Research Square

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Epidemiological, Pathological and Histomolecular Phenotyping Patterns of Female Breast Cancer: A Single Center Study in Al-Madinah City of Saudi Arabia

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Research Article

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Abstract

Background

Breast cancer is the most prevalent cancer among women globally and in Saudi Arabia.

Objectives

This study aimed to identify breast cancer histo-molecular patterns among women diagnosed with breast cancer in Al-Madinah, Saudi Arabia.

Design:

Observational retrospective design.

Setting:

Single center medical oncology department.

Patients and methods:

Saudi and expatriate women diagnosed with breast cancer between 2018 and 2020 at a medical oncology center in Al-Madinah City.

Main outcome measures:

Temporal trends analyzed by age group and histo-molecular patterns.

Sample size:

284 women diagnosed with breast cancer.

Results

Mean patient age was 51 (± 13.4) years, with 82.4% aged > 40 years. Invasive ductal carcinoma was diagnosed in 93.3% of cases. There was no significant statistical difference in breast cancer diagnosis and staging among the different age groups or diagnostic years (all $p > 0.05$), but stage II breast cancer was the most prevalent, in 37.0% (n = 105) of cases. Numerically more stage III/IV cases were diagnosed

in 2020 than in 2018 and 2019. Distant metastasis was present in 24.7% (n = 68) of patients, most commonly to lung and bone. Predominant tumor size across all molecular subtypes was T2 (2–5 cm) (n = 122; 45.2%). In molecular profiling, Luminal A (hormone receptor positive/HER2-negative) was most prevalent (52.5%), followed by triple-negative (hormone receptor negative/HER2-negative, 19.0%), HER2-enriched (hormone receptor negative/HER2-positive, 15.5%), and Luminal B (hormone receptor positive/HER2-positive, 13.0%).

Conclusions

Despite the awareness and screening programs implemented at the national level since 2015, late-stage breast cancer prevalence in Saudi Arabia remained higher than that reported in other countries. Molecular subtype distribution was similar across 2018–2020.

Limitation:

Lack of Ki-67 data for the majority of patients; single-center design.

Introduction

Breast cancer ranks as the second most frequently diagnosed cancer globally and the most diagnosed cancer among females, leading to the highest number of cancer-related deaths [1]. Millions of new breast cancer cases are reported annually, accounting for approximately one in four cancer cases among women and 15% of cancer-related deaths in both developed and developing countries [2]. In Saudi Arabia, the National Cancer Center (NCC) reported that 31% of women's cancer cases across all ages occurred in the breast, with 2,459 new female breast cancer cases in 2020 [3]. The crude incidence rate of breast cancer steadily increased from 11 per 100,000 in 2001 to 28 per 100,000 in 2020 [3]. The 5-year survival rate for patients with metastatic breast cancer in Saudi Arabia and worldwide remains poor, at approximately 25%, significantly lower than the survival rate for localized disease [4]. The available epidemiological distribution and histo-molecular phenotyping patterns of breast cancer in Saudi Arabia remain limited, despite the significant burden of the disease.

Breast cancer diagnosis age differs between countries. In the United States, the median age at diagnosis is 62 years, whereas in Saudi Arabia the median age is 50 years [5, 6]. Breast cancer in Saudi Arabia presents with distinct characteristics compared with countries such as the United States, with a higher prevalence among younger populations and more commonly manifesting as higher-grade tumors diagnosed at advanced stages [7, 8].

Breast cancer exhibits diverse histological characteristics, with invasive ductal carcinoma (IDC) being the most common subtype, followed by invasive lobular carcinoma (ILC) and others; current histological classification alone fails to fully capture this heterogeneity [9]. Additional biomarkers have therefore

been introduced to improve tumor prognostication, including TNM staging, grading, distant metastasis, and hormonal and molecular markers such as estrogen receptor, progesterone receptor, and HER2 status [10]. Integration of HER2 status into molecular subtyping over the past three decades has significantly altered treatment strategies and prognosis [11]. HER2, a proto-oncogene encoding the HER2 receptor, is amplified in approximately 30% of breast cancer cases [12], and patients with HER2-positive disease can benefit from targeted therapies such as trastuzumab, lapatinib, and pertuzumab [12].

Although histological features, patient age, and disease stage have been widely studied for prognosis and treatment, growing interest exists in exploring breast cancer trends across different ages and molecular patterns over time. This study aimed to analyze breast cancer cases in Al-Madinah City, Saudi Arabia, and correlate them with recent histo-molecular patterns and epidemiological distributions, to offer a comprehensive understanding of breast cancer epidemiology in this region.

Methods

Patients Selection and Stratification

This study was approved by the Institutional Review Board (IRB) of King Fahad Hospital, Madinah, Saudi Arabia (study reference: ADCARE; IRB approval dated 11 October 2020). The study included 284 female patients diagnosed and treated at the Medical Oncology Center at King Fahad Hospital in Al-Madinah City, Saudi Arabia, between 2018 and 2020. All enrolled patients were aged > 18 years, diagnosed clinically and histologically with breast cancer of different types and stages, and included both Saudi nationals and expatriates living and working in Saudi Arabia. Clinical information, including age, nationality, and pathology reports, was obtained from hospital medical records. Pathology reports contained each patient's specific histological diagnosis, including tumor histological subtype (IDC, ILC, or others including mucinous, metaplastic, and solid papillary carcinoma), tumor grade (G1–3), TNM staging (tumor [T] size < 2 cm, 2–5 cm, or > 5 cm; N, lymph node metastasis by number; and M, metastasis to distant sites), and hormonal/molecular markers subclassifying breast cancer into Luminal A (HR+/HER2−), Luminal B (HR+/HER2+), HER2-Enriched (HR−/HER2+), and triple-negative (HR−/HER2−). All patients underwent treatment according to current National Comprehensive Cancer Network (NCCN) guidelines. This information is summarized in Table 1.

Statistical Analysis

Descriptive data are presented as mean ± SD for continuous variables and frequencies (percentages) for categorical variables. Association between categorical variables and diagnostic year was assessed using the chi-square test (Fisher's exact test where expected cell counts were small); two-tailed p-values with 95% confidence intervals were used throughout, with $p < 0.05$ considered statistically significant.

Results

Results were analyzed over the 3-year period 2018–2020 (n = 284; 90 patients in 2018, 81 in 2019, and 113 in 2020). Mean patient age was 51 ± 13.4 years (range 25–90 years). Patients aged ≥ 40 years (n = 234, 82.4%) outnumbered those aged < 40 years (n = 50, 17.6%), confirming that breast cancer diagnosis in this cohort was prevalent in the older population. More patients were diagnosed at a younger age in 2020 than in 2019, though the difference was not statistically significant (p = 0.139 across all three years) (Fig. 1). Most patients were Saudi nationals (n = 204, 71.8%), predominantly aged 40–69 years.

[Figure near here]

Molecular marker distribution did not differ significantly across the three years (p = 0.414). Luminal A (HR+/HER2−) was the most prevalent subtype overall (52.5%), followed by triple-negative (19.0%), HER2-Enriched (15.5%), and Luminal B (13.0%) (Fig. 3). Triple-negative disease was numerically more common in 2020 (23.0%) than in 2018 (15.6%) or 2019 (17.3%). Molecular subtype distribution differed significantly across age groups (chi-square p = 0.023; Fig. 4): the proportion of Luminal A (HR+/HER2−) disease rose from 36.0% in patients aged < 40 years to 69.7% in patients aged ≥ 70 years, while triple-negative disease fell correspondingly from 30.0% to 3.0% over the same age range, with HER2-positive subtypes (Luminal B and HER2-Enriched combined) comprising a relatively stable 28–34% of cases across all age bands.

[Figures 3 and 4 near here]

Table 1
Characteristics of the study population, breast cancer cases 2018–2020 (n = 284).

Characteristic	Total (n = 284)	2018 (n = 90)	2019 (n = 81)	2020 (n = 113)	p-value
Nationality — Saudi	204 (71.8%)	62 (68.9%)	57 (70.4%)	85 (75.2%)	0.573
Nationality — Non-Saudi	80 (28.2%)	28 (31.1%)	24 (29.6%)	28 (24.8%)	
Age < 40 years	50 (17.6%)	16 (17.8%)	9 (11.1%)	25 (22.1%)	0.139
Age ≥ 40 years	234 (82.4%)	74 (82.2%)	72 (88.9%)	88 (77.9%)	
Histology — IDC	265 (93.3%)	83 (92.2%)	76 (93.8%)	106 (93.8%)	0.339
Histology — ILC	11 (3.9%)	2 (2.2%)	4 (4.9%)	5 (4.4%)	
Histology — Other*	8 (2.8%)	5 (5.6%)	1 (1.2%)	2 (1.8%)	
Grade 2	135 (54.0%)	44 (57.9%)	41 (54.7%)	50 (50.5%)	0.541
Grade 3	112 (44.8%)	30 (39.5%)	33 (44.0%)	49 (49.5%)	
Grade 0–1	3 (1.2%)	2 (2.6%)	1 (1.3%)	0 (0.0%)	
Clinical stage I	22 (7.7%)	10 (11.1%)	7 (8.6%)	5 (4.4%)	0.310
Clinical stage II	105 (37.0%)	33 (36.7%)	35 (43.2%)	37 (32.7%)	
Clinical stage III	85 (29.9%)	27 (30.0%)	22 (27.2%)	36 (31.9%)	
Clinical stage IV	72 (25.4%)	20 (22.2%)	17 (21.0%)	35 (31.0%)	
Tumor size T1 (< 2cm)	26 (9.6%)	12 (14.3%)	7 (8.9%)	7 (6.5%)	0.136
Tumor size T2 (2–5cm)	122 (45.2%)	40 (47.6%)	40 (50.6%)	42 (39.3%)	
Tumor size T3 (> 5cm)	59 (21.9%)	12 (14.3%)	16 (20.3%)	31 (29.0%)	
Tumor size T4 (extended)	63 (23.3%)	20 (23.8%)	16 (20.3%)	27 (25.2%)	
Nodal status N0	79 (29.2%)	25 (30.9%)	29 (36.7%)	25 (22.5%)	0.377
Nodal status N1 (1–3 LN)	149 (55.0%)	42 (51.9%)	39 (49.4%)	68 (61.3%)	
Nodal status N2 (4–9 LN)	42 (15.5%)	14 (17.3%)	11 (13.9%)	17 (15.3%)	
Nodal status N3	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	
Distant metastasis (M1)	68 (24.7%)	16 (19.5%)	17 (21.2%)	35 (31.0%)	0.130
Luminal A (HR+/HER2-)	149 (52.5%)	52 (57.8%)	45 (55.6%)	52 (46.0%)	0.414
Luminal B (HR+/HER2+)	37 (13.0%)	8 (8.9%)	10 (12.3%)	19 (16.8%)	

Characteristic	Total (n = 284)	2018 (n = 90)	2019 (n = 81)	2020 (n = 113)	p-value
HER2-Enriched (HR-/HER2+)	44 (15.5%)	16 (17.8%)	12 (14.8%)	16 (14.2%)	
Triple negative (HR-/HER2-)	54 (19.0%)	14 (15.6%)	14 (17.3%)	26 (23.0%)	

**Other histology includes mucinous adenocarcinoma, metaplastic carcinoma, and solid papillary carcinoma. Denominators for grade, tumor size, nodal status, and metastasis exclude patients with the variable not recorded (see Results text for evaluable denominators). p-values from chi-square test across the three diagnostic years.*

Discussion

Breast cancer stands as the most frequently diagnosed cancer in women worldwide [1]. Its incidence has been rising owing to diverse environmental factors, decreased awareness, and inadequate early screening in low- and middle-income countries [13–15]. The average age at breast cancer diagnosis varies among countries; in several cancer registries the mean age at diagnosis is 48 years [16]. Western countries typically diagnose breast cancer in women around age 60 years, whereas Arab countries tend to diagnose it at younger ages [17]. An NCC study spanning 1990–2010 estimated the most prevalent age for breast cancer diagnosis in Saudi Arabia at 39 years, roughly a decade earlier than the typical age of first diagnosis in Western countries [18]. Since 2017, a shift in this age trend has occurred, with more cases diagnosed around age 50 years [19]. Our study, focused on the period 2018–2020, similarly observed variation in age at diagnosis, with the majority of patients diagnosed after age 40. This divergence in age at diagnosis between Arab and Western populations may be attributable to social, economic, and population dynamics [20], underscoring the importance of screening programs from early adulthood. Studies have suggested a potential association between HER2 overexpression, ethnic variability, and younger age at initial presentation [21]; however, our findings show no correlation between age at diagnosis and disease stage in either younger or older women.

In our sample, stage II breast cancer was the most prevalent stage and stage I the least common, a pattern that typically correlates with tumor size and extension; across all four molecular subtypes, the most common tumor size at diagnosis was T2 (2–5 cm). Despite a nationwide campaign promoting early breast cancer screening initiated in 2015, approximately 55% of patients in this cohort were diagnosed at stages III or IV, notably higher than typically reported in Western countries [22–24]. A numerical increase in T3–T4 disease (tumor size > 5 cm or tumor extension) toward the end of 2020 may reflect the impact of COVID-19-related lockdowns, which halted cancer screening programs and, alongside fear of infection, likely delayed care-seeking and diagnosis for many patients [25].

Molecular phenotyping has increasingly been used to explore the relationship between breast cancer diagnosis age and disease prevalence over time. A study by Cortet et al. in France found no significant

annual trends in the proportion of each molecular subtype [26]. A comparative study between Saudi Arabian and Swiss patients (1988–2002) reported a significantly higher rate of HER2 amplification (31%) among Saudi patients than Swiss patients [27]. A study conducted in Riyadh between 2010 and 2014 by Alnegheimish et al. reported an HER2-positive rate of 26.8% [28]. In 2021, Zekri et al. studied 1,867 patients with breast cancer and found HER2 expression in 29.9% of patients [17]. These findings are consistent with the current study, in which HER2 was expressed (Luminal B and HER2-Enriched combined) in 28.5% of patients.

The most common molecular subtype identified in this study across 2018–2020 was Luminal A (HR+/HER2−), in 52% of patients, consistent with previously published Saudi data [9, 28–31]. Compared with previously published data from Al-Madinah, this study showed a slight decrease in HR+/HER2 + cases and an increase in HER2-Enriched cases [9]; the observed distribution of molecular subtypes was otherwise similar to that reported in other Saudi cities. By contrast, a study from India reported HER2-Enriched as the most common molecular subtype [32], potentially reflecting that cohort's younger age distribution (49% aged < 40 years). Variation in HR/HER2 expression across populations may reflect racial and genetic differences, meaning prognosis and treatment approaches may vary between patient populations, as hormone receptor status is not solely tied to HER2 status. Zekri et al. and Mohammed et al. similarly found no significant association between HR and HER2 receptor status [17, 33].

These findings align with the ongoing shift toward a more stressful and less healthy lifestyle in Saudi Arabia, which may contribute to increased smoking prevalence among Saudi women; smoking for more than 10 years has been associated with an approximately 10% higher risk of breast cancer compared with non-smoking [34]. Conversely, multiple full-term pregnancies have been associated with reduced breast cancer risk [13, 35], and the Saudi total fertility rate has fallen from 7.6 in 1960 to 2.4 in 2020 [36]. This study also found a higher detection rate of breast cancer in 2020 than in 2019, possibly reflecting increased general disease awareness following the COVID-19 pandemic.

This study adds to the literature on breast cancer trends in Saudi Arabia. A limitation is the limited availability of Ki-67 data, accessible for only 52 patients; however, there is no strong evidence that Ki-67 availability changes treatment regimen selection [37], and most centers do not routinely require this marker. Additionally, data were collected from a single center, which may limit the generalizability of these findings.

Conclusions

This study presents breast cancer incidence trends over a 3-year period. Molecular subtype trends were similar between 2018 and 2020, with only slight differences. Higher stage, tumor size, lymph node metastasis, and distant metastasis were numerically more common in 2020. Although national awareness campaigns and screening programs have been implemented since 2015, late-stage diagnosis in Saudi Arabia remains high, which does not align with the screening program's goal of increasing early-stage diagnosis to improve outcomes. Further research into individual and cultural factors that may

influence breast cancer screening uptake is needed, alongside larger multicenter studies examining risk factors together with breast cancer histo-molecular phenotype, to monitor trends and guide prevention efforts.

Declarations

Conflict of interests:

The authors have no relevant conflicts of interest to disclose.

Declarations

Ethics approval and consent to participate:

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of King Fahad Hospital, Madinah, Saudi Arabia (study reference: ADCARE; IRB approval dated 11 October 2020).

Informed consent:

Informed consent was not required for this study.

Consent for publication:

Not applicable.

Funding:

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Author Contribution

Nasser Mulla — conceptualization, data registry, methods, writing, and editing; statistical analysis, writing, and editing, critically reviewed and approved the final draft and is responsible for the content and similarity index of the manuscript.

Availability of data and material:

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request. Patient identifiers were removed and replaced with non-identifying study

codes prior to analysis.

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Figures

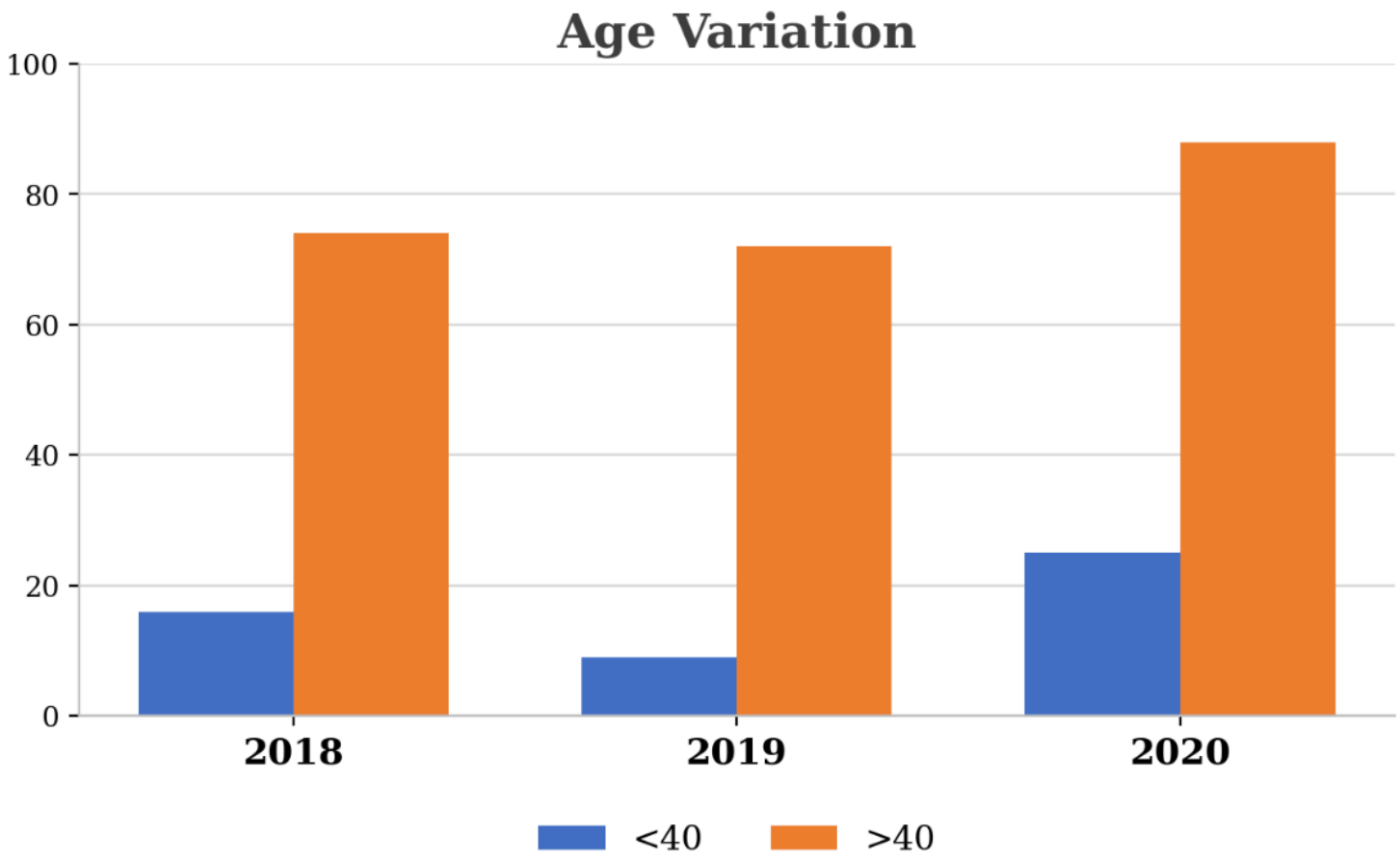


Figure 1

Age variation among female breast cancer cases in Al-Madinah City of Saudi Arabia for the three years (2018–2020).

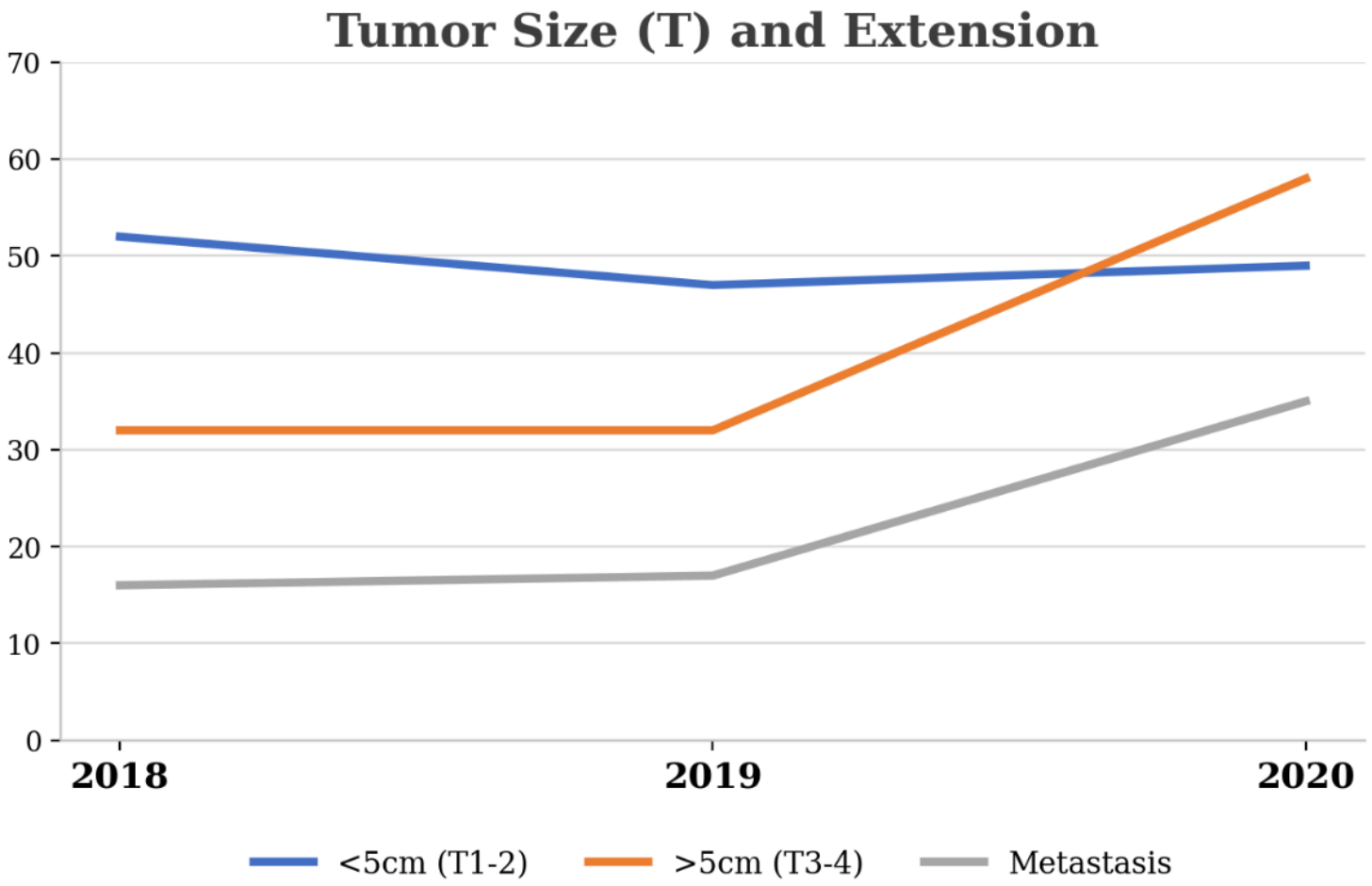


Figure 2

Tumor size and tumor extension among female breast cancer cases in Al-Madinah City of Saudi Arabia for the three years (2018–2020). Values for <5cm (T1-2) at 2018 were corrected from the originally submitted figure (62→52) to match the validated Table 1 counts (T1 n=12 + T2 n=40 = 52 in 2018).

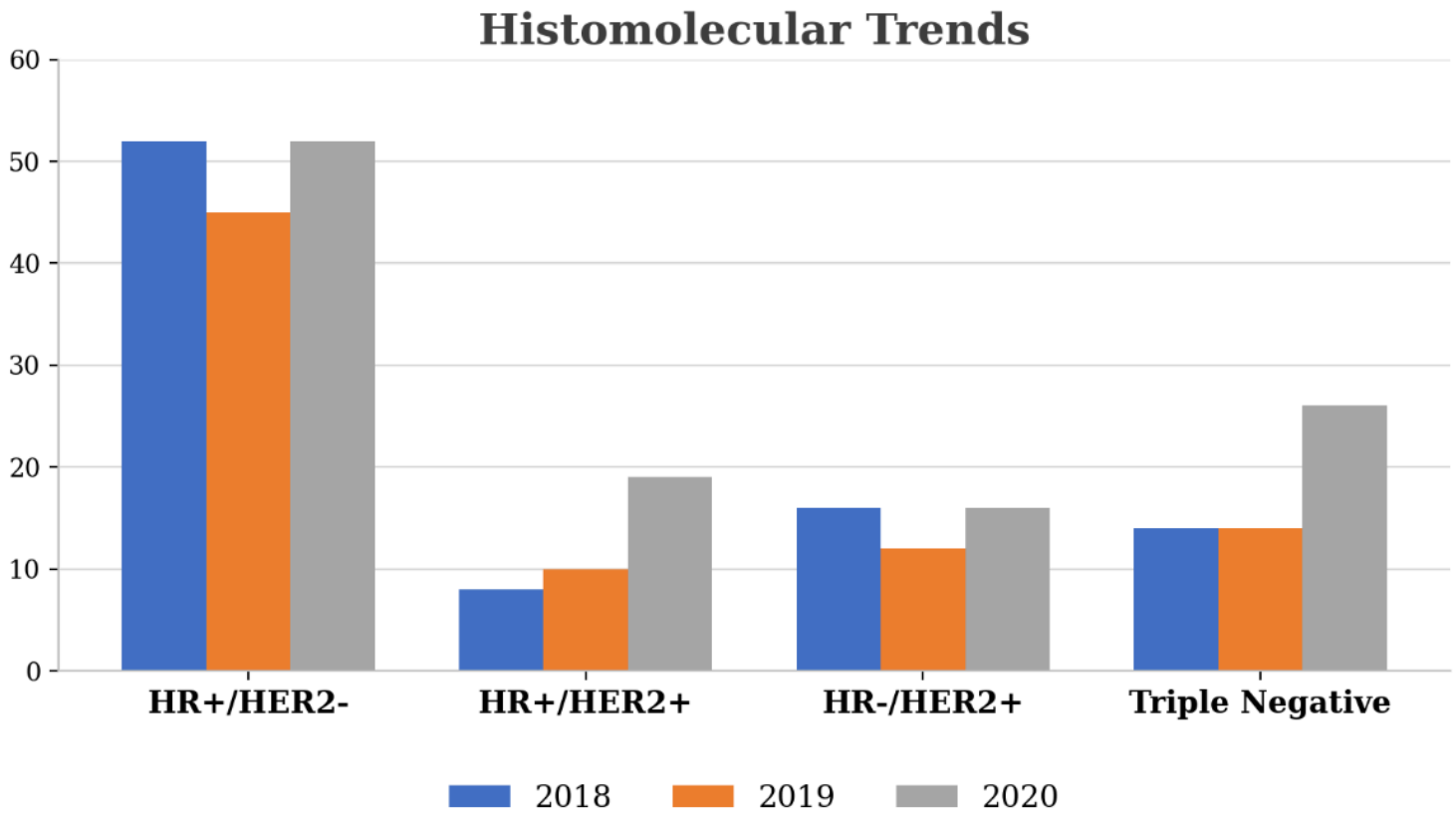


Figure 3

Molecular markers trend among female breast cancer cases in Al-Madinah City of Saudi Arabia for the three years (2018–2020).

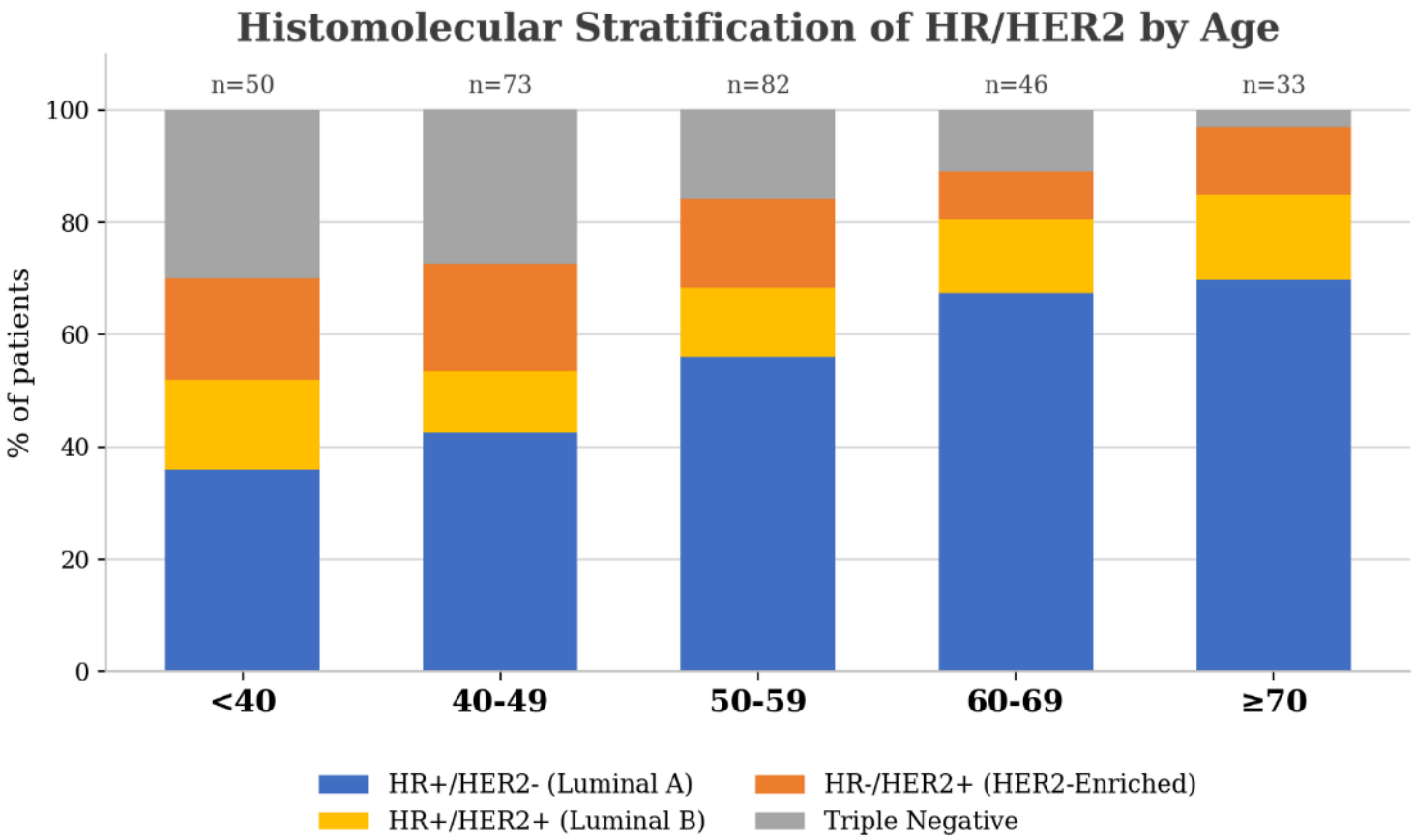


Figure 4

Histomolecular stratification of HR/HER2 status across different breast cancer patient ages (n=284; chi-square p=0.023). The proportion of Luminal A (HR+/HER2-) disease rises from 36.0% in patients <40 years to 69.7% in patients ≥70 years, while triple-negative disease falls from 30.0% to 3.0% over the same age range.