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Epidemiology and Histopathology of Breast Cancer in Iran versus Other Middle Eastern Countries

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Abstract

Background: Breast cancer is the most prevalent cancer among females worldwide. This study compares the results of the most cited published Iranian studies and studies from other Middle East countries on breast cancer with data from the Ministry of Health and Medical Education and approximately 2000 cases from the Cancer Research Center of Shahid Beheshti Medical University of Iran.

Methods: Data from the Cancer Registry System of the Ministry of Health and Medical Education and the Cancer Research Center were obtained in addition to data from other published Iranian articles to increase the accuracy of incidence, prevalence, disease burden, risk factors, clinical staging, clinical pathology, biological markers, clinical subtypes, and survival rate of breast cancer in the last decade and compare the epidemiological data with other areas of the world.

Results: Overall, breast cancer was the most common cancer in Iran. The age-standardized rate for breast cancer was 33.21 per 100,000 according to the latest national databases. The mortality rate for breast cancer has not changed in the past 30 years in Iran. The age-standardized rate for mortality was 14.2 per 100,000 with a mean age of 49.84 years. The most common cancer in Iran is invasive ductal carcinoma. In our last review, 65.5%-70.5% of cases were in the early stages (1 and 2) and less than 30% were in the advanced stages. The five-year overall survival rate was estimated at 72% in women and 60% in men. The stage and number of positive lymph nodes significantly affected the survival rate.

In the Gulf Cooperation Council, ASR of the Kingdom of Saudi Arabia was (12.9), Bahrain (46.4), Kuwait (44.3), Qatar (35.5), United Arab Emirates (19.2), and Oman (14.4) per 100,000.

Conclusion: Our study shows that epidemiology and histopathology of cancer is different with other neighborhood countries and is multi-dimension and needs multi-center involvement from government authorities, clinicians and scientists.

Keywords: Breast cancer, Epidemiology, Biomarker, Pathology, Iran

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Introduction

According to GLOBOCAN report, approximately 1.38 million new Breast cancer cases have been diagnosed in 2008 and 1.67 million in 2012.[1] Therefore, breast cancer comprises 23% of all female cancers.[2] The most common cancers in females are breast or cervical cancer worldwide, with the exception of China (lungs), South Korea (thyroid), Mongolia and Vietnam (liver).[3]

Female breast cancer incidence rates varied internationally by more than 13-fold in 2008 between different countries and ranged from 8.0 cases per 100,000 in Mongolia and Bhutan to 109.4 per 100,000 in Belgium. North America and Northern Europe had the highest age-standardized rates (ASR), whereas the lowest rates were in Asia and Africa.[3,4] Worldwide, the incidence of breast cancer increased by 3.1% annually between 1980 and 2010.[5]

An estimated 1 in 8 women in the United States will develop this disease. The rate is very high in Eastern (93.1 per 100,000) and Western (89.7 per 100,000) Europe according to a GLOBOCAN report (Table 1).[2]

In the Gulf Cooperation Council, the Kingdom of Saudi Arabia had the lowest ASR (12.9), whereas Bahrain had the highest (46.4) followed by Kuwait (44.3), Qatar (35.5), United Arab Emirates (19.2), and Oman (14.4)per 100,000.[6]

Age standardized rate (ASR) for breast cancer incidence in 2012 was 33.21 (Iran national database), 28.1 (Iran, Globocan), 41.9 (Eastern Mediterranean Region), 82.1(European Union), 85.8 (Australia and New Zealand), 79.8 (Canada) and 92.9 (USA).

The incidence of breast cancer by age and geographic distribution shows that in developing countries this incidence is 23% in young adults (15-49 years) versus 10% in developed countries. In menopausal females (>50 years) the incidence is 28% in developing countries versus 39% in developed countries.[7] Hence, menopausal females from developed countries have a greater incidence of cancer.

According to the 2014 GLOBOCAN database, there was no significant difference in the incidence, mortality, and prevalence of breast cancer in Iran compared to the worldwide database (Table1).[1]

According to the developing countries databases, the cumulative probability for breast cancer incidence in individuals aged 15-79 years in Iran increased during the previous 30 years as follows: 1.4 (0.9-2.9) in 1980; 1.8 (1.1-2.8) in 1990; 2.1 (1.9-2.4) in 2000; and 2.2 (1.8-2.7) in 2010.[7] Figure 1 shows the increased incidence rate of breast cancer from 2005-2008 in Iran.

Based on the Iranian Cancer Registry Report in 2009, there were 8616 women diagnosed with breast cancer with an ASR of 28.1 per 100,000 females.[8] Table 2 shows the ASR of breast cancer in Iran (2005-2006) according to the National Cancer Registry system.

The prevalence of breast cancer has shown an annual 3.1% increase worldwide from 1980 to 2010.[5] The five-year prevalence of breast cancer showed that the estimated number and proportion

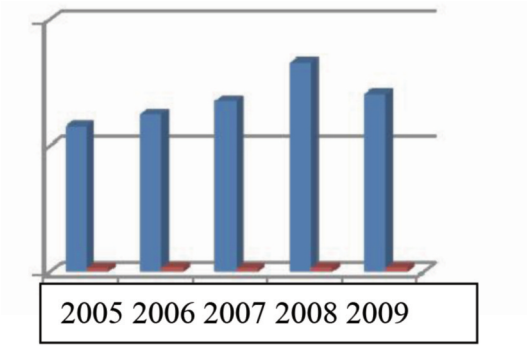

Figure 1. Trend in age-specific rate (ASR) for breast cancer from 2005 to 2009 in Iran.

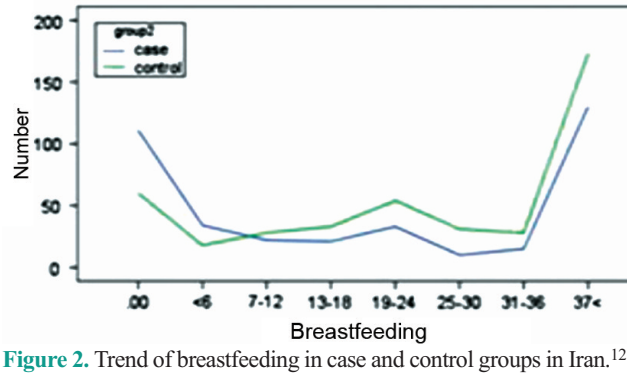

Figure 2. Trend of breastfeeding in case and control groups in Iran.[12]

Table 1. Difference in incidence, mortality and five-year prevalence between the worldwide database and Iran (2014).[1]

Breast cancer	Number	Incidence (%)	ASR(W)	Number	Mortality (%)	ASR (W)	Number	5-year prevalence (%)
World	1,676,633	25.2	43.3	521,817	14.7	12.9	6,255,391	36.4
Iran	9795	24.5	28.1	3304	14.2	9.9	34105	37.7

ASR: Age-standardized rate (W): World Standard Population

of people with breast cancer during the previous 5 years was 6,255,391 worldwide and 34175 in Iran.[1] According to result of unpublished research from Cancer Research Center, Shahid Beheshti University of Medical Sciences, the five-year prevalence of breast cancer was 28750 in 2006.

Akbari et al. reported that the mean age for breast cancer in Iran was 5 years earlier in Iranian women compared to women from developed countries (Table 3). According to the national cancer registry database, 57.6% of breast cancer cases were seen in women <50 years of age.[10, 11]

Breast cancer is the second leading cause of cancer deaths (15.4%) in developed countries after lung cancer. In Iran, it is the fifth leading cause of cancer deaths like other parts of the world and it is estimated 14.2% of death.[1,11,12]

The global total number of deaths from breast cancer has increased from 250000 (95% CI: 239000-296000) in 1980 to 425000 (359000-453000) in 2010, at an annual increase of 1.8%.[7] From 1980 to 2010, deaths among reproductive-aged women from breast cancer increased 1.8% per year. The proportion of breast and cervical cancer deaths in women younger than 50 years varied from 0.13 in central Europe to 0.37 in the Middle East.[7] Table 4 shows the cumulative probability for breast cancer deaths among individuals aged 15-79 years in the last 30 years in Iran.[7]

The age standardized mortality rate (ASR) did not substantially change during the past 30 years; this rate in Iran (14.2) was similar to developed countries such as USA (14.9), Canada (13.9), Australia and New Zealand (14.5), Turkey had a mortality rate of 11.9 per 100,000[13] whereas the mortality rate in India was 12.7 per 100,000[14] The ASR of IRAN is less than other countries in our region Eastern Mediterranean region (EMRO) (8.6).[1]

Materials and Methods

Numerous published data exist that pertain to breast cancer status in Iran in the Cancer Research Center (CRC), Shahid Beheshti Medical University. These data cover epidemiological, clinical, pathological, radiological, economical, geographical distribution, ethnicity, efficacy and benefit of diagnostic and therapeutic intervention for breast cancer. In the current study, we have collected and organized these data to determine the actual status of breast cancer in Iran. The main data

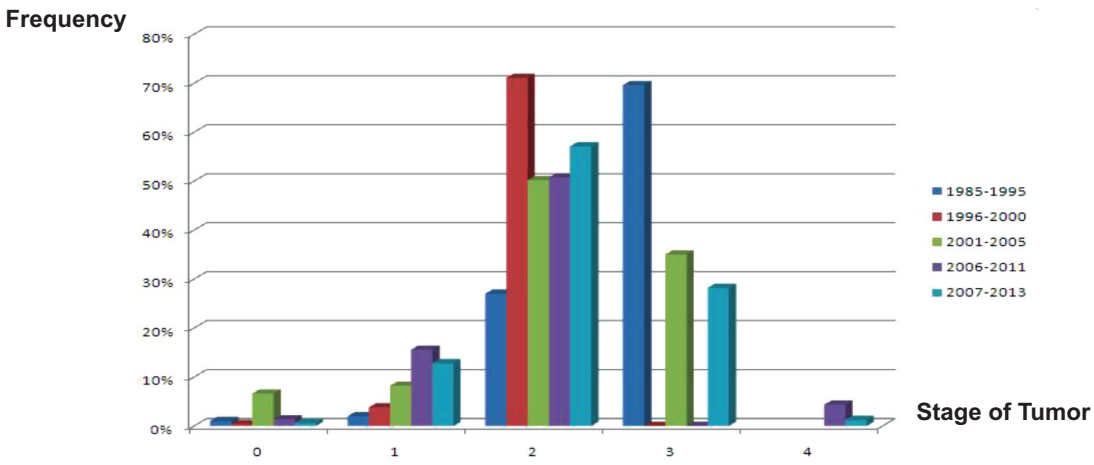

Figure 3. Trend for clinical stage of diagnosed breast cancer in Iran (1985-2013).

source was obtained from the Cancer Registry Department of the Health Ministry, data extracted from published articles, and data provided by the CRC at SBMU. There were some published data from other institutes in Iran, which were not compared and compiled with our data. We attempted to compare the status of breast cancer in Iran with other areas of the world according to international data from International Agency for Research on Cancer (IARC), GLOBOCAN, and specially with published articles from Middle East countries and other sources for comparison.

Results

Age and gender

In Iran, the mean age at breast cancer diagnosis according to various published articles was 47.95-54.6 years. According to the national database the mean age was 49.84 years and half of the patients (median) were ≤48 years of age.[11] In a research, the median age of breast cancer in Iran was reported 49 years.[15] The most common patient age group was 41-49 years (34.5%),[9-12,16-19] however another study reported 45-54 years of age.[20]

The rate of breast cancer in men was 2.8%, which was much higher than other parts of the world.[11]

Risk and protective factors

WHO reported that breastfeeding, higher physical activity, and healthy weight are associated with a lower risk of breast cancer.[3]

Protective factors included young age at first full-term pregnancy and multiparity are highlighted in breast cancer. 1-3 parities are the most protective effects.[12,18,21,22]

The role of long-term breast feeding of 18-24 months per child had significant protective effects.[12] In one study by Akbari et al., it was shown that 70% of breast cancer cases and 86% of controls had histories of breast feeding, whereas 29.5% of breast cancer cases and 14% of controls had no history of breastfeeding. This study showed that fewer patients fed the kids and other patients

Table 2. Age-specific rate (ASR) for the incidence of breast cancer in Iran from 2005-2006 (n = 5981).[9]

Age groups (years)	Incidence rate
15-19	0.02
20-14	0.78
25-29	5.91
30-34	14.74
35-39	33.14
40-44	47.90
45-49	74.03
50-54	74.31
55-59	69.28
60-64	69.09
65-69	48.58
70-74	43.71
75-79	4453
80-84	58-45
≥ 85	22.09
Crudo rate	17.44
Age specific rate (weighted)	23.06

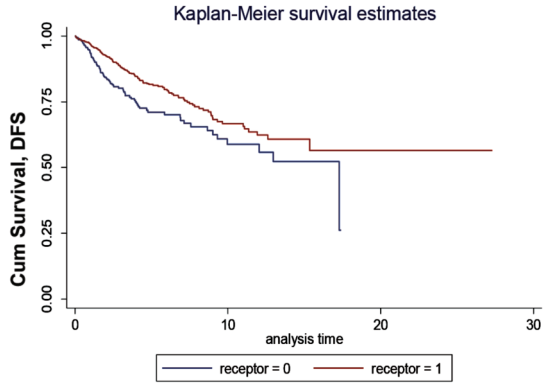

Figure 4. Disease-free survival (DFS) in patients with breast cancer recurrence in Iran. Variables significantly influenced DFS according to univariate analysis.

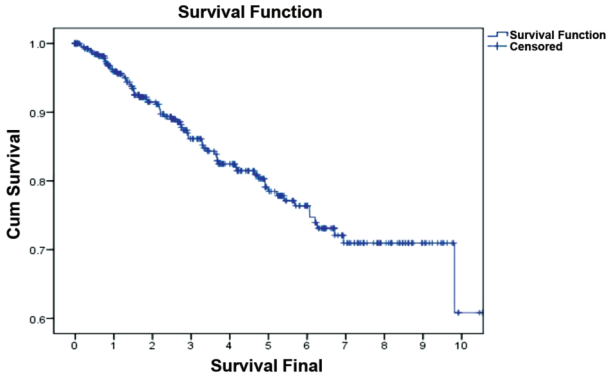

Figure 5. Overall survival for breast cancer patients (national data).[11]

Table 3. Age distribution of breast cancer patients according to age (years) in Iran.

Age (years)	Number	Percent
<30	39	6.4
30-34	42	6.9
35-39	89	14.5
40-44	114	18.6
45-49	125	20.4
50-54	83	13.5
55-59	59	9.6
60-64	23	3.8
65-69	22	3.6
70-74	17	2.8

had less time breast feeding. (Figure 2).[12,22]

However, tobacco consumption and overweight increased the risk for breast cancer (P=0.02 and 0.04, respectively). Increased body mass index (BMI), as a risk factor, was calculated in one study. The results showed that mean BMI (SD) in cases [27.9 (3.9)] compared to the controls [26.3 (4.3)] significantly differed (P=0.004).[23]

In a published study, oral contraceptive (estrogen, progesterone) is not a risk factor for breast cancer.[12,21-23]

A significant difference existed between cases that had a positive family history for breast cancer (22.8%) compared to 16.9% for controls.[12,21,22]

Pathology

Statistical analysis of 5 studies showed that invasive ductal carcinoma (89.5%-93%) was the most frequent cancer followed by invasive lobular carcinoma (2.8%-5.9%). The frequency of *in-situ* carcinoma was 1.2%-3.2%; other types were <7%.[11,16,18,22,24] The data Analysis of data pooled from 2224 cases at the Cancer Research Center showed a little difference in frequency of different types of breast cancer (Table 5).

Clinical staging

From 2006-2011, there were a number of Iranian studies conducted on breast cancers. These studies included more than 1606 patients - 65.5% diagnosed with early stage breast cancer and 34.5% with advanced stage cancer.[25,26] However, data from the CRC for 2007-2013 of 1812 cases

Table 4. The cumulative probability for death attributed to breast cancer death in Iran.

Year	Death Rate	95% Confidence Interval (CI)
1980	0.6	0.3-1.1
1990	0.7	0.4-1.1
2000	0.7	0.7-0.8
2010	0.7	0.5-0.8

(unpublished data) showed that 70.5% of patients had early stage breast cancer and 29.5% had advanced stage cancer.

A comparison of the 2001-2005 report with the 65% early stage cancer finding showed a slight change to 2006-2011 (67.62%). Improvements in medical practice and earlier diagnosis in the past decade is responsible for this down staging.[8,10,17,24-27]

Stage of tumor

Between 1985-1995 (P=0.24) and 2007-2013 (P=0.1), there was no significant difference in the stages 0 and 1 disease; however there were significant difference in patients with stages 2 and 3 during the mentioned years (P<0.001; P<0.001). It means the patients were diagnosed in earlier stages in recent years (2007-2013) (Table 6, Figure 3).

Biologic markers

Biological biomarkers like tumor size, grade, histologic feature, and lymph node status, can provide information on disease prognosis and outcome. According to studies in the last 12 years, estrogen receptor (ER), progesterone receptor (PR), and P53 were available, and the C-erb oncogene was available only for 7 years. Only ER was related to age, which meant that older patients had increased ER positivity, which possibly explain the better prognosis with increased age.[26,28,29]

Table 7 shows the range of positive receptors in five different studies. A tremendous difference in reported HER2 (14%-71%) existed, which appeared to be from differences in how HER2 was measured and the test quality.

A national policy should be designed to

standardize laboratories that evaluate HER2 receptor in order to unify the results obtained in future studies.

Recurrence and survival

In early stage breast cancer, all cases who were less than 70 years of age with a tumor size greater than one cm or lymph node positive undergo adjuvant chemotherapy. All hormone receptor positive patients received hormone therapy. In terms of surgical type, all lymph node positive patients and those who undergo breast conserving surgery received radiotherapy.

A study of overall survival, disease-free survival (DFS), and recurrence has reported that only two factors correlated with recurrence: absence of two steroid receptors and lymphovascular invasion (LVI).[30] Although early detection with no lymph node involvement and small tumor size are important in patients with breast cancer, the type of bio-marker involved should also be considered when survival is investigated.

According to a new published study from the CRC database, age lower than 40, higher stage at time of diagnosis, higher grade of tumor, large tumor size and negative ER and PR are important factors in early and late recurrence.[31] The median interval for recurrence or DFS was 3.6 years (range: 0-24.18 years). Disease-free survival was 96% at one year and 80% 5-years after diagnosis (Figure 4). Relapse was observed in 54% of cases 1-5 years after treatment.[31]

The 5-year overall survival rate was not related to the type of surgery,[10, 30] and estimated 72% in women and 60% in men. Hence, the survival rates for men were less than the global overall survival rate.[11]

Overall survival significantly differs by stages and number of positive lymph nodes. The five-year survival rates of 81%-88% and ten-year survival rates of 77%-81% have been reported.[10]

A national Iranian study conducted in 2010 on over 6147 patients reported a five-year survival rate of 71% (Figure 5).[11]

When survival was computed according to cancer subtypes, a new finding was established.

In the four breast cancer subtypes, the luminal A subtype (ER+ or PR+ and HER2-) was the most common, whereas the HER2 enriched subtype (ER-, PR- and HER2+) was the least common with the highest and the lowest five-year survival probabilities.[32]

Table 5. Analysis of data pooled from 2224 cases at the Cancer Research Center (CRC).

Pathology	Percent
DCIS	4.0
IDC	79.3
1IDC+DCIS	1
ILC	9.1
MIXED IDC+ILC	2.9
IDC+Paget	0.4
Paget	0.3
Other	0.4

DCIS: Ductal carcinoma in situ IDC: Invasive ductal Carcinoma ILC: Invasive lobular Carcinoma

Discussion

Breast cancer, with an ASR of 33.2 per 100,000 is the most common cancer in Iranian females. The lowest is 8.0 cases per 100,000 in Mongolia and highest at 109.4 per 100,000 in Belgium. Yearly, the ASR has increased by 1.5 per 100,000.[33]

Pakistan has the second highest ASR in the Middle East with 50.3 per 100,000.[34,35] In the Gulf Cooperation Council, the Kingdom of Saudi Arabia had the lowest ASR (12.9), whereas Bahrain had the highest (46.4) followed by Kuwait (44.3), Qatar (35.5), United Arab Emirates (19.2), and Oman (14.4) per 100,000.6 Western Turkey had an ASR of 50 per 100,000 compared to Eastern Turkey with 20 per 100,000. This difference was due to the Western life style.[36] The average ASR was 25.8 per 100,000 in different states of the India.[14]

This study intended to find the differences in statistical results of Iranian studies and the CRC-SBMU_database of approximately1700 new cases. The mean age of different Iranian studies was 47-50 years. The mean age in Pakistan was 48.6 years[34,35] 48 years in Saudi Arabia.[6]

The most common pathologic type was infiltrating ductal carcinoma (77%-89.8%) in the

Table 6. Clinical Staging for breast cancer in Iran according to 5 published articles and the CRC data pool (1985-2013).

Stage	1985-1995 N=903(%)	1996-2000 N=778(%)	2001-2005 N=1265	2006-2011 N=1250	2007-2013 N=1812
0	9(1%)	2(0.4%)	43(6.6%)	17(1.36%)	10(0.6%)
1	18(2%)	21(3.8%)	53(8.2%)	194(15.52%)	234(12.8%)
2	244(21%)	392(71.1%)	326(50.2%)	634(50.74%)	1034(57.1%)
3	632(69.9%)	136(24.7%)	220(35%)	309(24.72%)	511(28.8%)
4	-	-	-	54(4.34%)	23(1.26%)

Iranian studies[27,32,37] and 85.2% according to a study in Pakistan.[34]

The clinical stages of the tumor according to studies from 1985-2005 showed improvement; the tumors have been down-staged according to tumor size and number of positive lymph nodes.[16] A ten year study (1985-1995) reported early stage cancers consist of 30% of cancers which improved to 64%-75% after 2006.[9,27,32,37]

A 2013 study from Saudi Arabia reported that 40% of cases had advanced stage with breast masses that measured >10 cm in 58% of females. A study published in 2017 from India reported 45.7% of patients were advanced stage.[14] In Pakistan, 60.7% of cases had stage 2 disease.[34] A study from Northeast Iran that included 797 patients reported that 48.4% had early breast cancer and 51.6% had advanced breast cancer. This finding was similar to the CRC results with 54.5% early breast cancer and 45.5% advanced cancer.[10,11]

According to the frequency of advanced stage disease in different Iranian studies (30%-36%), it seems that health system notification for increasing the early detection program should be improved.

Because of the key role of biomarkers such as steroid receptors, C-erb (HER2) in correct management of this disease, the importance of further investigations and standard evaluation of biomarkers should focus on different regions of Iran.

There was no significant relation between tumor size and biologic markers in the studies. Only PR negativity had a relationship to more positive lymph nodes. Positive P53 was associated with increased metastasis in one study without any relation with steroid receptors. In that study, overall survival and DFS significantly differed in P53 positive and P53 negative metastatic patient groups.[28,29]

Two studies in 2005 and 2009 showed no relationship between biomarkers and tumor recurrence.[26,28] However a recently published study showed negative biomarkers (ER-, PR-, HER2-) had a poorer prognosis in the 4 subtypes. ER- HER2+ had shorter survival compared to ER+HER2- cases.[32]

Akbari et al. reported that in the absence of ER and LVI, the probability of tumor recurrence increased. Other receptors had no association with recurrence. Therefore, negative ER status along with other proliferative indexes could increase the risk of recurrence.[30] A recently published CRC study showed that high grade and stage, younger age, negative ER status, LVI and LN positive were the most common risk factors for recurrence.[31]

In a research by Akbari et al. the possibility of death in patients with visceral recurrence (P=0.001, HR=8.04) was greater than locoregional and bone recurrence (P=0.031, HR=4.42) and also more than local recurrence.[31]

According to the standardized mortality ratio (SMR), the five-year mortality was 6.74, for the 10-year period was 6.55, and 1.26 for the 15-year period. Total mortality amongst Iranian women of all ages was 0.13%-1.9%. The 15-year SMR was similar in breast cancer patients and the normal population.[8] The data obtained from mortality rate recorded in Pakistan showed that 36% of total deaths were for breast cancer patients.[34] Turkey had a mortality rate of 11.9 per 100,000,[13] whereas the mortality rate in India was 12.7 per 100,000.[14]

Conclusion

Breast cancer is the most prevalent cancer in Iranian females, therefore, a critical investigation into its epidemiology is necessary. Our study has attempted to compare different Iranian studies, neighboring countries, and the world in terms of breast cancer mortality, prevalence, staging, recurrence and survival. The differences in findings from Iranian studies and other countries indicate the multi-dimensional aspect of this cancer and necessitates multi-center involvement by governmental authorities, clinicians, and scientists.

Funding/support

None declared.

Conflict of Interest

No conflict of interest is declared.

Table 7. Percentage of positive biomarkers in five published articles and the Cancer Research Center (CRC) data pool.

Biomarkers	Range (%)	CRC cases N=1788 (%)
ER	45.5-67	72.2
PR	43-65.5	65
P53	18.7-35	36
HER2	14-71.05	24.3

ER: Estrogen receptor; PR: Progestrone receptor.

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