RESEARCH ARTICLE

Trends in Epidemiology, Clinical and Histopathological Characteristics of Breast Cancer in Iran: Results of a 17 Year Study

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Abstract

Background: Breast cancer (BC) is the top cancer among women worldwide and the most frequent malignancy among Iranian women over the past few decades. The increasing trend and high mortality rate of BC in the developing world necessitates studies concentrating on its characteristics in countries in Asia. The current study focused on clinical and histopathological features of BC among Iranian females. Materials and Methods: This retrospective study involved 714 Iranian patients with histopathologically proven BC undergoing resection of primary tumours and axillary clearance. Demographic, clinical and histopathological data were obtained and studied between ten year age groups (≤40 years, 41-50 years, 51-60 years, 61-70 years, and ≤71 years) in four chronologic phases from 1994-2009. Results: Mean age of patients was 49.4±13.1 years. Most of cases (33.2%) were in 41-50 group. Mean size of primary tumors was 3.94±2.47 cm and 87.1% of cases had infiltrative ductal carcinoma. Modified radical mastectomy was the most common method of surgery carried out (48.8%). Some 57.1% of tumors were in pT2 and tumor size decreased significantly during the period (p<0.05). The most common BC stage was llla (27%). Lower BC stages (0 and 1) constituted 13.9% of the diagnosed tumors. Our series of patients aged ≤40 had larger tumors (mean 4.73±3.02 cm) compared to older age groups (p=0.003). Lower stages (0 and I) were more frequent among the oldest patients while nearly 50% of patients aged ≤40 had tumor stage III. We also observed a significant decreasing trend in the mean LN count (p<0.05) and blood vessel invasion (p=0.023) from younger to older age groups. Conclusions: More aggressive disease for younger age groups, earlier peak incidence age and high rate of advanced BC at the time of diagnosis among Iranian women, were the main findings of this study.

Keywords: Breast cancer - epidemiology - staging - tumor type - trends - Iran

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Introduction

Breast cancer (BC) is the most common cancer among women worldwide, accounting for 16% of all female cancers and the leading cause of cancer related death in women (Parkin and Fernandez, 2006). It has been reported that 232,340 new female cases with invasive BC (29% of all newly diagnosed cancers) and 64,640 new cases with insitu BC (85% DCIS) are projected to be diagnosed in USA in 2013 (Siegel et al., 2013). In the developing world, the increasing trend of disease is worrying which might be attributed to increased life expectancy, changes in lifestyle and urbanization, associated with higher BC risk (Parkin and Fernandez., 2006; Porter., 2009). The incidence of BC among young Asian women is moderate but is increasing and may be more than two fold higher than western countries (Agarwal et al., 2007; Karihtala et al., 2010). Previous studies showed that BC has become the most frequent malignancy, comprising 24.4% of all neoplasms among Iranian women during past decades (Mousavi et al., 2007; Harirchi et al., 2011), with a crude incidence rate of 17.81 and an ASR of 23.65 in the year 2006 (Mousavi et al., 2009). Even after adjusting for age, most of Iranian patients are at least one decade younger than their western counterparts (Harirchi et al., 2004; Mousavi et al., 2007) and present with advanced stages of disease (Harirchi et al., 2000). Due to lack of enough evidences describing age distribution, clinicopathological characteristics and stage of BC in Iran, it is difficult to investigate ongoing and future condition of the disease and consider the best preventive and therapeutic approach to lower the burden of it (Mousavi et al., 2007; Harirchi et al., 2011). Considering this fact along with high mortality rate of BC in developing countries (such as Iran) (Shibuya et al., 2002; Harirchi et al., 2011), it is crucial to organize epidemiological studies with demographic trend analysis concentrating mainly

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on the recent changes in age distribution for primary and secondary prevention of BC (Mousavi et al., 2008; Harirchi et al., 2010). Aging is considered as one of the main risk factors for developing new BC events (Gennari et al., 2004; Molino et al., 2006; Benz, 2008). Almost, 50% of BC occurs in women ≤65 years and more than 30% in women ≤70 years in developed nations (Yancik et al., 2001). The highest incidence of BC in Iran is among women in their fifth decade of life (Mousavi et al., 2007; Harirchi et al., 2011). High rate of young population in Iran (mean age: 30.33 in 2011), necessitates establishing age-oriented screening and treatment plans for Iranian women. The current study allowed us to assess overall spectrum, some clinical and epidemiological characteristics of BC among Iranian females while comparing the proportion of patients in five age groups during a period of 17 years. In order to identify variations in tumor characteristics based on age, we investigated association of patient's age with tumor size, axillary lymph node involvement (ALNI), stage of BC, vascular invasion (lymphatic and/or blood vessel invasion) and histopathological type of the disease. Since these findings can provide basic data about BC in Iran, it may be appropriate to contribute findings of this study developing long-term strategies to reverse increasing trend of BC in Iran and other developing countries.

Materials and Methods

This retrospective study involved 714 Iranian patients with histopathologically proven breast cancer undergone resection of primary tumor and axillary dissection between 1994 and 2009 at Shohadaye Tajrish University Hospital, Shahid Beheshti University of Medical Sciences, Tehran-Iran. All of histopathological diagnoses were established at the department of Pathology of Shahid Beheshti University. The local ethics committee approved the study protocol. Demographic, clinical and histopathological data were obtained from the study population. We selected patients based upon the following criteria: having histologically proven BC; known histopathological nodal status; no distant metastases at the time of registration, no previous treatment for BC, no previous or concomitant malignancy. Patients who had immeasurable primary tumor size (Tx), micro residue of primary tumor, metastasis from other organs to breast at the time of registration, previous invasive BC events, previous chemotherapy for BC, unknown histologic types or suspicious diagnosis were excluded from our study, resulting in a dataset of 714 patients. Pathologic staging for malignant tumors was collected from patient's pathologic records and coded according to the American Joint Commission on Cancer staging (AJCC) manual 5th edition (1997). We assessed following variables: age at diagnosis as a continuous covariant, gender, clinical characteristics of tumors (side and location), maximal tumor diameter as indicated in pathology reports (cm), histopathological data (type and subtype), kind of surgery carried out, peritumoral lymphatic and/or blood vessels invasion and axillary lymph node (ALN) status. BC pathologic reports were studied in four chronologic phases: phase 1 (1994-1997), phase 2 (1998-2001),phase 3 (2002-2005) and phase 4 (2006-2009). Consequently, we were able to evaluate alternations in BC features in each phase and during the whole mentioned period. Also, subjects were stratified into five age groups: ≤40 years, 41-50 years, 51-60 years, 61-70 years, and 71≤ years. Cut-off age for young women has varied from 35-40 years in some studies (Fisher et al.,1997; Colleoni et al., 2002; Harirchi et al., 2011). We selected 40 years or under, since it provided a group of reasonable size which was compatible with other studies. The 41-50 year group was considered as mostly premenopausal subjects and 51-60 as most postmenopausal patients. Frequency and percentage of patients within each of the age categories were computed. Variables were compared between all groups and relationships between them were evaluated. For patients underwent bilateral axillary dissection we reported the number and involvement of nodes in both sides. With multicentric tumors the larger parameter was considered and patients with bilateral tumors were included only once. The pathological size (pT) and larger diameter of tumors (in cm) were recorded for each patient. pTs were classified as: pT0 (no primary tumor), pT1 (<2cm), pT2 (2-5cm), pT3 (<5cm) and pT4(skin or chest wall involvement). The number of pathologically examined ALN (pN) evaluated on the likelihood of finding at least one lymph node positive for disease and categorized as pN0 (no LN involvement), pN1 (1-3), pN2 (4-9) and pN3 (10<). The total number of lymph nodes and the number of involved nodes were both determined. We also investigated tumor histopathologic types listed below: infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), ductal carcinoma insitu (DCIS) and lobular carcinoma insitu (LCIS). Subtypes evaluated were as following: not otherwise specified (NOS), sirrhiosis, pure tubular, pure medullary, pure colloid (mucinous), comedo, adenocarcinoma and Paget's disease. Few less common forms were classified as 'other' in both tumor types and subtype groups. A small number of patients represented with some other categories like breast sarcoma and metaplastic sarcoma that were not included in our analysis. Cases with mixed subtypes were not recruited in our study. Evidences of DCIS presenting in conjunction with any special invasive breast cancer subtype did not influence our categorization pattern. Additional biologic predictive factors (e.g. over expression of p53, epidermal growth factor receptor, c-erb2) and hormone receptor status (estrogen and progesterone) was not available for all patients. Therefore, this information was not considered in the final analysis. During the last years of study sentinel lymph node biopsy (SLNB) was performed in some cases, followed by complete axillary dissection, regardless of the histological nodal findings. Patients who underwent SLNB were included in our study but were not considered separately. Their data was being included in the total number of dissected lymph nodes.

Statistical evaluation

Descriptive statistics were reported as frequencies and percentages, or means and standard deviations. An independent t-test was considered to compare the scores of each of the measures and some of the parameters

data between two groups. One-way ANOVA analysis of variance followed by post hoc Newman-Keuls testwas utilized for statistical analyses of parameters between all groups. The Pearson correlation and linear regression model was also used to examine the relation between some parameters. A p-value of less than 0.05 was considered statistically significant. Data were analyzed using SPSS, version 16 (SPSS Inc., Chicago, IL).

Results

From 1993-2009, 714 medical records diagnosed as primary BC in females were reviewed and included in our study. We excluded patients who had metastatic disease at presentation (n=12), previous chemotherapy (n=8), patients whom primary tumor could not be assessed (n=29), unknown pathological nodal status (n=11), micro residue of primary tumor (n=16), Paget's disease of nipple without tumor (n=4) and suspicious diagnosis (n=2). Elimination of cases missing studied variables left 714 BC subjects. Information on clinical and tumor characteristics of patients is demonstrated in Table 1. Mean age of all participated cases at the time of diagnosis was 49.35±13.1 years. The average age at the time of diagnosis increased during this survey, but it was not significant (p=0.581). Modified radical mastectomy (MRM) (48.8%) was the most common method of surgery carried out. Tumors were found more commonly in the upper outer quadrant (UOQ) (52.6%). Mean size of primary tumor in 630 evaluated patients was 3.94±2.47 cm (ranged from 0.4-21cm). Evaluation of tumor local extension (pT0 to pT4) revealed a significant difference (p<0.001). More than half (57.1%) of females with breast malignant lesions were in pT2, which was followed by pT1: 21.6%, pT3: 20.2%, pT4: 0.6% and pT0: 0.5%. The majority of cases (80.4%) had IDC. More than 50% of patients showed the histological subtype of NOS. Overall, number of examined lymph nodes (LN) ranged from 1 to 53 with a mean count of 11.9. Proportion of LNI was significantly distributed (p<0.01) as the following: pN0: 36.6%; pN1: 24.6%; pN2: 21.4% and pN3: 17.7%. Considering BC stage, the most common among all patients was IIIa (27%). Of 181 studied patients with reported peritumoral vascular and 55 lymphatic vessels status, 61.9% and 87.3% patients showed evidences of invasion, in order.

Table2 shows tumor features between five age groups. There was a significant difference in the number of patients between groups (p<0.01).The majority of cases (33.18%) had 41-50 years old, while patients aged ≥71 constituted only 6.0% of the study population. Although patients in all age groups had an approximately mean tumor size of 3–4cm, there was a significant difference between groups considering this variable (p=0.001). The noticeable finding of this study was that mean tumor size differed significantly between younger and older cases (p<0.01). Patients aged ≤40 had larger tumors (4.73±3.02 cm) compared to the age groups 41-50 (3.89±2.37cm; p=0.002), 51-60 (3.56±1.93cm; p<0.001) and 61-70 (3.7±2.13cm; p=0.003). Interestingly, the mean tumor size slightly increased again after age ≥71 (4.16±2.81 cm). Proportions of BC local extension also differed between the age groups (p<0.001). Frequency of T3 tumors in older age groups was significantly lower than younger and moderate age groups. Furthermore, there were significant differences regarding tumor stages based on age categories (p<0.001). We found a significant increasing trend for the proportion of tumor stages 0 and I from younger to older age groups (p<0.05). Lower stages (0 and I) were more

Table 1. Clinical and Tumor Characteristics of 714 Breast Cancer Patients

Parameters		Results
Total number of patients		714
Age (n=667) (year)		49.35±13.1
	Mean	49.35
	Range	12-90
Tumor side (n=639)	Right	338 (52.8%)
	Left	301 (47%)
	Bilateral	0.20%
Surgery type (n=701)	MRM	339 (48.8%)
	Biopsy	233 (33.2%)
	Simple Mastectomy	83 (11.8%)
	Lumpectomy	32 (4.6%)
	Others	14 (2%)
Tumor location (n=196)	UOQ	103 (52.6%)
	Central	28 (14.3%)
	LOQ	23 (11.7%)
	UIQ	20 (10.2%)
	LIQ	15 (7.7%)
	M.C	7 (3.5%)
Tumor Size (n=630), (mean, cm)		3.94±2.47
	Mean	3.94
	Range	0.4-21
	pT0	3 (0.5%)
	pT1	136 (21.6%)
	pT2	360 (57.1%)
	pT3	127 (20.2%)
	pT4	4 (0.6%)
LN count (n=462)	Mean	11.9
	Range	0-53
LN involvement (n=465)	Mean	4.53
	Range	0-50
	pN0	168 (36.6%)
	pN1	114 (24.6%)
	pN2	99 (21.4%)
	pN3	82 (17.7%)
Stage at presentation (n=444)	0	33 (7.4%)
	I	29 (6.5%)
	IIa	98 (22.1%)
	IIb	87 (19.6%)
	IIIa	120 (27%)
	IIIb	2 (0.5%)
	IIIc	75 (16.9%)
Tumor invasion (n=688)	Invasive	633 (92%)
	Non-invasive	55 (8%)
Histological type (n=709)	IDC	570 (80.4%)
	DCIS	50 (7.1%)
	ILC	21 (3%)
	LCIS	2 (0.3%)
	Others	66 (9.3%)
Tumor subtype (n=219)	NOS	126 (57.5%)
	Comedo	22 (10%)
	Scirrhosis	12 (5.5%)
	Mucinous	12 (5.5%)
	Medullary	12 (5.5%)
	Adeno.ca	8 (3.7%)
	Paget	7 (3.2%)
	Tubular	4 (1.8%)
	Others	16 (7.3%)
Vascular invasion (n=181)	Yes	112 (61.9%)
	No	69 (38.1%)
Lymph invasion (n=55)	Yes	48 (87.3%)
	No	7 (12.7%)

frequent among the oldest patients while nearly 50% of patients aged ≤40 had tumor stage III. Moreover, we found a rise in the proportion of tumor stages IIa and IIb by increasing age. In contrast, tumor stage IIIc declined by increasing age (p<0.05). We also observed a significant decreasing trend in the mean LN count from younger to older age groups (p<0.05). Women aged 41-50 had higher LN counts (mean =12.6±6.6) compared to the age groups 41≥ (11.97±6.14; p=0.44), 51-60 (12.12±6.75; p<0.57) and 61-70 (11.27±8; p=0.23). We also detected an increase in chance of LNI (pN2 and pN3) for younger ages (p<0.01) but a decreased risk of pN1and pN0 (somewhat

Table 2. Overall Demographics and Tumor Characteristics in Different Age Groups

Age in years		Patients evaluated	≤40 years n	%	41-50 years n	%	51-60 years n	%	61-70 years n	%	≥71 years n	%
Overall number		666	168	25.2	221	33.1	150	22.5	87	13	40	6
Tumor size	pT0	2	0	0	2	1	0	0	0	0	0	0
	pT1	127	30	20.1	40	20.3	29	20.2	15	34.4	13	35.1
	pT2	336	74	49.6	118	59.8	81	61.3	47	63.5	16	43.2
	pT3	120	45	30.2	36	18.2	21	14.8	11	17.2	7	18.9
	pT4	4	0	0	1	0.5	1	1.3	1	3.4	1	2.7
Tumor Stage (n)	0	32	6	5.7	10	7.5	8	7.4	5	9.2	3	13
	I	27	5	4.7	9	6.7	9	8.8	2	3.7	2	8.6
	IIa	92	22	20.9	30	22.5	25	24.5	13	24	2	8.6
	IIb	82	19	18	29	21.8	14	13.7	14	25.9	6	26
	IIIa	113	31	29.5	32	24	30	29.4	12	22.2	8	34.8
	IIIb	2	0	0	1	0.7	0	0	1	1.8	0	0
	IIIc	69	22	20.9	22	16.5	16	15.6	7	12.9	2	8.6
LN involvement (n)	pN0	156	40	36	49	35.2	42	40.3	20	35.7	7	30.4
	pN1	105	21	18.9	39	28	18	17.3	17	30.3	9	39.1
	pN2	95	27	24.3	27	19.4	27	25.9	10	17.8	4	17.3
	pN3	76	23	20.7	24	17.2	17	16.3	9	16	3	13
Lymph invasion	47	13	27.6	18	38.2	8	17	5	10.6	3	6.3	
Vascular invasion	99	29	29.2	37	37.3	16	16.1	11	11.1	6	6	
Surgery type (n)	MRM	321	82	50.9	103	48.8	79	54.4	39	45.8	18	46.8
	Biopsy	217	59	36.6	67	31.7	49	33.7	30	35.2	12	25
	Simple Mastectomy	73	16	9.9	24	11.3	15	10.3	11	12.9	7	18.7
	Lumpectomy	31	4	2.4	17	8	2	1.3	5	5.8	3	9.3
Histological type (n)	IDC	529	132	79	168	76.7	130	86.6	69	79.3	30	75
	DCIS	47	8	4.7	18	8.2	11	7.3	7	8	3	7.5
	ILC	20	2	1.1	11	5	2	1.3	4	4.5	1	2.5
	LCIS	2	0	0	1	0.4	0	0	1	1.1	0	0
	Others	34	25	14.9	21	9.5	7	4.6	6	6.8	6	15

Table 3. Clinical and Tumor Characteristics of Patients with Breast Cancer During Study

Years of Study		Patients evaluated	1994-1997 n	%	1998-2001 n	%	2002-2005 n	%	2006-2009 n	%
Overall number		712	141	19.8	180	25.3	208	29.2	183	25.7
Tumor size	pT0	3	0	0	1	0.6	2	1.09	0	0
	pT1	136	27	21	27	17	42	22.9	40	24.8
	pT2	360	67	52.7	95	60.1	107	58.4	91	56.5
	pT3	127	34	26.7	33	20.8	32	17.4	28	17.3
	pT4	4	0	0	2	1.26	0	0	2	1.2
Tumor Stage (n)	0	33	8	8	12	10.5	10	7.7	3	2.9
	I	29	5	5	7	6.14	6	4.65	11	10.8
	IIa	98	20	20	25	21.9	31	24	22	21.7
	IIb	87	18	18	23	20.1	28	21.7	18	17.8
	IIIa	120	34	34	22	19.2	32	24.8	32	31.6
	IIIb	2	0	0	1	0.87	0	0	1	0.99
	IIIc	75	15	15	24	21	22	17	14	13.8
LN involvement (n)	pN0	168	31	30.3	46	38.9	49	36.5	42	38.5
	pN1	114	24	23.5	27	22.8	36	26.8	27	24.7
	pN2	99	31	30.3	18	15.2	25	18.6	25	22.9
	pN3	82	16	15.6	27	22.8	24	17.9	15	13.7
Lymph invasion		48	11	22.9	16	33.3	15	31.2	6	12.5
Vascular invasion		112	10	8.9	13	11.6	51	45.5	38	33.9
Surgery type (n)	MRM	339	79	56.4	97	55.1	95	48.2	68	39
	Biopsy	233	34	24.2	59	33.5	66	35.5	74	42.5
	Simple mastectomy	83	21	15	16	9	34	17.2	12	6.89
	Lumpectomy	32	6	4.2	4	2.2	2	1.01	20	11.4
Histological type (n)	IDC	570	114	80.8	136	75.5	168	80.7	152	84.4
	DCIS	50	11	7.8	17	9.4	14	6.73	8	4.44
	ILC	21	5	3.5	6	3.3	3	1.44	7	3.88
	LCIS	2	0	0	0	0	2	0.96	0	0
	Others	66	11	7.8	21	11.6	21	10	13	7.2

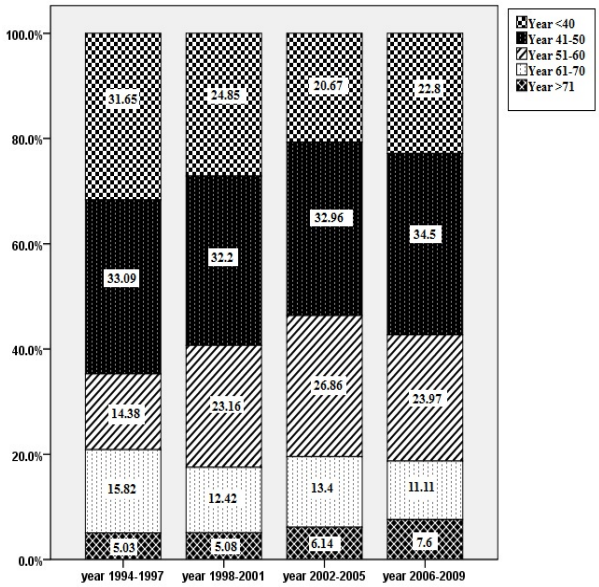

Figure 1. Distribution of Age Groups Over the Course of Study

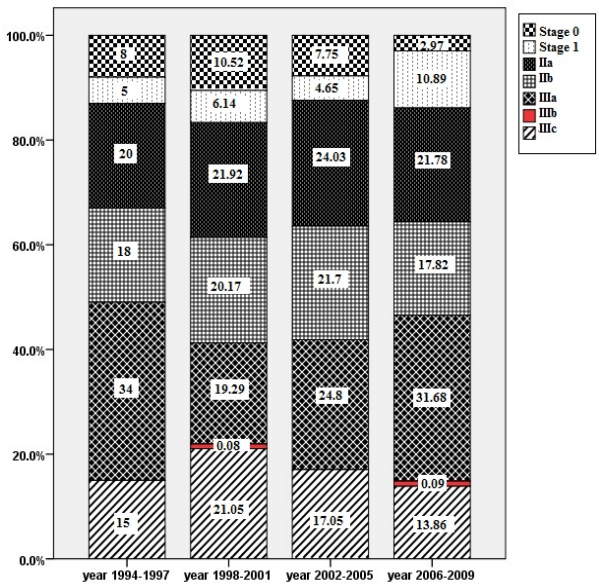

Figure 2. Distribution of Percentage of Tumor Stage Over the Course of Study

weaker and not statistically significant). Older cases had considerably lower mean number of LNI (9.42±5.74; p=0.02). MRM was the most common type of surgery carried out among all age groups. Our data also illustrated that there was a relation between age and tumor type. It appears that patients with NOS, scirrhosis and comedo carcinomas were older than patients with other tumor subtypes. However, except for the NOS group, most histological subtypes were rare, and the low sample sizes did not permit a reliable assessment of differences between them. So, we couldn't fully verify association between tumor type and subtype with age in this study.

Although there were some slight fluctuations in the mean age of patients in each group over 17 years, women 41-50 years of age had the highest (nearly mean percentage of 32%) and those ≥71 years of age had the lowest frequency of BC in each phase (Figure1). Most recently, the highest proportion (34.5%) of BC was detected among patients aged 41-50 (p<0.01), which was followed by 23.97% and 22.8% in age groups 51-60 and ≤40 years. Between 1993 and 2009, there was a trend for a lower frequency of BC among patients aged ≤40 and 61-70, but this difference was not statistically significant (Figure 1).Patients aged 51-60 had rate of increasing, from 14.38% to 23.97% (p<0.01). Similarly an increase in the percentage of BC was also seen among age groups ≥71, but it was not significant.

Frequency of blood vessels invasion considerably declined by increasing age (p=0.023). This finding reflects evidences of less aggressive disease in older cases. Lymphatic vessels invasion also decreased in a same pattern, but it was not statistically significant (p=0.98). Moreover, we observed a positive correlation between blood and lymphatic vessel involvement (p=0.009). Table 3 summarizes demographics and tumor characteristics of patients in four chronologic phases from 1993 to 2009. Generally, proportion of patients has risen from 19.8% to 25.7% throughout the survey. Tumor size decreased significantly from 4.28±2.54 cm in phase 1 to 3.72±2.26cm in phase 4 (p<0.05). Local extension of tumors also differed in four phases (p<0.001). pT2 was dominant (nearly55%) in each phase (p<0.001), while pT0 and pT4 were less frequent (p<0.001). A slightly increasing trend in the frequency of pT1 was observed from 21.09% to 24.84% during the survey, but it wasn't statistically significant (p=0.126). Another point was a decreasing trend in the frequency of pT3 from 26.77% in phase 1 to 17.39% in phase 4 (p<0.05). The percentage of tumor stages also differed among four phases (p<0.001).

Figure 2 demonstrates variations in BC stages at the time of diagnosis during the study period. The proportion of stage I BC increased from 5% in phase 1to 10.89% in phase4 (p<0.05), while stage 0 BC decreased from 8% to 2.97% over the survey. Overall, a fluctuating trend in the diagnosis of early BC (stages 0 and 1) was observed: 13%, 16.66%, 12.4% and13.86% of cases in phase1 to 4 had stages 0 and 1, respectively. The proportion of patients presenting with stage II BC (IIa and IIb) increased from phase 1 to 3; 38%, 42.09% and 45.73% of cases were stage IIa and IIb in phases 1,2 and 3, respectively. Advanced BC (IIIa, IIIb, IIIc) also increased from phase 2 to 4(phase 2: 40.42%, phase 3:41.85%, phase 4: 42.43%).In phase 1,3 and 4, stage IIIa BC was the highest diagnosed stage (p<0.001), while stage IIIb BC was the least popular in four phases (p<0.001).The most considerable point for stage IIIc BC, was a decline in the proportion of cases; 21.05%, 17.05%, 13.86% from phase 2 to 4, in order.

Another finding was a drop in the mean number of counted LN from 13.58±8.26 to 10.31±5.47over the survey (p<0.05). Although, it was not significant (p=0.136), the high rate of LNI was considerable. Nearly 92% of patients in each period had LNI and there were no significant differences regarding this item in four phases (p=0.326). In terms of surgical management, although, MRM was the most common treatment done among all age groups (nearly 50%), use of MRM decreased significantly by 17% during the survey (p<0.01). Furthermore, nearly 80% of patients in each period had IDC and there were no significant differences regarding proportion of invasive tumor between age groups (p=0.341).

Discussion

BC is the top cancer in women worldwide and is increasing specially in developing countries, where most of cases are diagnosed in late stages (Agarwal et al., 2007; Mousavi et al., 2008), a finding that is indicated in the current study, as well. Rate of increasing BC in developing countries is reported as 3-4% (Parkin et al., 2001). Paucity of data linking probable factors to increased risk of BC in the developing countries is still a problem (Porter, 2009). In Iran, BC is the most common primary cancer among women (24 per 100,000) and the proportion of newly diagnosed cases has gone up, recently (Mousavi et al., 2009; Harirchi et al., 2011). In our study, the percentage of patients diagnosed with BC has risen from 19.8% in 1994 to 25.7% in 2009. Also, mean tumor size declined significantly during this period ($p<0.05$). This may indicate advances in finding new cases and an increase in Iranian female's general awareness about BC. The majority of our cases (33.18%) had 41-50 years. This 10 years earlier peak incidence age for Iranian women is different from developed countries (Parkin and Fernandez, 2006; Smigal et al., 2006) but resembles to developing nations(Agarwal et al., 2007) and corresponds with other studies done in Iran (Mousavi et al., 2007; 2008; Harirchi et al., 2011). Some biomarker studies and clinical data point that late-onset BC is biologically less aggressive with a slower growth than early-onset (Fisher et al., 1997; Benz, 2008). The current study has supported this idea to some extent. In contrast, a number of studies indicated that older subjects are often diagnosed with high-risk tumors in comparison with younger ones (Molino et al., 2006; Botteri et al., 2010). In our series of patients, we found considerable differences in BC features among younger and older ones. The youngest age group had larger tumors compared to other groups ($p=0.003$). Also, younger age was related with an increased chance of LNI (more pN2 and pN3). Patients under 50 years were more likely to have stage III BC. Furthermore, higher frequency of stages 0 and 1 in ≥71 years, a decline in stage III by increasing age and more frequent pT3 in older cases show that tumors in older age groups are less aggressive than younger. Our findings are in line with a study by Winchester et al. (1996). In a previous study on 1800 post-menopausal BC patients aged 55 and older, 73% were diagnosed with stage I and II BC and 10% had stage III and IV (Yancik et al., 2001). Fisher et al. (1997) indicated an increase in LN metastases in patients younger than 40 and a drop among the oldest old group (70< years). Vascular invasion (lymphatic and/or blood vessels) showed a progressive reduction with increasing age in their study, too, like the current survey. In a study done by Colleoni et al. (2002), women younger than 35 years had more vascular or lymphatic invasion compared to those 35-50 years. But, no trends with age were observed for pathological stage according to TNM in their study. According to this study, it appears that BC has a more favorable pattern in older age groups. In our study, BC stage III was the most common. Lower BC stages (0 and 1) constituted 13.9% of the whole diagnosed tumors. This reveals the fact that most of tumors were detected at advanced stages. This corresponds with the result of another study done in Iran (Harirchi et al., 2000) and can be contributed to delayed patient presentation (Sharma et al., 2012). According to our study, the proportion of patients presented with stage II BC (IIa and IIb) increased from phase 1 to 3 and declined in phase 4. Frequency of advanced BC (IIIa, IIIb, and IIIc) also rose from phase 2 to 4 of the survey. Another important point of the current survey was the high proportion of patients with LNI at the time of diagnosis. Despite a relative reduction in the proportion of LNI during the period of 17 years, it is still high in phase 4 which indicates more aggressive disease at the time of diagnosis and a worse consequence among Iranian patients. Results of a previous study performed in Iran by Harirchi et al.(2011) revealed an increase in stage 0 and 1 during 1985-2005. Most of tumors in that study were in pT2. Similarly, they found high rate of patients with LNI at first visit (Harirchi et al., 2011). However, Harirchi et al. (2011) concluded a down-staging trend in BC among Iranian women during past decades. In a literature review done by Mousavi et al. (2007), stage II BC was the most common BC stage among Iranian women during 1998-2005 and nearly 72% of patients had tumors <2cm. They also found high rate of LNI at the time of presentation. Indeed, the frequency of advanced BC in Iran is high and despite all considerable improvements in the diagnostic tools during past decades (Harirchi et al., 2010), the frequency of advanced BC rose in the last phases of study. Even, if we had the metastatic status of the study population, patients might be placed in higher stages, as well. In our previous study, we found that tumor size is a significant predictor of axillary LNI; 84.3% of patients with tumors ≤2 cm, had axillary nodal metastases. Additionally, we observed more blood vessels, skin, areola-nipple involvement by increasing tumor size (Orang et al., 2013), so it is an essential point to detect tumors at smaller diameters. Moreover, lower age of BC in Iran (40s) in comparison with western world (50s) necessitates introducing effective screening programs which are suitable for our women. Age of natural menopause among Iranian women is 50.4±4.3 years (Mohammad et al., 2004). It seems that BC affects most of our cases in premenopause age. This might explain why mammography is a less accurate screening tool for our patients; considering the fact that higher breast density in younger age groups reduces mammography sensitivity and detection of microcalcifications (Foxcroft et al., 2004). Due to lack of enough evidences supporting effectiveness of mammography screening for women 40-49 years (Medical Advisory Secretariat., 2007), simple, realistic, particular, efficient and evidence based screening programs that correspond well with the pattern of BC in Iran should be established as a crucial part of our future strategies to reverse the increasing trend of disease (Mousavi et al., 2008; Porter., 2009). Our study therefore provides some complementary information on the age distribution, stage and nature of BC in a developing country that might help health care systems and physicians reorganize and implement strategies to improve preventive and therapeutic approaches to lower the burden of BC in these countries. Major limitations of our study concerns lacking data about menopausal age, family history, type

of disease presentation (being symptomatic or not) and biologic factors. As stated, this study observed high percentage of middle-aged patients with advanced disease in Iran. But, our findings might not explain the reason of it. There are ongoing efforts to investigate biologic and genetic differences that may affect BC presentation in developing countries. In our opinion, finding the barriers to BC care in developing countries should be highlighted in future studies.

In conclusion, more aggressive disease for younger age groups, earlier peak incidence age and high rate of advanced BC at the time of diagnosis among Iranian women, were the main findings of this study. It may be appropriate to contribute these findings to develop long-term strategies for reversing the increasing trend of BC in Iran and other developing countries.

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