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Reproductive Factors and Breast Cancer Prognosis: The Possible Role of Cesarean Delivery

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The study has not been been presented previously in a congress or symposium.

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Objective: To evaluate the possible associations between tumor pathological characteristics and reproductive factors in women with breast cancer, including method of child delivery.

Materials and Methods: Patients diagnosed as breast cancer between January 2012 and April 2013 in Ankara University Hospitals who had at least one full term pregnancy were included. Data upon pathological prognostic features of tumors and reproductive history of patients were obtained from patient files.

Results: 434 patients with breast cancer were included. Mean age at the time of breast cancer diagnosis was 49.2±10.7 years. History of at least one cesarean delivery was present in 17% of the patients (n=75). Axillary lymph node positivity was related to younger age at first full-term pregnancy (p=0.018), and higher number of parities (p=0.001) in estrogen receptor positive (ER+) breast cancer patients. Although extracapsular invasion was related to shorter time interval since last parity to cancer diagnosis in the whole population (p=0.029), this association disappeared when patients were categorized according to ER status. However, in ER+ patients, history of cesarean delivery was associated with extracapsular invasion (p=0.023). Also, our findings indicated that patients with history of cesarean delivery were diagnosed with breast cancer at younger ages, and after a shorter time interval since last parity (p<0.001). Tumor size (p=0.001), grade (p=0.046), axillary lymph node positivity (p=0.001), lymphovascular invasion (p<0.001), and shorter duration of time since last parity to breast cancer diagnosis (p=0.029) were indicators of metastatic disease.

Conclusion: Our findings indicate that history of cesarean delivery may be associated with poor prognosis in ER+ patients with breast cancer.

Keywords: Breast cancer, cesarean, pregnancy, prognosis, reproductive history

INTRODUCTION

Breast cancer (BC) is the most common type of cancer besides skin cancer, and the second most common cause of cancer-related deaths following lung cancer among women worldwide [1, 2]. According to the latest report of American Cancer Society, lifetime risk of a woman to be diagnosed with BC is approximately 13%. Although BC mortality has declined gradually probably due to early detection by screening and advancing treatment methods [1], tumor related factors play an important role on disease prognosis. Tumor grade and stage, hormone receptor status along with Her-2/neu gene amplification, involvement of axillary lymph nodes, and other pathological features of the tumor such as extracapsular and lymphovascular invasion, and age at diagnosis are main prognostic indicators of BC [3-7].

Reproductive factors such as early menarche, late menopause, having first full-term pregnancy (FFTP) after age 30, not breastfeeding, and not having a full-term pregnancy are associated with BC risk [8], and possibly also prognosis [9-11]. The impact of reproductive history on BC prognosis has been subject to several studies, the outcomes of which have been contradictory [12-19]. It was suggested that reproductive factors may have effect not only on BC survival, but also on tumor characteristics [11]; or from a different point of view, reproductive factors may effect mortality by influencing tumor characteristics. To date, studies investigating the subject mostly focused on mortality, and only one included type of delivery as a part of reproductive history [20]. The rationale of including delivery method as a part of reproductive history is that plasma oxytocin levels differ between women having normal vaginal delivery and cesarean section [21-23], and oxytocin receptors have been shown and proven active in BC cells as in normal breast tissue [24]. Since oxytocin has been shown to inhibit cell proliferation in BC cell lines [25, 26], it seemed justifiable to include delivery method in our study as a part of reproductive history.

The main aim of this study is to evaluate the relationship between reproductive factors and BC tumor characteristics associated with disease prognosis. We also comparatively analyzed the components of reproductive history in BC patients with and without a history of cesarean delivery.

MATERIALS and METHODS

Patients who were followed up with the diagnosis of BC in Ankara University Hospitals between January 2012 and April 2013 were assessed retrospectively. Subjects with a history of at least one full term pregnancy were included. All patients had pathological confirmation of BC. Data upon pathological characteristics of the tumor (tumor size, axillary lymph node involvement, tumor grade, estrogen (ER), progesterone (PR) receptor and Her-2 expression, extracapsular or lymphovascular invasion status) were obtained from pathology examination reports. Information about patient characteristics and reproductive history were collected from patient files. As reproductive characteristics, we have evaluated number of pregnancies and child deliveries, delivery method,

age at first and last full-term pregnancies, time interval since last pregnancy to BC diagnosis, duration of lactation (as a total of all deliveries). Ages at menarche and menopause were recorded. History and duration of oral contraceptive (OC) use were also noted.

Patients were categorized as premenopausal or postmenopausal BC according to the time of diagnosis. All gestations, whether full-term or not, were included in the number of pregnancies while only full-term pregnancies were considered in statistical analysis. Patients were categorized according to their number of full-term pregnancies (1, 2, ≥3); age at FFTP (≤20, between 20-30, ≥30 years); and age at menarche (< 12, between 12-15, ≥15 years). Time interval since last pregnancy to BC diagnosis was considered as a continuous variable. Since the associations between reproductive factors and tumor characteristics could vary depending on ER expression, patients were further grouped as ER positive (ER+) and ER negative (ER-), and analyzed accordingly.

All processes in the study were in accordance with the ethical standards of the local institutional research committee (21-682-12) and with the 1975 Declaration of Helsinki, as revised in 2000. According to the retrospective nature of the study, informed consent was not taken from the subjects.

SPSS-24 program was used for statistical analysis (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Normally distributed variables were given as mean values with standard deviations while non-normally distributed variables were given as median values with ranges. Independent sample t-test, Mann Whitney U test, Fisher and Chi-square tests were used in two group comparisons and Spearman and Pearson test were used for correlation analyses whenever appropriate. We applied the same statistical methods on a subgroup with ER positive patients. A p value less than 0.05 was considered statistically significant.

RESULTS

A total number of 434 women with BC were included to the study. Mean age at BC diagnosis was 49.2±10.7 years. Median body mass index (BMI) of the study population was 28.41 kg/m^2, and

33.4% (n=145) had a BMI ≥ 30 kg/m^2. Median age at menarche and mean age at menopause were 13 and 46.7±6.2 years, respectively; and more than half of the patients (n=234, 53.9%) were diagnosed in the postmenopausal period. Median gravida and parities of the subjects were 3 and 2, respectively. History of at least one cesarean delivery was present in 17% of the study population (n=75). In patients who ever used OCs (28.1%), mean duration of drug use was 1.11±2.8 years. Main characteristics of the patients and reproductive parameters were presented at Table 1.

Surgical and histopathological features were given in Table 2. As expected, most common type of surgery was modified radical mastectomy (71.9%), and most common pathological type of tumor was invasive ductal carcinoma (76.5%). Tumors were mostly T2 according to tumor size, and grade II according to histological characteristics. More than half of the patients had axillary lymph node metastasis (53.5%), while only 15.4% of the patients were stage IV at the time of BC diagnosis. Majority of the tumors were ER (79.3%) and PR positive (69%), but Her-2 negative (75.4%). Only 6.5% of the subjects were triple negative. Extracapsular and lymphovascular invasion were present in 19.8% and 27.6% of the tumors, respectively.

In the entire study population, number of parities were higher (p=0.023), median age at first full-term pregnancy (FFTP) was lower (p=0.016) and median duration of lactation was longer (p=0.009) in axillary lymph node positive patients, regardless of menopausal status at diagnosis. However, when patients were grouped according to ER expression, statistical significance disappeared for ER-, but remained in ER+ patients (p=0.018 for median age at FFTP and p=0.001 for number of parities). Of note, the rate of obesity increased as the number of parities increased (p<0.001), and of women whose FFTP was under age twenty, 51.7% was obese at the time of BC diagnosis. However, no statistically significant difference was detected between obese and non-obese patients, regarding axillary lymph node positivity (p=0.126).

On the other hand, median age at last full-term pregnancy (LFTP) was older (p=0.039), and time since last parity to BC diagnosis was shorter (p=0.029) in patients with tumors showing extracapsular invasion. Notably, these associations disappeared when the patients were categorized according to ER expression. Interestingly, extracapsular invasion was associated with history of cesarean delivery in only ER+ patients (p=0.023). Also, the rate of lymphovascular invasion increased as the age at menarche (< 12 years vs. between 12-15 years vs. ≥15 years) increased in ER+ patients (p=0.004).

Tumor size (p=0.001), grade (p=0.046), axillary lymph node positivity (p=0.001), lymphovascular invasion (p<0.001), and shorter duration of time since last parity to BC diagnosis (p=0.029) were indicators of metastatic disease.

As patients were grouped according to history of cesarean section, we were not able to detect any differences regarding pathological characteristics

Table 1. Main characteristics and reproductive history of breast cancer patients

		Range
Mean age at diagnosis (years±SD)	49.2±10.7	20-79
Median BMI (kg/m^2)	28.41	16.9-47.0
Gravida (n)	3	1-19
Parity (n)	2	1-7
Median age at first child delivery (years)	21	14-45
Median age at last child delivery (years) (N=364)	28	17-52
Total duration of lactation (median months)	24	0-144
Median age at menarche (years) (N=433)	13	10-18
Mean age at menopause (years±SD) (N=330)	46.7±6.2	27-56
OC use ever (n, %) (N=430)	121 (28.1%)	
Mean OC duration (years±SD) (N=430)	1.11±2.8	0-20
Caesarean delivery ever (n, %)	75 (17.3%)	

SD: Standard deviation; BMI: Body mass index; OC: Oral contraceptive.

'Total N' represents the number of patients available to evaluate the given parameter.

Table 2. Surgical and histopathological features of tumors

	N (%)
Type of surgery	
MRM	312 (71.9)
BCS	101(23.3)
SM	21/4.8
Tumor type	
IDC	332 (76.5%)
ILC	20 (4.6%)
Mixed IDC/L	16 (3.7%)
DCIS	14 (3.2%)
Other	52 (12%)
Tumor localization	
Left	199 (45.9)
Right	226 (52.1)
Bilateral	9 (2.1)
Tumor size*	
<2 cm	138 (31.7)
2-5 cm	228 (52.5)
>5 cm	62 (14.2)
Tumor grade	
I	43 (9.9)
II	238 (54.8)
III	140 (32.2)
ER positive	344 (79.3)
PR positive	295 (68)
HER-2 positive	107 (24.6)
Triple negative	28 (6.5)
Lymphovascular invasion	120 (27.6)
Extracapsular invasion	86 (19.8)
Axillary lymph node involvement	232 (53.5)
Distant metastasis	67 (15.4)

MRM: Modified radical mastectomy; BCS: Breast conservative surgery; SM: Simple mastectomy; IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma; Mixed IDC/L: Mixed invasive ductal and lobular carcinoma; DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; PR: Progesteron receptor; HER-2: Human epidermal growth factor receptor-2.

* In situ tumors excluded (n=428)

of the tumors in patients with and without cesarean history (Table 3), except increased extracapsular invasion in ER+ subgroup of patients (p=0.023). Our findings indicated younger age at BC diagnosis and shorter time interval since last parity to BC diagnosis in women with history of cesarean delivery (p<0.001 for both). Although there was no difference between the total number of childbirths between groups, median BMI was lower (p=0.007), and total duration of lactation was shorter in cesarean group (p<0.001) (Table 4).

DISCUSSION

Our study evaluated clinical findings, tumor pathological characteristics, and reproductive history of women with BC; and examined possible associations in between. We have found that axillary lymph node positivity was associated with younger age at FFTP and higher number of parities in ER+ BC patients. Although extracapsular invasion was related to shorter time interval since last parity to BC diagnosis in the entire study population, this association disappeared when patients were categorized according to ER status. However, in ER+ subgroup of patients, history of cesarean delivery was associated with extracapsular invasion, and later age at menarche with lymphovascular invasion. Also, our findings indicate younger age at BC diagnosis and shorter time interval since last parity to BC diagnosis in patients with history of cesarean delivery.

Early menarche is reported to be a risk factor for developing BC, due to higher duration of exposure of breast tissue to endogenous estrogens [2]; yet it is controversial whether it is related to poor prognosis or not. Some studies reported early age at menarche to be associated with poor BC survival [11, 18]. Conversely, it was suggested that older age at menarche may be indicating poor survival in a subgroup of Luminal A-like subtype (ER and PR positive and low-grade tumors) BC patients [27]. Similarly, in a subgroup of ER+ patients we have found that lymphovascular invasion became more common as the age at menarche increased. Poor prognosis with older age at menarche in hormone receptor positive patients was also reported in other studies [28, 29]. However, several studies revealed no relationship with age at menarche and BC mortality [13, 30, 31].

Regarding parity and BC prognosis, some researchers reported higher mortality rates with increased parity [14, 18, 32], while some found no association in between [13, 15, 17], and one reported a U-shaped relationship [19]. Higher parity was related to poor survival in a large cohort of BC patients diagnosed before age 50, even after adjusting for other confounding factors that may affect survival, such as tumor stage and grade [14]. As in our study, Trivers KF, et al. reported that women with higher number of child birth showed higher rates of axillary lymph node positivity

Table 3. Comparative evaluation of pathological characteristics of the tumors in patients with and without caesarean section

	Caesarean ever (n, %)	NVD only (n, %)	p
Tumor grade			
I	6 (8.3)	37 (10.6)	
II	37 (51.4)	201 (57.8)	0.49
III	29 (40.3)	109 (31.3)	
ER positive	54 (73)	289 (80.5)	0.16
HER-2 positive	18 (24.3)	89 (24.8)	1.0
Triple negative	5 (6.8)	23 (6.4)	1.0
ALN positive	38 (51.4)	193 (53.8)	0.79
Extracapsular invasion	20 (27)	65 (18.1)	0,11
Lymphovascular invasion	21 (28.8)	98 (27.3)	0.78
Distant metastasis	12 (16.2)	55 (15.3)	0.86

ER: Estrogen receptor; PR: Progesterone receptor; HER-2: Human epidermal growth factor receptor-2; ALN: Axillary lymph node

Table 4. Comparative evaluation of patient characteristics and reproductive history in patients with and without caesarean section

	Caesarean ever (n=75)	NVD only (n=359)	p
Mean age at diagnosis (years±SD)	42.8±8.7	50.4±10.6	<0.001
Median BMI (kg/m^2)	27.27 (16.9-41.41)	28.65 (17.67-47.03)	0.007
Median age at first child delivery (years)	26 (15-40)	21 (14-45)	<0.001
Median age at last child delivery (years)	31 (20-40)	28 (17-52)	0.001
Gravida (n)	2 (1-8)	4 (1-19)	<0.001
Parity (n)	2 (1-4)	2 (1-7)	NA
Total duration of lactation (median, months)	14 (0-74)	24 (0-144)	<0.001
Time since last parity to BC diagnosis (years, median)	11 (0-32)	23 (0-36)	<0.001
Mean OC duration (years±SD)	0.79±2.05	1.18±2.9	0.43

NVD: Normal vaginal delivery; SD: Standard deviation; BMI: Body mass index; BC: Breast cancer; OC: Oral contraceptive.

[18]. It should be noted that women with four or more childbirths were included in high parity group, and it was suggested that the proliferative effect of pregnancy on the breast may play a role on poor prognosis. Although pregnancy induces terminal differentiation of the mammary gland, and therefore provides protection against carcinogenesis; proliferative effects may become more prominent as the number of pregnancies increases [33].

Several studies reported no impact of breastfeeding on BC prognosis [13, 17, 34], while some reported better prognostic markers or lower risk of mortality [16,32]. Although our findings indicate a relationship between duration of lactation and axillary lymph node positivity; we think that it is highly difficult to reveal the effect of breastfeeding on BC prognosis separately, since duration of lactation is clearly correlated with number of parities.

The possible impacts of age at FFTP on prognosis and mortality could be attributed to the changing effects of pregnancy on mammary gland according to age [33, 35, 36]. A study which included postmenopausal BC patients suggested that older age (>35 years) at FFTP increases the risk of BC mortality [13], while another study including premenopausal BC patients reported higher mortality related to younger age (<18 years) at FFTP [18], and one study reported a U-shaped relationship [37]. However, Alsaker MD, et al. revealed that the effect of older age at FFTP on survival diminished when tumor stage and grade were included in the analysis in premenopausal women with BC [14]. On the other hand, Butt S, et al. reported higher tumor grade with increasing age at FFTP in postmenopausal BC patients [15]. Our findings indicate that axillary lymph node positivity became more common in both pre- and postmenopausal women with BC as the age at FFTP

decreased, which may indicate more aggressive tumor behavior. However, this correlation was only present for ER+ patients.

Disagreement between studies investigating the relationship between time interval since last parity to BC diagnosis and disease prognosis is relatively less. One of the various explanations for poor prognosis in BC patients who were diagnosed recently after delivery is the possible delay in diagnosis due to both patient-related factors and pregnancy-related changes in breast density [18]. Secondly, pregnancy seems to increase the risk of BC transiently after birth but reduce the risk in following years [38, 39]. Finally, the poorer prognostic characteristics of tumors in these women may be due to their relatively younger age [40-42]. Several studies suggested higher mortality in patients if diagnosed recently after birth [12, 17, 18]. In our study, extracapsular invasion was more common in patients who got BC diagnosis after a shorter time interval since their last pregnancy.

The reason to include delivery method when evaluating the effects of reproductive factors on breast cancer prognosis was the higher levels of plasma oxytocin during normal vaginal delivery than cesarean section [21-23], and the inhibitory effect of oxytocin on cell proliferation in BC cell lines [25, 26]. A former study reported that cesarean delivery was related to increased incidence of both extracapsular and lymphovascular tumor invasion. Although, it should be noted that patients in cesarean group had significantly higher rates of OC use [20]. We have also reached such a conclusion in ER+ subgroup of our patients irrespective of OC status. Also, age at the time of BC diagnosis was significantly younger in patients with a history of cesarean delivery.

Our study has several limitations. First of all is the low number of included patients. Secondly, our study is a retrospective cross-sectional study which did not assess long term patient outcomes such as mortality. Finally, we did not collect data on the patients' socioeconomic status, which could have had impact on reproductive history, such as higher birth rates.

CONCLUSION

In conclusion, we have evaluated the possible associations between pathological characteristics of tumors in women with BC and reproductive factors, including method of delivery. Our findings indicate higher number of parities and younger age at FFTP were associated with axillary lymph node positivity, and shorter time interval between childbirth to BC diagnosis was associated with both extracapsular invasion and metastasis; all suggestive of poor prognosis and survival. Also, our study confirmed poor prognostic tumor characteristics in patients with history of cesarean delivery, but only in ER+ subgroup.

CONFLICT of INTEREST

The authors declare that they have no conflict of interest. No institutional, private or corporate financial support were received for the study.

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