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Understanding the paradigma of opportunistic screening

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ABSTRACT

Objectives: To provide demographical and pathological characteristics of breast cancer patients diagnosed in a tertiary clinic with opportunistic screening and diagnostic workup and compare the results with the available national and global breast cancer statistics.

Methods: Clinical and pathological data of breast cancer patients diagnosed in our tertiary breast clinic between March 14, 2017 and February 28, 2020 have been entered into a database and analyzed retrospectively. Results were analyzed and compared with the national and global statistics.

Results: The total number of patients included in this study were 137 and the number of tumors was 145. Sixty-four (46.7%) patients were detected in screening. All of the patients were female. The mean age was 51.8 years. Eighteen (13.1%) patients were young females (< 40 years), 55 (40.1%) were in 40-49 years, 26 (18.9%) in 50-59 years, 24 (17.5%) in > 60-69 years, 14 (10.2%) in > 70 years. Of the invasive cancers, 100 (79.4%) were invasive ductal, 15 (11.9%) invasive lobular, 6 (4.8%) pleomorphic lobular, 4 (3.2%) papillary, and 1 (0.8%) tubular cancer. Distribution of stages were: 13.1% stage 0, 38.6% stage I, 29.6% stage II, 10.3% stage III, and 8.2% stage IV. The mean tumor diameter was 26.6 mm. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) were positive in 82.5%, 61.9% and 15.8% of the tumors respectively.

Conclusions: Results of this study are in accordance with the latest results of the National Breast cancer database, a project governed by the Turkish Federation of Breast Disease Societies (TMHDF), considering the tumor size, age distribution, histologic subtype analysis, receptor status. However, the percentage of early-stage tumors was higher in this study.

Keywords: Breast cancer, histology, stages, molecular subtypes, opportunistic screening

Breast cancer is the most frequently diagnosed cancer in women in almost all regions of the world and the most frequent cause of death from cancer [1, 2]. Genetic, geographic, racial, and ethnic differences influence breast cancer characteristics and prognosis. Therefore breast cancer control plans may vary in different regions of the World. To obtain clinical and pathological profiles of breast cancer in different populations is a critical step in determining better screening and disease management protocols.

The Cancer Control Department (CCD) was founded in 1983 to keep reliable cancer records for cancer control. After that National Breast cancer database, a project governed by the Turkish Federation of

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Breast Disease Societies (TMHDF) was embarked. Breast cancer records from 36 centers throughout the country have been collected in this database since 2005 [3, 4]. The final up to date results of the breast cancer registry program were published in 2019 [4]. The reported incidence of breast cancer in Turkey increased more than 2-fold from 24/100.000 in 1993 to 50/100.000 in 2017. Almost 20.000 patients were diagnosed with breast cancer in Turkey between May 1, 2005, and April 17, 2017, according to data recorded by NBCRP. The majority of patients (68%) were at stage 2 or higher and almost half of the patients (48.6%) had axillary lymph node involvement accordingly.

The Bahcesehir Breast Cancer Screening Project (BBCSP) is the first organized population-based breast cancer mammographic screening project in the country and provided data on mammography screening in Turkey. It is a 10-year-long program (2009-2019) implemented in Bahçeşehir, a large region of Istanbul, Turkey. Healthy women aging between 40-69 were invited and screened in every two years of the 10 years. Their first results were published in 2014 [5]. BBCSP resulted in a change in the stage distribution of breast cancers with a significant increase in early-stage cancers. Based on these results Ozmen *et al*. [6] showed the efficacy and cost-effectiveness of breast cancer screening between ages 40 and 69 in their study and concluded that an organized population-based screening program may be cost-effective in Turkey and other developing countries.

This study aims to compare the types and stages of clinically detected and opportunistic screening-detected breast cancers diagnosed in a tertiary reference breast clinic to the national data of TMHDF and the population-based screening of BBCSP.

METHODS

In this study, we analyzed the data of 137 breast cancer patients who were registered in the period from March 14, 2017 to February 28, 2020. The patients who applied to our clinic for screening or diagnostic purposes or who were referred for biopsy after a diagnostic workup in another center were included in this study. A total of 10,015 patients referred to the clinic during this period and 5,984 patients had an opportunistic mammography screening. Histopathologic confirmation was made after US-guided core needle, US-guided or stereotactic vacuum-assisted biopsies. Patients' age, gender, tumor size, stage, histologic type and grade, receptor status, molecular subtype were recorded in a database.

Histologic types and staging were done according to WHO classification and American joint committee on Cancer and histologic grade according to Scarf Bloom-Richardson classification [7].

Estrogen receptor (ER) and progesterone receptor (PR) expression values higher than 1% was accepted as positive. Human epidermal growth factor receptor-2 (HER-2) expression with a (+++) results in immunohistochemistry method or suspected cases a (++) result in immunohistochemistry method) a positive SISH or FISH evaluation were considered as positive Her 2 receptor status. Molecular subtypes were classified as; Luminal A (ER or PR positive + HER-2 negative, ki-67 < 14%), luminal B (ER or PR positive and ki-67 ≥ 14%), luminal B HER-2 enriched (ER or PR positive, HER-2 positive), triple-negative (ER, PR and HER-2 negative) and HER-2-positive (ER and PR negative, HER-2 positive).

This study was approved by the Institutional review board (Acıbadem Mehmet Ali Aydınlar Univer-

Table 1. Age distribution of breast cancer patients

Age groups	Number of cancers	%	Number of women	%
20-29	2	1.4	2	1.5
30-39	18	12.4	16	11.7
40-49	56	38.6	55	40.1
50-59	28	19.3	26	18.9
60-69	26	17.9	24	17.5
> 70	15	10.3	14	10.2
Total	145	100	137	100

sity, decision number: 2020-05/30). The study was conducted according to the Declaration of Helsinki.

Statistical Analysis

For statistical analysis, Pearson chi-square analysis was used in data analysis, and asymptotic or exact *p* values were given. Definitive statistics were shown as frequency and percentile. $p < 0.05$ was accepted as statistically significant.

RESULTS

The number of primary breast malignancies diagnosed after the biopsies carried out in our tertiary breast clinic was 145 in the time interval between March 14, 2017 to February 28, 2020. Eight patients had bilateral involvement wherein six bilateral invasive breast tumor was found, in one patient one side was invasive cancer while the contralateral side was DCIS and one

Table 2. Comparison of data of breast cancer patients in current study with the national statistics

	National Data	Overall Cancers
Number of patients	19503	137
Mean age	51.8	51.8
< 40 (years) (%)	16.6	13.1
≥ 40 (years) (%)	83.4	86.8
≥ 70 (years) (%)	10	10.2
Mean tumor size (cm)	2.5	2.6
DCIS (%)	4.7	13.1
PN0 (%)	51.4	64.3
Stage (%)		
0	4.7	13.1
I	28.5	38.6
II	48.3	29.6
III	14.5	10.3
IV	4	8.2
Histologic subtype (%)		
IDCa	76.9	79.4
ILCa	6.5	11.9
IMCa (IDCa+ILCa)	4.2	4.8
Others	12.4	4.0
Expression status (%)		
ER+	72.5	82.5
PR+	62.3	61.9
HER-2 positive	21.8	15.8
Ki-67 < 14 (%)	35	32.5
Molecular subtype (%)		
Luminal A/B	78.3	80.1
HER-2	9.6	9.5
Triple negative	12.1	10.3

IDCa = invasive ductal carcinoma, ILCa = invasive lobular carcinoma, IMCa = invasive mixed carcinoma, ER = Estrogen Receptor, PR = Progesterone Receptor, HER-2 = human epidermal growth factor receptor-2

Luminal A = ER+, HER-2 (-), Ki67 <14%, Luminal B = ER+, HER-2 (+/-), Ki67 ≥ 14%

patient had bilateral DCIS. The total number of patients diagnosed with breast cancer or DCIS was 137. Of these cancer patients, 64 (46.7%) were diagnosed in screening and the rest 73 (53.3%) were diagnosed after a clinical finding. Clinical findings of the diagnostic group patients were palpable mass and/or skin changes such as retraction or discoloration. A total of 279 biopsy procedures were performed for screening-detected lesions. Of these; 217 were done by US-guided core needle, 11 US-guided vacuum, and 41 stereotactic-assisted vacuum biopsies were performed.

Two interval cancers showed due to high breast density (BI-RADS type B breast density in one and C in the other). Neither of the lesions were visible in the screening mammograms. These two patients presented with palpable lesions in the breast 9 months and 11 months after the screening.

The ages of the patients ranged between 27 and 93. The median and mean ages were 48 and 51.8, respectively. The mean age of patients was 53.2 for the screening group and 50.6 for the diagnostic group. The percentage of patients younger than 40 was 13.1%. The age distribution of the patients is given in Table 1.

Both breasts were affected similarly (51.7% right, 48.3% left). Tumors were found to be located most commonly in the upper outer quadrants of both breasts (50.3%). Thirty-two (25.3%) invasive cancers were multifocal or multicentric.

The pathologic diagnosis of 19 (13.1%) of the tumors were DCIS. The rest 126 (86.9%) lesions were invasive breast cancer. Of the invasive cancers, 100 (79.4%) were invasive ductal, 15 (11.9%) invasive lobular, 6 (4.8%) pleomorphic lobular, 4 (3.2%) papillary, and 1 (0.8%) tubular cancer. Histologic subtype distribution of the invasive tumors are given in Table 2 and Table 3. Multifocal/multicentric invasive carcinomas had the same histology and a single phenotype

Table 3. Stages, lymph node involvement and distribution of molecular subtypes according to the detection method

	Screening -detected cases	Diagnostic cases
Stage *		
0	11 (16.1%)	8 (10.3%)
I	38 (55.8%)	18 (23.3%)
II	13 (19.1%)	30 (38.9%)
III	3 (4.4%)	12 (15.5%)
IV	3 (4.4%)	9 (11.6%)
Total	68	77
Regional Lymph Nodes of Invasive cancers**		
N0	45 (78.9%)	36 (52.2%)
N1	9 (15.8%)	24 (34.8%)
N2	1 (1.8%)	1 (1.5%)
N3	2 (3.5%)	8 (11.6%)
Total	57	69
Molecular Subtypes of Invasive cancers***		
Luminal A	25 (43.9%)	23 (33.3%)
Luminal B (Her-2 negative)	21 (36.8%)	24 (34.8%)
Luminal B (Her-2-positive)	2 (3.5%)	6 (8.7%)
HER-2	5 (8.8%)	7 (10.1%)
Triple negative	4 (7%)	9 (13%)
Total	57	69

*Stages are given for each breast in bilateral cases (145 cases). ($p < 0.001$) ** Lymph node involvement is given for the axillary finding of each breast (126 invasive cancers – 6 bilateral). ($p = 0.009$) ***Molecular subtypes ($p = 0.489$)

in terms of hormone receptors, human epidermal growth factor receptor 2, and molecular subtypes except for cases with associating DCIS; thus, immunohistochemical analyses of the index tumor was sufficient for invasive cancers.

Table 2 shows the comparison of data of breast cancer patients in the current study with the national statistics. The distribution of the stages of these patients at diagnosis was as follows: Stage 0: 13.1%, Stage I: 38.6%, Stage II: 29.6%, Stage III: 10.3%, and Stage IV: 8.2%. The stages according to the detection method (screening or diagnostic) are given in Table 3. Eight patients had bilateral tumors and each breast was staged separately. Lymph node involvement rates of invasive cancers were given in Tables 2 and 3.

Stage 0+1 cancer (TisN0M0 and T1N0/N1miM0) rates for screening and diagnostic group were 72.0% and 33.6% ($p < 0.001$) respectively while pN0 tumor rates were 78.9% and 52.2% respectively ($p = 0.009$). The mean tumor diameter was 26.6 mm and the median tumor size was 20 mm (6-110 mm). Mean and median tumor sizes in screening group were 21.4 mm and 15 mm (ranging between 6 mm and 60 mm) whereas 30.8 mm and 22 mm (ranging between 7 mm and 100 mm) in diagnostic patients respectively.

The rate of Ki-67 value equal to and higher than 14% was in 67.5% of the tumors, while those with a Ki-67 value of > 20% was 42.8 %. Estrogen (ER), progesterone (PR), and HER-2 receptor expression were positive in 82.5%, 61.9 %, and 15.8% of the tumors respectively. The molecular subtype distribution of the overall cancers are given in Table 2. The distribution of molecular subtypes was not significantly different in screening and diagnostic groups ($p = 0.489$) (Table 3).

Summary profile of the screening group and diagnostic group patients for comparison are given in Table 4: 72% and 33.6 % were early-stage, 78.9% and 52.2% were pN0, 84.2% and 76.8% were luminal type, the mean age was 53.2 and 50.6 years, the mean tumor diameter was 21.4 mm and 30.8 mm, median tumor diameter was 15 mm and 22 mm respectively.

DISCUSSION

Breast cancer incidence and mortality rates are rising in developing countries such as Turkey in contradiction to decreasing breast cancer-related mortality rates in developed countries [8]. Westernized lifestyle (weight gain and increasing age at first birth and decreasing number of children born to women), aging population, and opportunistic screening may explain the increase in breast cancer incidence [9]. Downward mortality trends in developed countries reflect the success of screening and improvements in breast cancer management.

The median age of breast cancer in the USA is 62 which means that 50% of patients are over 62. However, in Turkey, the national data showed the median age as 51 and the most populated age group was 45-49 [4]. This can be attributed to the young population age in Turkey. The national breast cancer screening period was changed from 50-69 to 40-69 years of age based on the national data which revealed that the breast cancer cases under 50 years of age constituted 48% of all cases in Turkey [3]. Furthermore, BBCSP showed that more than half of the cancers (55.6%) were detected between 40-49 years in screening [5]. In this study, the results are in accordance with previous findings such as 40-49 being the most populated age group with a 51 year mean age for cancer detection. On the other hand, 13.1% of the patients in our study were younger than 40 while 53.2 % of patients

Table 4. Summary profile of the cancers in screening and diagnostic group for comparison

	Screening-detected	Diagnostic
Stages 0 + 1 cancers	72.0%	33.6%
pN0	78.9%	52.2%
Luminal type cancers	84.2%	76.8%
Mean Age (years)	53.2	50.6
Mean tumor diameter (mm)*	21.4	30.8
Median tumor diameter (mm)*	15	22

*Invasive cancers only

were below 50. The results of this study also support the earlier onset of screening age before 50. The rate of female patients younger than 40 is 13.1% and in line with the 16.6% derivated from the national data [4]. An average of 20% of breast cancer cases in Europe occur in women younger than 50 while 36% is seen between ages 50-64 and the remaining over 64 [10]. In the US the percentage of young female patients under 40 is 4% [2]. This dramatic difference between national and US and European statistics may be attributed to a relative over-population in the younger women in Turkey. On the other hand, similar findings are reported in the Asian women stating the peak of incidence of breast cancer in between 40 and 50 years with an increase in incidence and rising mortality [11]. The authors remark the merit of further studies evaluating a possible contribution of environmental, genetic, or biologic factors.

In the United States, DCIS accounts for almost 20% of all newly diagnosed breast cancers [2]. However, DCIS patients constituted only 4.7% of all patients diagnosed with breast cancer in Turkey [4]. In our study 13.1% of tumors were DCIS. A relatively low percentage of DCIS patients in Turkish national statistics compared to US statistics can be explained by the lack of population-based screening programs and low breast cancer awareness. BBCSP showed high detection of DCIS and early-stage cancers in screening where 22% had DCIS, and 61% had stage I invasive breast cancer while only 16.6% of invasive cancers were axillary node-positive [5]. In the screening group of the current study, 16.1% of patients had DCIS, 55.8% had stage I cancer and 21.1% were node-positive cancers. Compared to BBCSP results we had a relatively lower percentage of stage 0 and 1 cancer but higher than the national data. A recent study showed similar findings with a lower DCIS detection rate in the opportunistic screening group compared to population-based organization [12]. They have explained this difference with a possible more effective evaluation of the mammograms in organized screening programs by specifically trained screening radiologists. Opportunistic screening was found less sensitive in detecting occult cancers compared to organized screening due to the lack of experience of the radiologists in the clinical setting because of fewer readings. [13]. However, this is not the case in breast specific radiology units. This may be true for centers where mammograms are read by general radiologists with fewer mammography reading experience. On the other hand, another study showed higher rates of DCIS in favor of the opportunistic screening compared to the organized program [14]. We agree on the differences in evaluating screening mammograms in a clinical setting and an organized screening program. However, it is unlikely to produce such an outcome as the evaluation in a breast clinic is long and detailed compared to screening settings and done by skilled radiologists on breast imaging. We can explain the difference in our clinic with the contamination of opportunistic screening by the attendance of women with hidden or unclaimed symptoms or findings. It is a high probability that women with findings may apply for annual screening mammograms without claiming their complaints and the rate of such application is not low in opportunistic settings. ACR benchmarks for mammography screening are as follows: median size of invasive cancers (in mm) 14.0, percentage node-negative invasive cancers 77.3%, percentage stage 0+1 cancer 74.8% [15]. Our results of screening-detected cancers are 15mm, 78.9%, and 72% accordingly. The percentage of pN0 and stage 0+1 cancers obtained by BBCSP are 83.4% and 83% [5]. Although our rates for both DCIS and stage 1 cancers were relatively lower than organized screening results of the BBCSP they were within the acceptable limits of international benchmarks [15].

The rate of stage 0+1 and pN0 cancers were higher in this study compared to the national data: pN0 cancers (64.3% and 51.4%, respectively) and stage 0+1 cancers (51.7% and 33.2%, respectively) [4]. In US and Europe, pN0 tumors were consisted of 53% and 46% while locally advanced tumors were twice as frequent in Europe (8%), and metastatic tumors were of similar frequency (5-6%) [16]. According to the SEER data from 1975 to 2012, the rate of T0 and T1 tumors increased from 36% to 68% and the rate of T3 or larger tumors decreased from 64% to 32% [17]. This significant change in favor of smaller tumors are attributed to the initiation of screening. Our findings are in line with the SEER data showing that 33.6% of the tumors detected in the diagnostic group are smaller than 2 cm while 72.0% in the screening group. Accordingly, findings of decreasing tumor size and stage are reported from various countries in Europe [18-23]. A similar finding is reported from Asia where stage III

cancers decreased from 40% to 20% from 1970 to 1990 in China and stage I cancers increased from 19.3% to 36% from 1970 to 1990 1996 to 2004 in South Korea [24].

In histologic subtype analysis of the current study invasive ductal carcinoma (79.4%) was the most frequent type similar to national (76.9%) statistics. Invasive lobular cancer (11.9%) was almost two-fold higher compared to the national data (6.5%). The percentage of mixed/pleomorphic type (IDca +ILca) was similar in both studies (4.8 and 4.2). According to US statistics, more than 75% of invasive breast cancers are invasive ductal carcinomas and invasive lobular carcinoma represents about 15% of invasive breast cancers [2].

When molecular subtypes obtained in this study are compared to national data the rate of Luminal type (80% vs 78%), HR(hormone receptor)negative/HER-2 positive (9.5 % vs 9.6%), and triple-negative (10.3% vs. 12.1%) tumors were similar [4]. According to SEER breast cancer subtype HR+/HER2- was the most common subtype, representing 73% of all cases, triple-negative breast cancer 12%, HR+/HER2+ breast cancer 11% HR-/HER2+ breast cancer 4% [2]. HR-/HER2+ cancer rate of this study and national statistics was higher than US results.

This study showed a significant difference between the opportunistic screening and diagnostic patients in terms of the axillary involvement ($p = 0.009$), stage of the cancer ($p < 0.001$), DCIS detection rate and mean tumor size which are the main benchmarks of a better outcome. A recent study evaluating the opportunistic screening showed its efficacy with a reduced mortality which was comparable to population-based screening outcomes [12]. Although our study does not provide its effect on mortality our screening results are comparable with the population-based screening of BBCSP and showed significant differences compared to diagnostic patients. On the other hand, studies show that opportunistic screenings are less cost-effective and end up with higher costs compared to an organized program. However, participation higher than 55% of the targeted population is recommended for the efficacy of an organized screening over an opportunistic approach [25]. We believe that raising the awareness and improvement of the facilities for opportunistic screening will be effective in the detection of earlier cancers in countries where participation of at least 55% of the targeted population is far from reach.

Limitations

The main limitation of this study is a possibility of contamination of the screening group by women with unclaimed symptoms or findings. As this is a tertiary diagnostic clinic this possibility has a higher potential. However, the similarity of our findings with the BBCSP lowers the likelihood of its unfavorable effects. Besides this, we have meticulously evaluated the patient files for the differentiation of screening and diagnostic applications. The second limitation of the study is its retrospective and one center design.

CONCLUSION

Results of this study showed that the cancers detected in this study are similar to the national data considering the tumor size, age distribution, histologic and molecular subtypes. To our knowledge, this is the first study in Turkey comparing opportunistic screening to clinical breast cancer detection and organized screening. Opportunistic screening in a tertiary clinic shows comparable results with the organized screening program. We believe that it is an effective screening method for countries with limited resources where participation of the critical mass (55% of the targeted population) is far from reach.

Main Points

*In this study there is a significant difference between the opportunistic screening and diagnostic patients in terms of the axillary involvement, stage of the cancer, and tumor size.

*Characteristics of cancers detected in this study are similar to the national data considering the tumor size, age distribution, histologic and molecular subtypes.

*Opportunistic screening in a tertiary clinic may show comparable results with the organized screening program.

Authors' Contribution

Study Conception: NG, İD, AA; Study Design: NG, EY; Supervision: EY; Funding: AS; Materials: İD; Data Collection and/or Processing: AA; Statistical

Analysis and/or Data Interpretation: NG; Literature Review: NG; Manuscript Preparation: NG and Critical Review: NG, AA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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