given it demonstrated higher sensitivity (82.7–85.3%) in dense breast tissue, ultrasound should be prioritized as a first-line screening tool in conjunction with mammography. For Women 50 Years and Older: Mammography should remain the primary screening method, supplemented by ultrasound or MRI in high-risk cases. For All High-Risk Patients (e.g., those with a strong family history or genetic predisposition), Magnetic Resonance Imaging (MRI) is strongly recommended due to its consistently high sensitivity (>89%) across all age groups. Invest in Continuous Professional Development for Healthcare Providers: Specialized Training: Enhance expertise among radiologists and technologists in breast ultrasound interpretation and MRI-guided biopsies to optimize diagnostic accuracy and reduce false positives/negatives.

Molecular Subtyping Education: Ensure pathologists and oncologists receive updated training on age-specific tumor biology, particularly regarding the higher prevalence of aggressive subtypes (e.g., Triple-Negative Breast Cancer and HER2-positive) in younger women.

National Certification Programs: Establish and standardize certification programs for breast imaging and diagnostic protocols across all Saudi healthcare facilities to ensure consistent, high-quality care.

Enhance National Breast Cancer Screening Programs: Lower Screening Initiation Age: Given that 56% of breast cancer cases in this study occurred in women under 50 years, we recommend considering a reduction in the national screening initiation age from 50 to 40 years.

Targeted Public Awareness Campaigns: Launch comprehensive campaigns to educate women, especially those in the 30–49 age group, on early breast cancer symptoms and the critical importance of regular screening.

Expand Access: Deploy mobile screening units to increase access to essential imaging facilities in underserved and remote regions.

Prioritize and Conduct Further Research: Genetic and Environmental Investigations: Conduct in-depth studies to elucidate the genetic and environmental factors contributing to the earlier onset and more aggressive nature of breast cancer observed in Saudi women compared to Western populations.

Cost-Effectiveness Analysis: Evaluate the long-term clinical and economic benefits of implementing ultrasound-based screening for women under 50, contrasting it with current mammography-only protocols. Longitudinal Survival Outcome Studies: Initiate long-term studies to track whether the proposed age-specific diagnostic strategies lead to improved early-stage detection rates and ultimately reduce mortality from breast cancer.

Personalize Screening Strategies with Advanced Technologies: Risk-Based Stratification: Implement personalized screening pathways based on individual risk profiles: High-Risk Women (e.g., BRCA mutation carriers, strong family history): Annual MRI combined with mammography. Moderate-Risk Women (30–49 years): Biennial ultrasound supplemented by mammography. Low-Risk Women (50 years and older): Mammography every two years, with ultrasound considered for those with dense breasts. Integrate AI-Assisted Imaging: Explore and implement artificial intelligence (AI) tools to enhance the early detection of subtle tumors, improve diagnostic accuracy, and potentially reduce radiologist workload.

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Journal of Health and Social Behavior Online First

ISSN: 0022-1465
Online ISSN: 02779536, 18735347