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RESEARCH

Retrospective Analysis of Clinicopathological Characteristics and Family History Data of Early-Onset Breast Cancer: A Single-Institutional Study of Hungarian Patients

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Abstract Patients at young age (≤ 35 years) diagnosed with breast cancer (BC) are considered to have poor prognosis. The aim of the present study was to retrospectively analyse clinicopathological characteristics and prognosis in a group of young BC patients. We included women diagnosed with invasive breast carcinoma younger than/or at the age of 35 years. Between 1999 and 2009, 107 women with early-

onset BC were selected from the database of the 2nd Department of Pathology at Semmelweis University. For clinicopathological comparison, 55 women (36–45 years), 214 women (46–65 years), 110 women (66–75 years) and 58 women ($76 \leq$ years) were also included in the analysis. Family history, clinicopathological and follow-up data were analysed. The tissue specimens were reviewed for histological type, nuclear grade, and estrogen receptor (ER), progesterone receptor (PgR), Ki67 and HER2 status (IHC4). The mean age in the study group was 31.6 years at the time of diagnosis. Histology showed a high incidence of grade III tumours in this group of patients (67.9 %), while only four cases (3.8 %) were considered grade I. According to the immunohistochemical results, 35.3 % of the study cases were considered as Luminal B (LumB: either being highly proliferative or co-expressing HER2) and 33.3 % as triple negative breast carcinomas (TNBC). The detailed questionnaire related to family history was completed and received in 49/107 cases (45.8 %). Analysis of these data revealed an affected family history of breast or ovarian carcinoma in first and second degree relatives in 51.0 %. A high proportion (52.0 %) of TNBC was observed among young women with a family history of the disease. Survival analysis of the 107 patients showed that 25 (23.3 %) women died until 31 December 2012. No significant difference in survival was detectable considering the regimen of systemic treatment ($p=0.188$). Regarding clinicopathological parameters, the immunophenotypes, grade, pT and pN values differed substantially between the age groups ($p=0.001$, for all), and the shortest relapse-free survival was seen among the youngest BC patients. This analysis illustrates that breast cancer arising in young women is characterized by the presence of less favorable subtypes such as LumB and TNBC. The increased proportion of TNBC was especially remarkable in the

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group of patients presenting with family history of the disease. The fact that a high rate of death occurred and no significant difference in OS were notable regarding the scheme of systemic therapies (neoadjuvant vs. adjuvant) highlight the necessity of the development of new treatment strategies.

Keywords Breast cancer · Early-onset · Family history

Introduction

Breast cancer is one of the most common cause of cancer-related death among women worldwide. According to the Hungarian National Cancer Registry (GRID), 6807 women were diagnosed with breast cancer in 2007 [1]. Although, breast cancer is relatively uncommon in young women it is considered to be the most frequent cancer in women <40. It is generally accepted that up to 4 % of breast cancer cases occur in women younger than 35 years [2, 3]. In many studies age younger than 35 years is considered as an independent predictor of poor outcome and patients <35–40 years at the time of diagnosis have been found to have a poorer prognosis compared with older patients, furthermore, multiple data have demonstrated that younger patients treated with breast carcinomas have a significantly higher rate of local recurrence compared with older patients [4, 5]. The group of Hanna et al. found that young women with breast carcinomas have a higher risk of dying of the disease as compared to middle-aged breast cancer patients even if carcinomas are diagnosed early and patients receive state-of-the-art treatment [5]. These results could partly be explained by the fact that young women are diagnosed more often at advanced stages, present unfavorable tumour characteristics or have a family history of breast cancer [6–9]. In a very recent study of Lin et al. it is suggested that these cancers occurring at a very young age may be considered as a distinct disease entity [10]. Due to the relatively low frequency of breast carcinomas in women aged ≤ 35 years there are few data on how risk factors predict breast cancer in younger women and the prognostic factors in this group have yet to be established. A proportion of breast carcinoma arising at young age are the so called pregnancy associated breast carcinomas (PABC). The incidence of breast cancer in pregnancy appears higher than previously reported with women over 35 being at greater risk [11]. In certain families it is clear that there is a predisposition to develop breast cancer inherited in an autosomal dominant way [12]. Previous studies have established that family history of the disease along with atypical ductal hyperplasia, or atypical lobular hyperplasia and carcinoma in situ (DCIS or LCIS) are important predictors of breast cancer risk [12]. The same study found that for women ≤ 35 years a significant family

history of breast cancer may be a stronger predictor for breast cancer development than the high risk lesions mentioned above [12]. The role of mutations in the tumour suppressor genes BRCA1 and BRCA2 has been extensively studied and it is considered that women who are carriers of these mutations present a high risk of developing breast cancer by the age of 50 [13, 14]. Although, testing for BRCA1 and BRCA2 mutations is expensive, analysis of these genes has important implications for the clinical management of people carrying these mutations. Several algorithms that predict the likelihood of carrying BRCA1 and BRCA2 mutations are being currently used in clinical practice [15–17].

According to pathological parameters, young women are more likely to have high grade hormone receptor negative tumours with a high proliferation rate and lymphovascular invasion [9, 18, 19]. In the study of Lin et al. it is presented that for women ≤ 35 years high Ki67 expression, TP53 mutations, ER negative status and HER2 overexpression were associated with shorter overall survival, and TP53 mutations, Ki67, HER2 overexpression are strong prognostic factors for these women [10].

The aim of the present study was to retrospectively evaluate clinicopathological characteristics and prognosis in a selected group of young Hungarian breast cancer patients ≤ 35 years.

Patients and Methods

Study Group

In our study we included patients younger than or at the age of 35 diagnosed with invasive breast carcinoma (group nr. 1). During the period between 1999 and 2009 107 women met these criteria altogether from the files of the 2nd Department of Pathology, Semmelweis University, Budapest, Hungary. Slides and blocks were identified from each of these patients, and clinicopathological and follow-up information were obtained. For comparison, 55 women (36–45 years) (group nr. 2), 214 women (46–65 years) (group nr. 3), 110 women (66–75 years) (group nr. 4) and 58 women (76 \leq years) (group nr. 5) diagnosed with breast cancer were also included in the clinicopathological analysis. Those cases, which were screen-detected breast cancers were excluded from the study.

Pathological Evaluation

Specimens were reviewed for histological type, nuclear grade and were stained for ER, PgR, Ki67, HER2 immunohistochemistry (IHC), as described further on and presented in Table 1. Histological grading was performed according to

Table 1 Source and dilutions of the four immunohistochemical markers analysed in this study

Antigen	Distributor, clone, dilution
ER	Novocastra, 6F11 (1:200)
PgR	Novocastra, 312 (1:200)
HER2	Novocastra, CB11 (1:150)
Ki-67	DAKO, MIB1 (1:100)

the Nottingham grading system. Proxies of the molecular subtypes were determined by immunohistochemical stains of ER, PgR, HER2, Ki67 and HER2 FISH.

Immunohistochemical reactions (IHC) were performed with automated immunostainer system (Ventana ES, Ventana Medical Systems, Inc., Tucson, AZ, USA) according to the manufacturer's instructions using the antibodies given in Table 1. The immunohistochemical slides were evaluated by two investigators independently (JK and LM). ER and PgR statuses were given according to the Allred scoring system, Ki67 positivity was measured as the ratio of positive tumour cell nuclei in the tumour and HER2 IHC was evaluated according to the guidelines, on a 0–3 scale standard protocol.

Fluorescent in situ hybridization (FISH) evaluation was performed by using HER2/CE17 Poseidon probes (KBI-10735, Kreatech Diagnostics, Amsterdam, The Netherlands). FISH results were evaluated according to the standard protocol: non-amplified if the HER2/CE17 ratio was less than 1.8, equivocal if this ratio was between 1.8 and 2.2, and amplified if the HER2/CE17 ratio was over 2.2. When discordant with HER2 IHC, the FISH results were taken into consideration.

ER and/or PgR expressing tumours with lower than 20 % Ki67 expression were considered luminal A (LumA). For ER and/or PgR and HER2 positive tumours and ER and/or PgR expressing tumours with more than or equal to 20 % Ki67 index, luminal B subtype (LumB) was assigned. Triple negative breast cancers (TNBC) were ER, PgR, HER2 negative. The HER2 overexpressing (3+ by IHC) or 2+ cases showing HER2 gene amplification by FISH and in the same time ER and PgR negative tumours were considered as the HER2+ subgroup.

Family History

A detailed questionnaire was composed and sent to the young breast cancer patients/affected families.

Statistical Analysis

The differences between the groups were analysed using chi-square test and the Kruskal-Wallis test with subsequent

post-hoc method. Relapse-free survival analyses were performed using the Kaplan-Meier method. Overall survival was determined as the time period from initial diagnosis to the time of death. The comparison between survival functions for different strata was assessed with the log-rank test. Statistical significance was confirmed when p values were < 0.05 . Statistical analysis was performed using Statistica 9.0 software (StatSoft, Tulsa, OK, USA) and SPSS 17 (SPSS Inc., Chicago, IL, USA).

Results

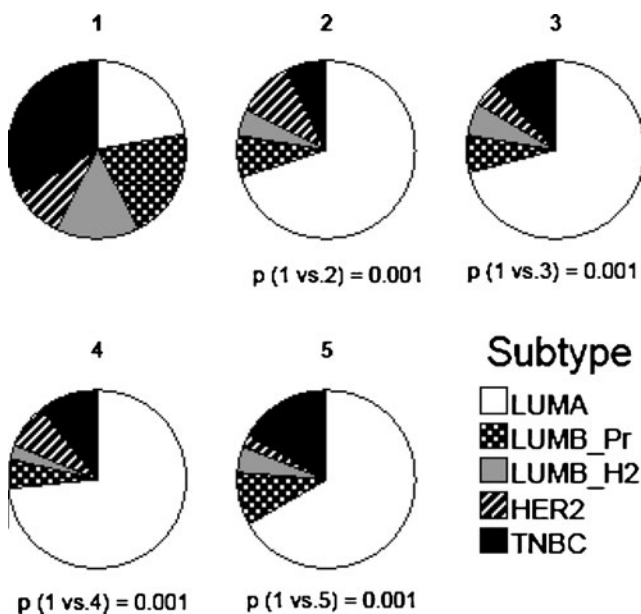
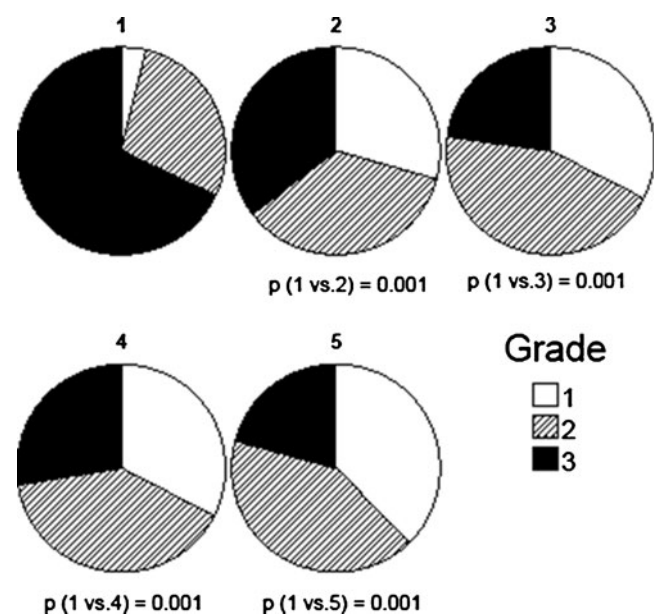
Clinicopathological Assessment Median age at the time of diagnosis in the early-onset age group was 31.64 years, the youngest patient being diagnosed with breast carcinoma at the age of 22. Histology showed a high incidence of grade III tumours in this group of patients (70 cases, 67.96 %), while only four cases (3.88 %) were considered grade I. In 29 cases (28.16 %) grade II cancer was diagnosed whereas in four cases (3.73 %) we have no data (cytology specimens only). According to the immunophenotypical results, which were available in 99 patients, 22 tumours were enrolled in LumA (22.22 %), 35 in LumB (35.35 %), 9 in HER2+ (9.09 %) and 33 in TNBC (33.33 %) subgroups.

The respective groups had a mean age at time of diagnosis as follows, 36–45 years: 41.95, 46–65 years: 54.53, 66–75 years: 70.09 and over 76 years: 80.66. We have compared the tumour characteristics of the women included in the study, shown in Table 2. Significant difference was detected in the comparison of the subtypes and grades between the early-onset breast tumours and the other age groups ($p < 0.001$ for all, Figs. 1 and 2, respectively). Pathological “T” and “N” status also differed but tumour size measured in mm's was similar in the overall population (Supplementary Figure 1).

Family History The detailed questionnaire related to family history was completed and received in 49 cases (45.79 %). Analysis of these data revealed positive family history of breast or ovarian carcinoma reported in first and second degree relatives in 25 cases (51.02 %). In 13 cases (26.53 %) no family history of breast or ovarian carcinoma was mentioned, whereas in 11 cases (22.44 %) other types of tumours were mentioned in first and second degree relatives. By accepting that the number of cases analysed is low, interesting results were found when comparing the group of patients with family history with the group of patients without family history of breast or ovarian carcinomas. An increased proportion (52 %) of TNBC was observed among younger women with a family history of the disease whereas in the group of patients without family history of breast and

Table 2 Tumour characteristics of the 544 women included in the study

Age group		1	2	3	4	5	<i>p</i> (chi-sq.)
Number of cases		107	55	214	110	58	
Subtype	<i>LUMA</i>	22.22 %	70.00 %	70.90 %	73.33 %	66.67 %	0.001
	<i>LUMB_Pr</i>	20.20 %	7.50 %	6.72 %	5.33 %	9.52 %	
	<i>LUMB_H2</i>	15.15 %	5.00 %	5.97 %	2.67 %	4.76 %	
	<i>HER2</i>	9.09 %	10.00 %	4.48 %	8.00 %	2.38 %	
	<i>TNBC</i>	33.33 %	7.50 %	11.94 %	10.67 %	16.67 %	
Grade	<i>1</i>	3.88 %	29.41 %	32.61 %	32.65 %	37.74 %	0.001
	<i>2</i>	28.16 %	35.29 %	44.57 %	39.80 %	41.51 %	
	<i>3</i>	67.96 %	35.29 %	22.83 %	27.55 %	20.75 %	
T	<i>1</i>	31.91 %	10.74 %	11.62 %	13.52 %	11.61 %	0.001
	<i>2</i>	39.36 %	27.52 %	29.33 %	27.05 %	27.10 %	
	<i>3</i>	2.13 %	30.20 %	29.52 %	28.11 %	28.39 %	
	<i>4</i>	1.06 %	30.20 %	28.95 %	29.89 %	29.68 %	
	<i>y0</i>	5.32 %	0.00 %	0.00 %	0.00 %	0.00 %	
	<i>y1</i>	8.51 %	0.00 %	0.00 %	0.00 %	0.00 %	
	<i>y2</i>	6.38 %	0.00 %	0.00 %	0.00 %	0.00 %	
	<i>y3</i>	4.26 %	0.00 %	0.00 %	0.00 %	0.00 %	
	N	<i>0</i>	25.58 %	41.46 %	44.72 %	44.83 %	
<i>1</i>		27.91 %	51.22 %	51.22 %	46.55 %	52.17 %	
<i>2</i>		15.12 %	7.32 %	4.07 %	8.62 %	4.35 %	
<i>3</i>		3.49 %	0.00 %	0.00 %	0.00 %	0.00 %	
<i>y0</i>		13.95 %	0.00 %	0.00 %	0.00 %	0.00 %	
<i>y1</i>		6.98 %	0.00 %	0.00 %	0.00 %	0.00 %	
<i>y2</i>		4.65 %	0.00 %	0.00 %	0.00 %	0.00 %	
<i>y3</i>		2.33 %	0.00 %	0.00 %	0.00 %	0.00 %	

**Fig. 1** Differences between the subtypes in the early-onset breast tumours and the other age groups**Fig. 2** Differences between the grades in the early-onset breast tumours and the other age groups

ovarian carcinoma the LumA tumours were found in higher percentage (46.15 %).

Survival Analysis To assess the prognosis of all the age groups, the relapse-free survival using Kaplan-Meier analysis of the above mentioned 544 breast cancer patients was performed. The early-onset groups displayed the worse prognosis when compared to others (Fig. 3).

As of December 2012, 25 out of 107 (23.36 %) women in the young BC population died. Accepting that the number of cases with known family history was relatively low, we did not find significant association ($p=0.975$) between OS and negative family history versus a family history of breast or ovarian carcinoma in first and second degree relatives (Fig. 4a). No statistically significant differences were observed ($p=0.188$) when comparing OS in patients with negative family history and patients having a family history of other types of tumours (Fig. 4b). No significant differences in survival ($p=0.188$) were detectable between the applied (neoadjuvant vs. adjuvant) chemotherapy (Fig. 4c).

When analysing the subtype of tumours in the group of patients who died (25 pts) we found that the highest number of deaths was observed in the LumB subgroup (36 %), followed by the TNBC subtypes (32 %), LumA types (20 %) and HER2+ cases (12 %).

Treatment data for the early onset breast cancer patients included in this study was available in 56 cases. Of these cases 24 patients (22.42 %) received neoadjuvant therapy whereas 32 patients (29.90 %) received adjuvant therapy. In 51 cases (47.66 %) no treatment data was available. No significant differences in survival were detectable between

the therapeutic strategies, although there was a tendency showing benefit for neoadjuvant therapy.

In 15 cases, PABC was diagnosed. No significant differences were detected in OS when comparing the PABC with the other group of young patients (Fig. 4d).

Discussion

According to literature data, younger patients affected by breast carcinoma have poor outcome [6, 20, 21]. There are increasing efforts to identify the group of patients considered high risk with higher specificity and sensitivity and there are serious debates regarding the factors responsible for breast cancer development at young age.

Breast cancer risk in females is increased in case of having either a first degree relative with breast or ovarian carcinoma, or having more than one relative affected by this disease [22, 23]. The Cancer Collaborative Group on Hormonal Factors in Breast Cancer (CGoHFIB) has estimated the cumulative incidence of breast cancer up to the age of 80 for patients with various numbers of first degree relatives with the following cumulative incidence results: 7.8 % for patients with no affected family, 13.3 % with one first degree relative and 21.1 % for patients with two first degree relatives [23].

In our study, by analysing the cases where the family history was reported we found that in 51.02 % of the cases a family history of breast or ovarian carcinoma was reported in first and second degree relatives. This high prevalence of positive family history of breast and ovarian carcinoma highlights a considerable contribution of genetic factors to early-onset breast cancer. Similar results were described by Loman et al. in 2001 by analysing family history of breast and ovarian cancers in the Swedish population. They found that almost half of the women with early-onset breast cancer had a family history of breast or ovarian cancer. They also found that 9 % of early-onset breast cancer cases are associated with germline mutation in the BRCA1 or BRCA2 genes [24].

Recent results of Evans et al. showed that few mutations were found in young women (< 35) without family history, demonstrating the importance of accurate documentation of the affected family members. Their study also pointed out that among sporadic breast cancer patients mutations are generally present in grade III cases and TNBCs [25].

In our study we found a high incidence of grade III tumours, while only four cases were considered as grade I tumour. According to the immunophenotypical results, which were available in 99 patients, 22 tumours were enrolled in LumA (22.22 %), 35 in LumB (35.35 %), 9 in HER2+ (9.09 %) and 33 in TNBC (33.33 %) subgroups.

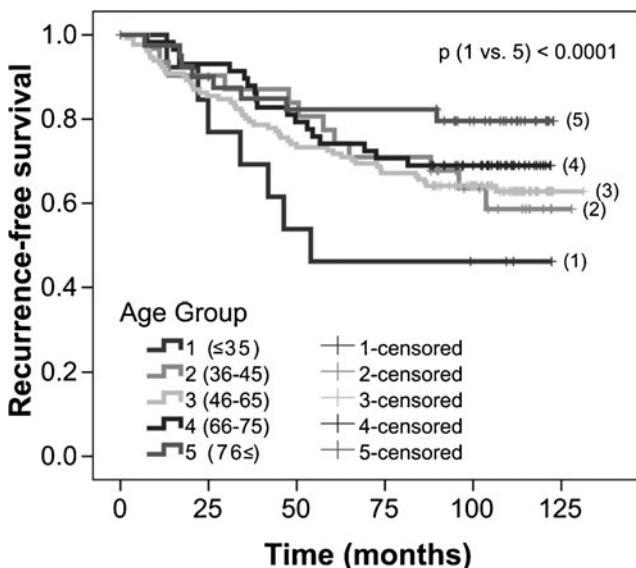
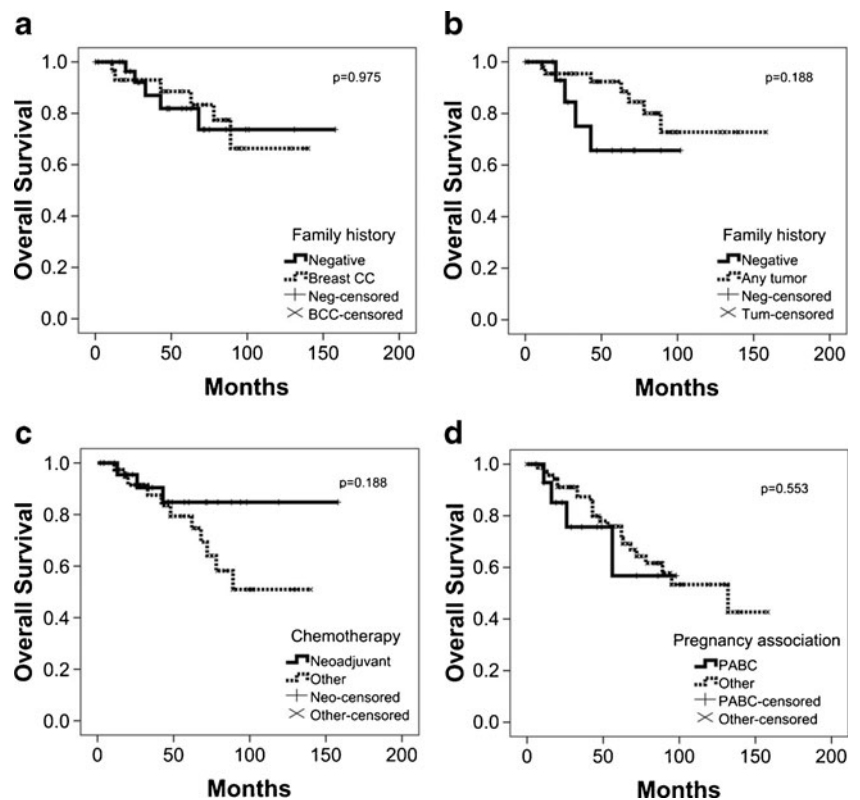


Fig. 3 The early-onset group displayed the worse prognosis when compared with the other groups

Fig. 4 No significant association between OS and negative family history versus a family history of breast or ovarian carcinoma in first and second degree relatives was detected (**a**). Survival of young breast cancer patients with negative family history versus positive family history of any tumour type other than breast carcinoma ($p=0.188$) (**b**). No significant differences in survival ($p=0.188$) were detectable between the applied therapies (neoadjuvant chemotherapy or adjuvant chemotherapy), although there was a tendency showing benefit of neoadjuvant therapy (**c**). No significant differences were detected in OS when comparing the PABC with the other group of young patients (**d**)



Patients with family history of breast or ovarian carcinomas were represented by increased proportion (52 %) among TNBC breast carcinoma cases when compared with the group of patients without family history of breast and ovarian carcinoma where the LumA tumours were found in higher percentage (46.15 %). In a very recent study by Jiang et al. by analysing a heterogenous population diagnosed with breast carcinomas it was found that in cancers diagnosed before the age of 50, women with a family history of breast cancer are more likely to have ER negative and PgR negative tumours compared to women without family history [26]. This information highlights the necessity of more detailed analyses of the family history especially in patients of younger age.

In 2011, van der Hage et al. found that for young patients, molecular subtype, tumour size and nodal status were independent prognostic factors for overall survival. They also mentioned that in their group consisting of 341 node-negative patients, patients with LumA tumours under 40 years of age had an overall survival rate of 94 % at 10 years compared with patients presenting basal-like tumours with only 72 % survival rate [27]. Another recent study found that breast cancer in younger women (less than 40 years of age) has distinct histopathological characteristics, but the authors did not find reduced survival in the younger patient group as compared with the group consisting of patients over 40 [28]. It is controversial how this differences present between breast carcinomas arising at the extremes age are explained. Anders

et al. suggest that these differences are strongly influenced by genes associated with intrinsic breast cancer subtype and grade both of which being correlated with age[29]. In an earlier study of Anders et al. it is presented that breast cancer arising in young women clearly represents a distinct biologic entity and is characterized by specific signaling pathway[30].

In our study, at the time of analysis 23.36 % of young BC patients died. An approximately similar high percentage of deaths was reported by van der Hage et al. in their study group consisting of patients less than 40 years of age [27]. The Korean Breast Cancer Society reported that young age was associated with a greater probability of death in breast cancer patients [31]. Upon analysing tumour subtypes in the group of patients who died we found that of the 25 patients, the highest number of deaths was observed in the LumB subgroup, followed by the TNBC subgroup, LumA subgroup and HER2+ subgroup.

We did not find significant association between OS and negative family history versus a family history of breast or ovarian carcinoma in first and second degree relatives. No significant differences in OS were detectable between the applied (neoadjuvant and adjuvant chemotherapy) regimens either.

The results presented in this study provide further negative data about breast cancer survival in relation to young age. We have found that breast cancer arising in young women is characterised by the presence of less favorable subtypes such

TNBC and LumB. The increased proportion of TNBC was especially remarkable in the group of patients with a family history of the disease. The fact that a high rate of death occurred irrespective of the applied therapies used suggests that new and more specific treatment guidelines should be developed in this patient group.

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