RESEARCH ARTICLE

Comparison between Early and Late Onset Breast Cancer in Pakistani Women Undergoing Breast Conservative Therapy: is There any Difference?

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Abstract

  Background: Early onset breast cancer is associated with poor outcomes but variable results have been reported. It is a significant problem in Pakistani women but remains under reported. Breast conservation plays an important role in surgical management of this younger patient group. The objective of this study was to determine the outcome of breast conservative therapy in patients with early onset breast cancer in our population and compare it with their older counterparts. Materials and Methods: A review of patients with invasive breast cancer who underwent breast conservation surgery at Shaukat Khanum Cancer Hospital from 1997 to 2009 was performed. Patients were divided into two groups i.e. Group I age ≤40 and Group II >40 years. A total of 401 patients with breast cancer were identified in Group I and 405 patients in Group II. Demographics, histopathological findings and receptor status of the two groups were compared. The Chi square test was used for categorical variables. Outcome was assessed on basis of 10 year locoregional recurrence free survival (LRRFS), disease free survival (DFS) and overall survival (OS) . For survival analysis Kaplan Meier curves were used and significance was determined using the Log rank test. Cox regression was applied for multivariate analysis. Results: Median follow up was 4.31 (0.1-15.5) years. Median age at presentation was 34.6 years (17-40) and 51.9 years (41-82) for the two groups. Groups were significantly different from each other with respect to grade, receptor status, tumor stage and use of neoadjuvant therapy. No significant difference was present between the two groups for estimated 10 year LRRFS (86% *vs* 95%) (p=0.1), DFS (70% *vs* 70%) (p=0.5) and OS (75% *vs* 63%) (p=0.1). On multivariate analysis, tumor stage was an independent predictor of LRRFS, DFS and OS. Conclusions: Early onset breast cancer is associated with a distinct biology but does not lead to poorer outcomes in our population.

Keywords: Breast conservative therapy - outcome - survival - early onset - late onset - Pakistan

Introduction

    The incidence of breast cancer is increasing alarmingly in Pakistani population and is 2.5 times higher than neighboring countries India and Iran (Shaukat el al., 2013). Breast cancer in women younger than 40 years of age has been associated with worse outcome and a distinct distribution of prognostic factors when compared with older counterparts (Adami et al., 1986; Chung et al., 1996; Sidon et al., 2003). This poor outcome in younger population is more significant for early stage of breast cancer. Gnerlich and colleagues retrospectively reviewed 15,548 patients with breast cancer younger than 40 years of age treated over a period of 15 years and found younger women to be at an increased risk of dying than their older control groups if diagnosed with Stage I and II disease. The risk of death was reduced for stage IV disease in these patients (Gnerlich et al., 2009). Breast conservative therapy has an established role in management of early stage breast cancer and has results comparable with mastectomy (Fischer et al., 2002; Kim et al., 2005; Litiere et al., 2012). After 20 years of follow up results of NSABP B-06 trial showed no significant difference in recurrence and survival rates for patients who received BCT versus mastectomy (Fischer et al., 2002). In younger women, BCT has been associated with increased risk of local recurrence but similar and occasionally better overall survival in selected patients when compared with mastectomy (Vrieling et al., 2003; Kroman et al., 2004; Bantema-Joppe et al., 2011). Kroman and colleagues in their population based series showed no difference in overall survival between younger patients who received

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BCT versus mastectomy despite and increased rate of local recurrence (Kroman et al., 2004). It was shown that 41% of all female cancers in Pakistan originated from breast with a mode age at presentation of 40 years and a median of 50 (Khokher et al., 2012). There is no data from Pakistan that reports outcomes of breast conservative therapy in younger patients with invasive breast cancer and compares them with older patients.

The objective of this study was to determine locoregional recurrence free, disease free and overall survival in women younger than 40 years of age undergoing breast conservative therapy for invasive breast cancer and compare it with their older counterparts.

Materials and Methods

Patients who underwent breast conservative therapy at Shaukat Khanum Memorial Cancer Hospital and Research Centre from 1997-2009 were retrospectively reviewed. A total of 928 patients underwent breast conservation. Patients who did not have invasive breast cancer and/or had significant missing data were excluded. A total of 806 patients were included in the study.

Institutional details

Breast conservative therapy comprised of surgery and radiation. Lumpectomy was performed in all patients and adjuvant radiation (50 Gray) to the breast with boost to the tumor bed (10 Gray) was the standard. Bilateral mammography was performed in all patients. In addition all patients had bilateral ultrasound (US) of the breast and axilla. Magnetic resonance imaging (MRI) was reserved for patients with inconclusive mammography due to dense breasts. All patients were discussed in multidisciplinary team meeting after initial workup and a treatment plan was finalized. Patients with locally advanced tumors and node positive disease received neoadjuvant chemotherapy. In these patients, axillary status was determined either on needle aspiration of clinically suspicious axillary nodes or US guided needle aspiration of clinically silent but radiologically suspicious nodes. From 2005 onwards, sentinel lymph node biopsies were performed and axillary dissection was reserved for patient positive on SLNB or needle aspiration of axillary lymph nodes. If there were no suspicious nodes on imaging, staging sentinel lymph node biopsy (SLNB) was performed before initiation of neoadjuvant chemotherapy. If patients had positive axillary lymph nodes, they underwent axillary dissection after completion of neoadjuvant chemotherapy at the time of lumpectomy. Patients who underwent upfront surgery had sentinel lymph node biopsy performed at the time of lumpectomy. If SLNB was positive, they had axillary dissection. The standard at our institute was to perform Level I and II axillary dissection. Level III was only removed if clinically involved. Main indication of adjuvant chemotherapy was T2 tumors and above, nodal positivity and poor differentiation. Post operatively patients were followed 6 monthly with yearly mammograms.

Statistics

In the current study, patients were divided into early (age ≤40 years) and late onset (>40 years) groups. A total of 401 patients with early and 405 patients with late onset breast cancer were included. Demographics, histopathological factors and treatment modalities were compared for both groups. Adverse events including local, regional and distant failures and deaths were compared between the two groups. Local failure was defined as recurrence of breast cancer in operated breast or chest wall. Regional failure was defined as recurrence in ipsilateral axillary, supraclavicular or internal mammary lymph nodes. All other failures were defined as distant failures. Locoregional recurrence free survival (LRRFS) was defined as the time from date of surgery to development of a locoregional failure. Disease free survival (DFS) time was defined as time from surgery to development of a local, regional or distant failure. Overall survival (OS) was defined as the time from surgery to death of patient irrespective of cause or loss to follow up. For categorical variables chi square test was used. Estimated 5 year LRRFS, DFS and OS was calculated using Kaplan Meier survival curves and Log rank test was used to determine significance. In addition, factors that were found significant on univariate analysis were included in multivariate analysis to determine their independent significance. Cox hazard model was used for this purpose. Hospital institutional review board granted exemption from formal review for this study.

Results

Patient characteristics

Median follow up was 4.31(0.1-15.5) years. Median age at presentation was 34.62 years (17-40) and 51.89 years (41-82) for two groups. Table 1 represents the demographics by histopathological variables and treatment modalities. Early onset patients had a significantly high number of poorly differentiated (249 versus 189) (p<0.0001) and advanced tumors (75 versus 44) (p=0.002).Triple negative tumors were also more common in younger patients (113 versus 67)(p<0.0001). Patients older than 40 years received hormonal therapy more often than their younger counterparts (255 versus 215) (p=0.007). This probably reflects the high numbers of ER/PR +ve tumors in this group.

Adverse events

Local recurrences were significantly high in younger patients (26 versus 13) (p= 0.03). Regional failures were also more common in younger patients but were not statistically significant (8 versus 5). Distant metastasis and deaths were more frequently observed in older patients however the difference did not reach statistical significance. Table 2 represents the results.

Survival analysis

The Estimated 10 year LRRFS, DFS and OS in two groups was 86% versus 95%, 70 % versus 70% and 63% versus 75% respectively. Although a difference existed, it did not reach statistical significance for LRRFS (p=0.1), DFS (p=0.5) and OS (p=0.1) in two groups. Figure 1 represents the results.

Univariate and multivariate analysis

On Cox univariate analysis tumor size stage and nodal involvement were statistically significant variables for locoregional recurrence. On multivariate analysis tumor size stage was the only independent predictor of locoregional recurrence. Advanced tumor size (T3/

T4) was associated with increased risk of locoregional recurrence [(HR of 3.141) (95%CI 1.6-5.9) (p<0.0001)]. For disease free survival, tumor size, nodal involvement and hormonal therapy were statistically significant variables on univariate analysis. All these factors were found to be independent predictors of local/regional/distant recurrence on multivariate analysis as shown in Table 3. On univariate analysis ER status, tumor size stage,

Table 1. Patient Characteristics and Treatment Modalities

		Age ≤ 40 N=401 Number	%	Age >40 N=405 Number	%	p values
Family history	Positive	63	16	54	13	NS
	Negative	283	70	298	73	
	Unknown	55	14	53	14	
Laterality	Left	188	47	210	52	NS
	Right	204	51	192	47	
	Bilateral	9	2	3	1	
Histology	Infiltrating Ductal	384	96	389	96	NS
	Infiltrating Lobular	6	1	8	2	
	Others	11	3	8	2	
Grade	Well Diff	21	5	25	6	<0.0001
	Moderately	119	30	180	44	
	Poorly	249	62	189	47	
	Unknown	12	3	11	3	
ER status	Positive	177	44	240	59	<0.0001
	Negative	218	54	160	40	
	Unknown	6	2	5	1	
PR status	Positive	177	44	220	54	0.015
	Negative	218	54	180	45	
	Unknown	6	2	5	1	
Her 2 neu	Positive	60	15	88	22	0.007
	Negative	231	58	192	47	
	Unknown	110	27	125	31	
Triple negative	Yes	113	28	67	16	<0.0001
	No	75	19	60	15	
	Unknown	213	53	278	69	
Tumor stage	T1/T2	326	81	361	89	0.002
	T3/T4	75	19	44	11	
Nodal involvement	N0	215	54	202	50	NS
	N+	186	44	203	50	
Overall Stage	I	44	11	53	13	NS
	II	270	67	266	66	
	III	87	22	86	21	
Neo adjuvant	Yes	107	27	87	21	NS
	No	294	73	318	79	
Adjuvant chemo	Yes	269	67	259	64	NS
	No	132	33	146	36	
Hormonal	Yes	215	54	255	63	0.007
	No	186	46	150	37	

Table 2. Adverse Events in Two Groups

	Age≤40 Number(%)	Age>40 Number(%)	Total Number	p value
Local Failures	26 (67)	13 (33)	39	0.03
Regional Failures	8 (61)	5 (39)	13	NS
Distant Failures	65 (46)	75 (54)	140	NS
Deaths	66 (46)	76 (54)	142	NS
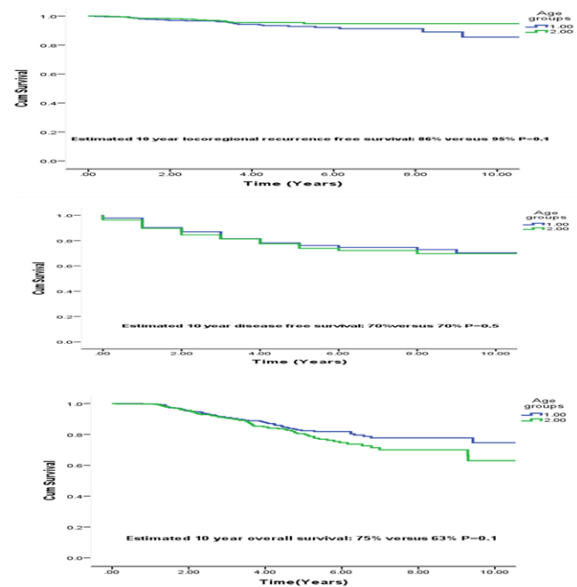
Figure 1. Estimated 10 year Locoregional Recurrence Free, Disease Free and Overall Survival in Early and Late Onset Breast Cancer Patients Undergoing Breast Conservative Therapy

Table 3. Significant Variables on Multivariate Analysis for Locoregional Recurrence, Disease Free and Overall Survival HR Hazard Rate CI Confidence Interval

			HR	95% CI	p value
Locoregional recurrence free status	Tumor stage	T1/T2	1	1.658-5.95	<0.0001
		T3/T4	3.141		
Disease free survival	Tumor stage	T1/T2	1	1.30-2.670	0.001
		T3/T4	1.866		
	Nodal involvement	N0	1	1.151-2.121	0.004
		N+	1.562		
	Hormonal therapy	No	1	0.502-0.912	0.01
		Yes	0.677		
Overall survival	Tumor Stage	T1/T2	1	1.419-3.011	<0.0001
		T3/T4	2.067		
	Nodal involvement	N0	1	1.25-2.462	0.001
		N+	1.754		
	Hormonal Therapy	No	1	0.409-0.8	0.001
		Yes	0.572		

nodal involvement and hormonal therapy were significant variables for overall survival. Tumor size stage, nodal involvement and hormonal therapy were independent predictors of overall survival. The risk of death was increased for advanced tumor size (T3/T4) and presence of nodal involvement (N+) i.e. [(HR 2.06) (95%CI 1.41-3.01) (p<0.0001)] and [(HR 1.75) (95%CI 1.25-2.46) (p=0.001)] respectively. Use of hormonal therapy resulted in a decrease in risk of death [(HR 0.57) (95%CI 0.49-0.8) (p=0.001)]. Table III represents significant variables. After adjustment for these independent factors age <40 or >40 years did not have an impact on locoregional recurrence, disease free and overall survival.

Discussion

The present study showed similar long term locoregional recurrence free, disease free and overall survival after breast conservative therapy in women younger than 40 years of age when compared to older women. These findings are consistent with previous reports of long term survival and locoregional control between younger and older patients) (Anderson et al., 1995; Chia et al., 2004; Bharat et al., 2009; Wei et al., 2010; Kheirelseid et al., 2011). There were significant differences between women younger than 40 years of age and their counterparts with respect to distribution of various histopathological and receptor status characteristics. Younger patients had significantly high number of advanced tumors with poor histopathological and receptor status characteristics. Despite these differences, locoregional recurrence free survival, disease free survival and overall survival in these two groups were similar.

Different age cut offs have been used to differentiate younger patients from their older counterparts and a variable range between 30-50 years is reported (Kroman et al., 2004; Elkum et al., 2007; Kwong et al., 2008; Mamoon et al., 2009; Gabriel et al., 2010; Kheirelseid et al., 2011). A cut off value of 40 has been used by in a number of studies to achieve a significant sample size as the incidence of breast cancer is very low at lower age limits. The risk of cancer falls from 6.6% for patients younger than 40 years to 2.4% at 35 years and 1 % under 30 years of age (Anders et al., 2009). For patients who received BCT at our institute, nearly half of the patients belonged to younger age group. This represents a significant patient population and is strikingly different from age specific patient distribution reported in the West. Indeed it has been shown that breast cancer in women younger than 40 years of age is on the rise in Asian population (Thapa et al., 2013; Keramatina et al., 2014; Wang et al., 2014). In parts of the world with well developed screening programs, routine screening is not performed for women <40 years of age due to low incidence of cancer in this age group. As a result, younger patients are not picked up on screening with early stage cancer and present when disease is well advanced and merits clinical attention (Foxcroft et al., 2004; Bollet et al., 2007). This in part explains the advanced stage at presentation for younger patients in regions with well developed screening programs. This explanation is not plausible in our population where screening programs have not been put into practice and factors like consanguinity and differential genetic makeup have been held responsible for younger women presenting with advance disease (Liede et al., 2003). In addition it has been shown that lack of awareness plays a major role in late presentation in Pakistani women and as much as 39% patients consider breast symptoms to be harmless in initial stages (Memon et al., 2013).

There is accumulating evidence associating worse outcomes in early onset breast cancer with underlying aggressive histopathological and receptor status characteristics. Lack of estrogen and progesterone receptors, poor grade of tumors and over expression of Her 2 Neu receptor have been linked to poor outcomes (Colleoni et al., 2002; Elkum et al., 2007; Anders et al., 2008; Kheirelseid et al., 2011; Miles et al., 2012). In the present study, tumor size, grade and receptors status characteristics were significantly different between the two groups. Younger patients had a higher number of poorly differentiated, triple negative tumors with advanced size. Despite differences in patient characteristics between two age groups, no long term difference in survival was observed. Conflicting results have been reported regarding role of young age as an independent predictor of locoregional recurrence and survival (Anderson et al., 1995; Chia et al., 2004; Rapiti et al., 2005; Elkum et al., 2007; Gnerlich et al., 2009; Kheirelsaid et al., 2011). Kheirelsaid and colleagues showed that despite differences in histopathological characteristics, there was no difference in local recurrence free survival in patients who received BCT versus mastectomy (152 versus 102 months)(p=0.45). They also showed no difference in OS (243 *vs* 299months) (p=0.57) between women younger than 40 years with those over forty (Kheirelsaid et al., 2011).

As evidence regarding association between biologically unfavorable tumors and young age accumulates, some have opted for more aggressive intervention for this patient group (Gnerlich et al., 2009; Miles et al., 2012). However literature remains divided on optimal management strategy for young age patients (Livi et al., 2010; Kheirelseid et al., 2011; Miles et al., 2012). The risk of local recurrence might increase by 7% per year for every decrease in year under the age of 40 for patients who undergo BCT (Bollet et al., 2007). Voogd and colleagues reported a risk of local recurrence 9 times higher in patients younger than 35 years who received BCT versus patients >60 years of age [(hazard ratio, 9.24; 95% confidence interval (CI), 3.74 to 22.81)] (Vooged et al., 2001). The recurrence risk was similar in these age groups after mastectomy. It has been reported that the annual risk of recurrence remains unchanged in a woman's life after treatment of breast cancer and translates to an increased cumulative risk of recurrence in younger women who have more years to live than their older counterparts (Kimura et al., 2007). In the present study, significant difference in local recurrence rate was found between the two age groups but regional and distant failures did not differ significantly. In addition number of mortalities, 10 year locoregional recurrence free, disease free and overall survival was not much different in two age groups. Independent predictors

of survival included tumor size, nodal involvement and hormonal therapy which support the previously published literature (Elkum et al., 2007; Miles et al., 2012). In the present study, despite significantly high number of T3/T4 tumors in younger patients; nodal involvement and overall stage did not vary much between groups.

Use of adjuvant hormonal therapy in younger patients with breast cancer has come to lime light with results of some recent trials (Aebi et al., 2000; EBCTCG, 2005; Morales et al., 2007). A meta analysis of adjuvant chemotherapy followed with tamoxifen for 5 years in early breast cancer in patients with ER +ve tumors showed an additional reduction in mortality of 31% in patients <50 years of age. The observed reduction in mortality was higher for patients <50 than patients in 51-69 age group (EBCTCG, 2005). Morales and colleagues randomized 1724 patients with operable breast cancer who received surgery and adjuvant chemotherapy into tamoxifen versus no tamoxifen arms. They observed a significantly improved recurrence free survival for patients with ER/PR +ve tumors with use of tamoxifen for 3 years (77% *vs* 70%) (p=0.014) (Morales et al., 2007). In the current study, statistically significant difference was present between two age groups with respect to use of hormonal therapy. Uneven distribution of ER/PR receptors between two groups is probably responsible for this difference. Furthermore, on multivariate analysis hormonal therapy was the only independent predictor of overall survival out of all the different medical interventions utilized. Use of hormonal therapy independently led to a decrease in risk of death. However it is difficult to assess if there were no underlying confounding interactions between use of hormonal therapy and biological behavior of cancers in the study population.

Due to retrospective nature of this study, histopathological and receptor information was not available for all patients. To account for this, patients with missing data were analyzed as a separate group for survival. In addition cancer specific mortality could not be calculated which might be significantly different in younger and older patients despite similar overall survival. Matching between two age groups with respect to patient characteristics was not possible due to limited number of patients in control group. Nevertheless multivariate analysis was performed to determine independent predictors of survival and significance of age groups was assessed after adjustment for these factors.

In conclusion, the current study provides valuable insight into characteristics of breast cancer patients in Pakistan. Breast cancer under the age of forty is not as uncommon in our population as it is in most other parts of world. Absence of screening programs and various social issues are responsible for delayed presentation which results in close to half of the population presenting with large tumors. Despite significant differences in histopathological and receptor characteristics, outcome in younger patients receiving breast conservative therapy is comparable to older counterparts in our population and is re assuring. Self-awareness programs and screening policies need to be developed to detect breast cancer at early stage and improve long term outcome for this malignancy.

References

Adami HO, Malker B, Holmberg L, Persson I, Stone B (1986). The relation between survival and age at diagnosis in breast cancer. *N Engl J Med*, **315**, 559-63.

Anderson BO, Senie RT, Vetto JT, et al (1995). Improved Survival in Young-Women with Breast-Cancer. *Ann Sur Oncol*, **2**, 407-15.

Aebi S, Gelber S, Castiglione-Gertsch M, et al (2000). Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer? *Lancet*, **355**, 1869-74.

Anders CK, Hsu DS, Broadwater G, et al (2008). Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol*, **26**, 3324-30.

Anders CK, Johnson R, Litton J, Phillips M, Bleyer A (2009). Breast cancer before age 40 years. *Semin Oncol*, **36**, 237-49.

Bantema-Joppe EJ, de Munck L, Visser O, et al (2011). Early-stage young breast cancer patients: impact of local treatment on survival. *Int J Radiat Oncol Biol Phys*, **81**, 553-9.

Bollet MA, Sigal-Zafrani B, Mazeau V, et al (2007). Age remains the first prognostic factor for loco-regional breast cancer recurrence in young (<40 years) women treated with breast conserving surgery first. *Radiother Oncol*, **82**, 272-80.

Bharat A, Aft RL, Gao F, Margenthaler JA (2009). Patient and tumor characteristics associated with increased mortality in young women (<= 40 years) with breast cancer. *J Surg Oncol*, **100**, 248-51.

Chung M, Chang HR, Bland KI, Wanebo HJ (1996). Younger women with breast carcinoma have a poorer prognosis than older women. *Cancer*, **77**, 97-103.

Colleoni M, Rotmensz N, Robertson C, et al (2002). Very young women (<35 years) with operable breast cancer: features of disease at presentation. *Ann Oncol*, **13**, 273-9.

Chia KS, Du WB, Sankaranarayanan R, et al (2004). Do younger female breast cancer patients have a poorer prognosis? Results from a population-based survival analysis. *Int J Cancer*, **108**, 761-5.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, **365**, 1687-717.

Elkum N, Dermime S, Ajarim D, et al (2007). Being 40 or younger is an independent risk factor for relapse in operable breast cancer patients: the Saudi Arabia experience. *BMC Cancer*, **7**, 222.

Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, et al (2002). Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*, **347**, 1233-41.

Foxcroft LM, Evans EB, Porter AJ (2004). The diagnosis of breast cancer in women younger than 40. *Breast*, **13**, 297-306.

Gnerlich JL, Deshpande AD, Jeffe DB, et al (2009). Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. *J Am Coll Surg*, **3**, 341-7.

Gabriel CA, Domchek SM (2010). Breast cancer in young women. *Breast Cancer Res*, **12**, 212.

Kroman N, Holtveg H, Wohlfahrt J, et al (2004). Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. *Cancer*, **100**, 688-93.

Kim KJ, Huh SJ, Yang JH, et al (2005). Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. *Jpn J Clin Oncol*, **35**, 126-33.

Kimura M, Yanagita Y, Fujisawa T, et al (2007). Study of time course changes in annual recurrence rate for breast cancer. Data analysis of 2209 patients for 10 years post surgery. *Breast Cancer Res Treat*, **106**, 407-11.

Kwong A, Cheung P, Chan S, Lau S (2008). Breast cancer in Chinese women younger than age 40: are they different from their older counterparts? *World J Surg*, **32**, 2554-61.

Kheirelseid EH, Boggs JM, Curran C, et al (2011). Younger age as a prognostic indicator in breast cancer: a cohort study. *BMC Cancer*, **11**, 383.

Khokher S, Qureshi MU, Riaz M, Akhtar N, Saleem A (2012). Clinicopathologic profile of breast cancer patients in Pakistan: ten years data of a local cancer hospital. *Asian Pac J Cancer Prev*, **13**, 693-8.

Keramatinia A, Mousavi-Jarrahi SH, Hiteh M, Mosavi-Jarrahi A (2014). Trends in incidence of breast cancer among women under 40 in Asia. *Asian Pac J Cancer Prev*, **15**, 1387-90.

Liede A, Malik IA, Aziz Z, et al (2002). Contribution of BRCA1 and BRCA2 Mutations to Breast and Ovarian Cancer in Pakistan. *Am J Hum Genet*, **71**, 595-606.

Livi L, Meattini I, Saieva C, et al (2010). The impact of young age on breast cancer outcome. *Eur J Surg Oncol*, **36**, 639-45.

Litiere S, Werutsky G, Fentiman IS, et al (2012). Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol*, **13**, 412-9.

Morales L, Canney P, Dyczka J, et al (2007). European Organisation for Research and Treatment of Cancer Breast Group; Scottish Breast Cancer Trials Group. Postoperative adjuvant chemotherapy followed by adjuvant tamoxifen versus nil for patients with operable breast cancer: a randomised phase III trial of the European Organisation for Research and Treatment of Cancer Breast Group. *Eur J Cancer*, **43**, 331-40.

Mamoon N, Hassan U, Mushtaq S (2009). Breast carcinoma in young women aged 30 or less in Northern Pakistan - the Armed Forces Institute of Pathology experience. *Asian Pac J Cancer Prev*, **10**, 1079-82.

Miles RC, Gullerud RE, Lohse CM, et al (2012). Local recurrence after breast conservation surgery: Multivariable analysis of risk factors and the impact of age. *Ann Surg Oncol*, **19**, 1153-9.

Memon ZA, Shaikh AN, Rizwan S, Sardar MB (2013). Reasons for patient's delay in diagnosis of breast carcinoma in Pakistan. *Asian Pac J Cancer Prev*, **14**, 7409-14.

Rapiti E, Fioretta G, Verkooijen HM, et al (2005). Survival of young and older breast cancer patients in Geneva from 1990 to 2001. *Eur J Cancer*, **41**, 1446-52.

Sidoni A, Cavaliere A, Bellezza G, Scheibel M, Bucciarelli E (2003). Breast cancer in young women: clinicopathological features and biological specificity. *Breast*, **12**, 247-50.

Shaukat U, Ismail M, Mehmood N (2013). Epidemiology, major risk factors and genetic predisposition for breast cancer in the Pakistani population. *Asian Pac J Cancer Prev*, **14**, 5625-9.

Thapa B, Singh Y, Sayami P, et al (2013). Breast cancer in young women from a low risk population in Nepal. *Asian Pac J Cancer Prev*, **14**, 5095-9.

Voogd AC, Nielsen M, Peterse JL, et al (2001). Differences inrisk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol*, **19**, 1688-97.

Vrieling C, Collette L, Fourquet A, et al (2003). EORTC Radiotherapy, Breast Cancer Groups. Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? *Eur J Cancer*, **39**, 932-44.

Wei R, Lau SS, Cheung PS (2010). Breast carcinoma in Chinese women: does age affect treatment choice and outcome? *Asian J Surg*, **33**, 97-102.

Wang LW, Yang GF, Chen JM, et al (2014). A clinical database of breast cancer patients reveals distinctive clinico-pathological characteristics: a study from central China. *Asian Pac J Cancer Prev*, **15**, 1621-6.