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Molecular and Clinic-Pathological Differences Between Screen-Detected and Symptomatic Breast Cancers in State of Qatar

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Abbreviations:

IHC: Immunohistochemistry; ER: Estrogen Receptor; PR: Progesterone Receptor; Her2n: Human Epidermal Growth Factor Receptor 2-Neu; Ki-67: Protein Encoded by the MKI67 Gene; LVI: Lympho-Vascular Invasion; TNM: Tumor, Lymph Node, Metastases

1. Abstract

1.1. Background: Breast cancer is the commonest cancer among women. Knowing breast cancer biomarkers provide useful tool for the development of effective cancer prevention, treatment, prognosis and better patient clinical outcomes.

1.2. Patient and Methods: A retrospective review for patients with Screen detected and symptomatic breast cancer for the period 2008-2016. We included females with early staged breast cancer (0-III), age 45-69 years at diagnosis. Cases with metastatic disease, male breast cancer and age <45 years at diagnosis were excluded.

1.3. Results: 85 women were included (43 screen-detected, 42 symptomatic). Mean follow-up was 7 years. Participants diagnosed through screening were younger than patients diagnosed after symptoms [p>0.0].

Most tumors were IDC type. Screen-detected tumors had lower histological grade (P >.05), less Lymph vascular invasion, smaller size tumors, negative lymph node involvement, earlier Stage and more hormone receptor positive tumors. Symptomatic cases showed more Her2 over-expression tumors with negative hormone receptor had more triple negative subtype.

Women with screen-detected tumors received more hormone therapy, less chemotherapy and had better 1,2,3-year survival.

1.4. Conclusion: Our study confirms that screen-detected breast cancer has better survival than symptomatic breast cancer diagnosed. Survival benefit is likely attributed to favorable tumor & molecular characteristics.

2. Introduction

Among women, breast cancer is the most common cancer and a major cause of cancer-related deaths worldwide [1]. In Qatar breast cancer incidence reached 38% of all cancers detected in females [11]. The breast cancer screening program, hospital based under Hamad Medical Corporation in Qatar was started in April 2008 and the national breast cancer screening was launched in 2016. Despite the increase of incidence of breast cancer, its mortality is slowly being reduced. This is largely due to screening, early diagnosis, adequate and improved breast cancer treatment. It looks like breast cancer screening affect prognosis. Repeatedly, randomized controlled trials of mammography in breast cancer screening has shown a reduction of 20-35% in mortality from the disease [2,3]. Moreover, data compared breast cancer cases diagnosed through screening and cases diagnosed after clinical presentation demonstrated better prognosis in the screen detected group [1]. This was initially attributed to the difference in tumor characteristics at diagnosis (tumor grade and size, lymph node involvement and stage)

but the difference in survival observed independent of these factors hints to the presence of another mechanism by which breast cancer screening affects prognosis [3,4,5]. Recent advances in molecular and cell biology have led to the identification of more detailed characteristics of mammary tumors. Immunohistochemistry (IHC) use on tissues separate breast cancer into several molecular subtypes (Luminal A, luminal B, Her2 rich and triple negative tumors) which has been associated with different clinical outcomes [3,6,7,8,9,10].

The objective of this study is to determine the molecular characteristics of screen detected breast cancer and to compare it with that of clinically detected breast cancer, in order to identify if differences in tumor biology may explain some of the biological heterogeneity of breast cancer and if differences in tumor biology has an effect on prognosis. This will help assess the importance of the detection method and weather it should be taken into account when making therapy decisions.

In this descriptive study we are going to review these two populations in terms of Clinic-pathological and biological tumor characteristics—estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2-neu (her2n), and protein encoded by the MKI67 gene (Ki-67) , tumor grade, LVI, TNM stage , in addition to clinical data that include nationality, age, menopausal status, as well as treatment difference that has been used in the two groups in terms of type of surgery, chemotherapy , radiotherapy, hormone therapy and targeted treatment. We will also look at the outcome in order to assess the prognosis and survival rate. Based in Qatar cancer registry 2015 [13] median age of diagnosis of breast cancer for Qatari women is 47 years old therefore the decision was made to lower the age of national screening at 45 years old. We believe that more complete understanding of the biological profile of breast tumors will be necessary to assess the true impact of tumor biology on the improvement in survival seen with screen detected vs symptomatic breast cancer patients.

3. Objectives

The primary Objectives of this study are to assess the Clinico-pathological differences between screen detected and symptomatic breast cancer cases and to determine the difference in the type of treatment needed between the two groups.

Our secondary Objectives are to identify the clinical outcome in both screen detected and symptomatic breast cancer cases; through finding out if there is difference in the tumor stage and biological markers at diagnosis and the 3-5 years disease free survival & overall survival in both screen detected and symptomatic breast cancer cases

4. Patient and Method

4.1. Study Population

The study was conducted at the National Centre of Cancer Care and Research Qatar after ethical approval from the research ethics committee of the Hamad Medical Corporation.

A total of 85 women were included in this retrospective data analysis, for two groups of patient sets of breast cancer based on method of diagnosis; Screen detected cancer and symptomatic breast cancer, for the period between 2008-2016. The criteria for inclusion were: Female patients with early staged breast cancer (0-III). Aged 45-69 years at diagnosis. Our exclusion criteria were cases with metastatic disease, male breast cancer and age below 45 years old at diagnosis.

Pathology Tumor characteristics (coded according to the international Classification of diseases for oncology, ICD-10) collected through retrospective review of histopathology reports. Data on tumor histological type, stage and nodal involvement were collected from the histopathology reports Assessment of the mitotic counts, tubule formation and nuclear pleomorphism was done to determine the nuclear grade. The method of tumor graduation has a score of 1-3 for each factor. The final grade is calculated by adding the score of the previous three parameters. The tumors are then classified as grade 1 (well differentiated or low-grade), grade 2 (moderately differentiated or intermediate grade) and grade 3 (poorly differentiated or high-grade) which has proven prognostic value [14].

Hormone receptor status was labeled as positive when the fraction of cells stained by the corresponding immunoreactions was equal or higher than 1%, according to American Society of Clinical Oncology

Pathologist 2010, HER-2/neu status for cases of 1+, 2+ or 3+ on IHC analysis were further evaluated by fluorescent in situ hybridization for HER-2/neu amplification or over expression according to (ASOCOP), proliferation rate was considered high when 20% or more cells were stained by Ki-67 antibody with data (tumor size, tumor grade, LVI ,hormone receptor, her2neu by IHS and FISH, stage, KI67) and individual outcome data (vital status at last follow-up and date of death). Type of treatment received, and participant status at the time of review as well as participants demographics.

4.2. Molecular subtype classification and immunostaining:

Tumors were classified into five molecular groups based on the expression of ER, PR, HER2, basal cytokeratins as follows:

subtype 1 (luminal A) ERþ and/or PRþ positive and HER2 negative KI6<20

subtype 2 (luminal B) ERþ and/or PRþ positive and HER2þ negative KI67 >20

subtype 3 (HER2 over-expressing) ER VE and PR_ VE and HER2þ +VE;

subtype 4 (ER_VE, PR_ VE, HER2_ VE triple negative)

subtype 5 ERþ and/or PRþ positive and HER2 positive (triple positive)

4.3. Statistical Analysis

For continuous variables, descriptive statistics are presented as median with the 25th to 75th percentiles or mean ± standard deviation, while, for categorical variables it is shown as numbers with percentages. The Relationships between two quantitative variables was investigated by using Pearson or Spearman's correlation analysis. The differences between the frequencies of categorical variables were evaluated with chi-square ($\chi 2$) and Fisher's exact for variables having expected frequencies of ≤ 5 for 50% or more cells. Unpaired t (Mann Whitney U test for skewed data) and ANOVA (Kruskal–Wallis test for skewed data) was used to compare mean/median values of different quantitative parameters between two or more than two groups. Cox regression analysis was used to determine the effect of various potential factors and covariates on tumor biology and prognosis in the 3-5 years post diagnosis. Survival analysis was performed using the Kaplan-Meier method followed by Log rank test to assess the differences in median OS and PFS between subgroups. Pictorial presentations of the key results were made using appropriate statistical graphs. A two-sided P value <0.05 was considered to be statistically significant. All statistical analyses were done using statistical packages SPSS 24.0 (SPSS Inc. Chicago, IL) and Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA).

5. Results

85 women were included in this study, of these 43 were screen detected breast cancer cases and 42 were symptomatic. Mean follow-up of the study population was 7 years (range 3–10 years).

Patient and pathological characteristics for both groups

The patient's demographics and tumor characteristics are summarized in Table 1

Of our cohort, 33% were Qataris and 67% were none-Qataris. Younger age group (<50 years old) patients were diagnosed mostly through screening (33% vs 17%), while older age (≥50 years old) was more diagnosed after development of symptoms (83% vs 67%) [p>0.0]. Premenopausal women were more likely to be diagnosed as screen detected breast cancer rather than symptomatic breast cancer (49% vs 31 %) in comparison to postmenopausal women who were more likely to be diagnosed after symptom development rather than through screening (64% vs 51%) (p>0.05).

Most of the tumors were IDC type with higher incidence in symptomatic cases (83%) compared to screen detected cases (70%) (p>0.05). Screen-detected tumors were more likely to have lower histological grade (19% vs 7% were grade 1) (P >.05). In keeping with the above findings, most of the screen detected tumors showed no Lymph vascular invasion (91% vs 38%). There was no significant difference in the ki67 % between the 2 groups (35% vs 38% had ki67 ≤20%, 23% vs 24% had ki67 >20%). Breast cancers identified through screening were smaller than those found without screening (44% vs 38% respectively had tumor size p2 cm). Tumors without lymph node involvement were seen in 70% of scree detected cases compared to 55% in symptomatic cases. For the overall tumor stage, stage 0 & stage I tumors were seen more in screen detected cases compared to symptomatic cases (12% vs 2%, 37% vs 26% respectively), while stage II & stage III tumors were found more in symptomatic cases rather than screen detected cases (58% vs 42%, 14% vs 9% respectively) (p>0.05) (Figure 1).

Hormone receptor positive tumors (Luminal A, B, Luminal unknown due to lack of ki67) were almost the same in screen detected cases & symptomatic cases (67% vs 66%), this might be due to the lack of ki67 figure in many cases. Her2 over-expression tumors with hormone receptor negative were higher in frequency in symptomatic cancer compared to screen detected cancer (11% vs 7%). Moreover, symptomatic cases had more triple negative subtype with hormone receptor & her2 negative compared to screen detected cases (12% vs 7%) (Figure 2,3).

Women with screen-detected tumors were more likely to receive adjuvant hormone therapy compared to women diagnosed after symptoms development (81% vs 64%). While women with symptomatic breast cancer are more likely to receive chemotherapy than screen detected breast cancer cases (81% vs 65%) (Figure 4).

Women with breast cancer diagnosed with screening had better 1 year survival (100% vs 98%), 2-year survival (98% vs 91%) and 3 year survival (92 vs 80%) compared to symptomatic breast cancer (Figure 5).

Table 1: The patient demographic and tumor characteristics

Parameters	*Screen detected (n=43)*		*Symptomatic (n=42)*		*P value*
	Value	*%*	*Value*	*%*	
Age					
Median age yrs	53 [43-65]		56 [45-69]		
< 50 yrs	14	33%	7	17%	*p>0.05*
≥50 yrs	29	67%	35	83%	
Nationality					
Qatari	14	33%	14	33%	*p>0.05*
Non-Qatari	29	67%	28	67%	

Menopausal status					
Post-menopausal	22	51%	27	64%	*p>0.05*
Pre-menopausal	21	49%	13	31%	
Peri-menopausal	0	0%	1	2%	
Tumor histological type					
IDC	30	70%	35	83%	p>0.05
ILC	4	9%	3	7%	
DCIS	5	12%	1	2%	
Histological grade					
1	8	19%	3	7%	*p>0.05*
2	17	40%	24	57%	
3	18	42%	13	31%	
LVI					
Negative	39	91%	16	38%	*p>0.05*
Positive	4	9%	13	31%	
n/a	0	0%	13	31%	
ki67					
≤20%	15	35%	16	38%	*p>0.05*
>20%	10	23%	10	24%	
n/a	18	42%	16	38%	
TNM stage Tumor size(T)					
T1	19	44%	16	38%	*p>0.05*
T2	21	49%	21	50%	
T3	2	5%	5	12%	
T4	1	2%	0	0%	
Lymph node (N)					
N0	30	70%	23	55%	*p>0.05*
N1	9	21%	16	38%	
N2	3	7%	3	7%	
N3	1	2%	0	0%	
Metastases (M)					
M0	43	100%	40	100%	*p>0.05*
Overall stage					
stage 0	5	12%	1	2%	p>0.05
Stage 1	16	37%	11	26%	
Stage II	18	42%	24	58%	
Stage III	4	9%	6	14%	

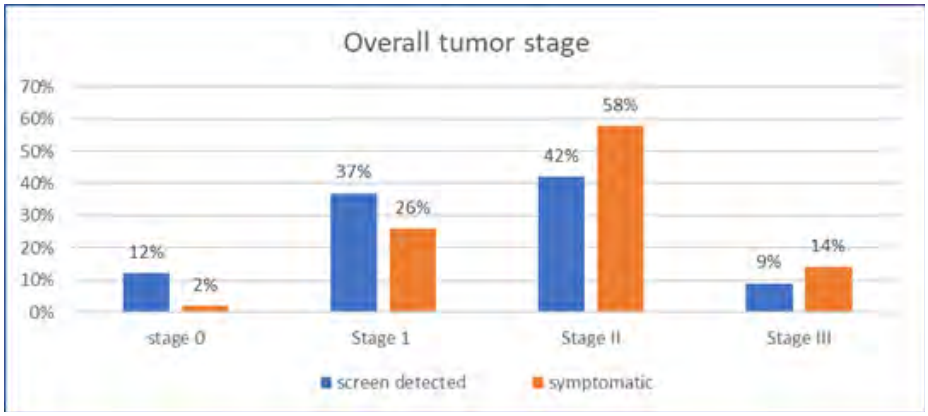


Figure 1: Overall tumor stage in screen detected and symptomatic breast cancer cases

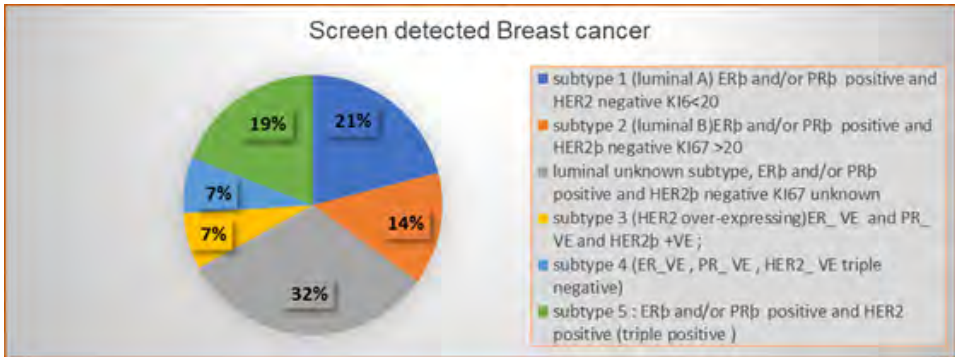


Figure 2: Breast cancer molecular subtype in screen detected breast cancer cases

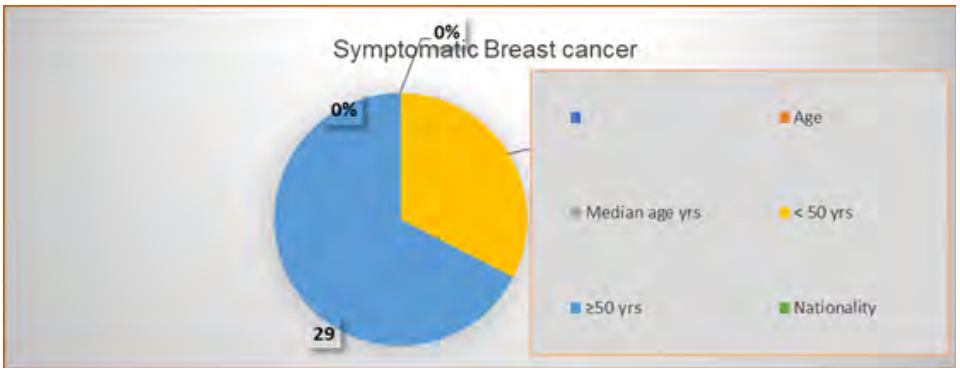


Figure 3: Breast cancer molecular subtype in symptomatic breast cancer cases

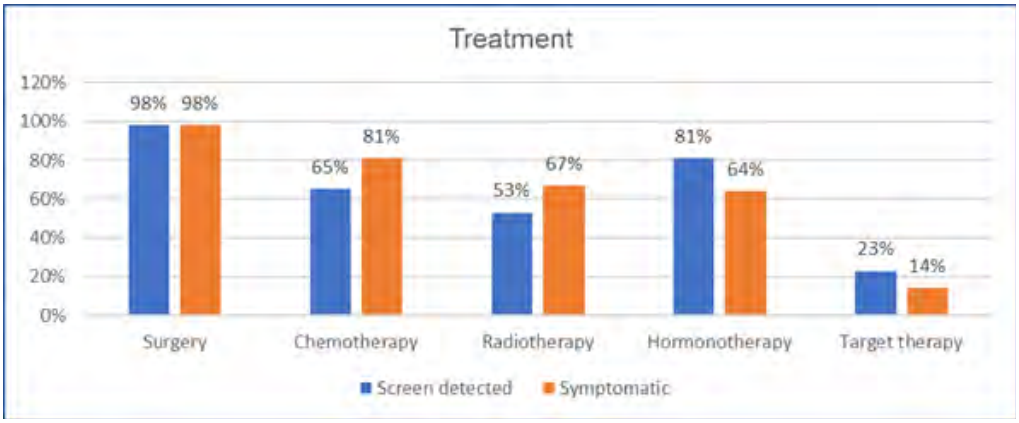
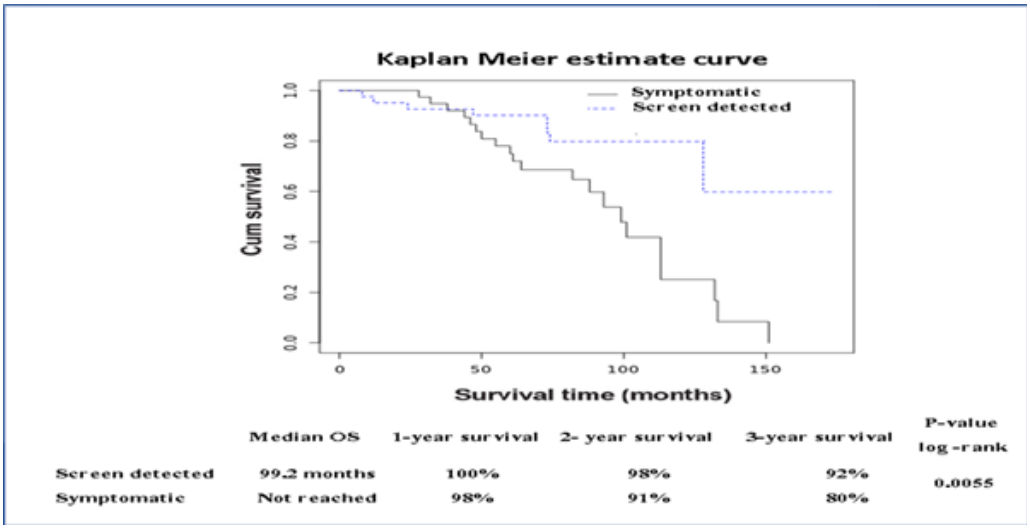


Figure 4: Treatment modalities in screen detected and symptomatic breast cancer



	Median OS	1-year survival	2- year survival	3-year survival	P-value log-rank
Screen detected	99.2 months	100%	98%	92%	0.0055
Symptomatic	Not reached	98%	91%	80%	

Figure 5: Median overall survival in screen detected and symptomatic breast cancer

6. Discussion

Mammographic screening of breast cancer has led to a reduction in breast cancer mortality of around 20% (Vainio, 2002). In Qatar, breast cancer screening was implemented in 2008. In this study we analyzed the clinico-pathological and the survival difference between screen detected breast cancer and symptomatic breast cancer in 85 women in the state of Qatar between 2008- 2016.

It was noticed that younger women were mostly diagnosed through screening while older age women were diagnosed after development of symptoms. This might be attributed to the different level of awareness and acceptance of screening between the two age groups.

We found that screen-detected cancers were smaller in diameter and were less likely to have lymph node involvement compared with symptomatic cancers, which is consistent with the results of previous study by Kim, Jiyoung, et al. 2012. We also found that Breast cancers identified through screening were smaller than those found without screening (44 vs 38% respectively had tumor size p2 cm) which is reflected on the better prognosis (Inari, Hitoshi, et al, 2017). Moreover, those tumors were identified at an earlier stage of development and had less lymph node involvement which consequently had survival benefit (Wishart et al, 2008). Our current analysis showed that screen-detected tumors were more likely to have lower histological grade, lower level of lymph vascular invasion and, as reported by Crosier et al, 1999, a higher proportion of hormone receptor positive tumors. These less aggressive pathologic characteristics of screen-detected cancers are also associated with less aggressive treatments, requiring more hormone therapy and less chemotherapy in the screen-detected group. This data review showed that women with breast cancer diagnosed through screening have better survival than women with breast cancer diagnosed after symptoms development (Joensuu et al, 2004).

7. Conclusion

In the present study we confirm that women with screen-detected breast cancers have a strong survival advantage compared to women with symptomatic breast cancers detected without screening. Moreover, our data analysis identified favorable clinico-pathological and molecular characteristics in the screen detected breast cancers. It is likely that survival benefit is attributed not only to small size tumors, early stage at diagnosis, lower histological grade and absence of lymph vascular invasion, but also to the current advances in precision medicine reflected in the observed more favorable molecular characteristics in the screen detected breast cancers.

With the apparent effect of breast tumors molecular classification on breast cancer management and prognosis, further studies are needed to focus on the impact of breast tumors biological profile on individual patient care and clinical outcome at national and international level.

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All Authors have no Conflict of Interest

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