Breast Cancer Research and Treatment (2019) 173:679–691
https://doi.org/10.1007/s10549-018-5032-3

EPIDEMIOLOGY

Clinical subtypes and prognosis in breast cancer according to parity: a nationwide study in Korean Breast Cancer Society

Sungmin Park[1] · Byung In Moon[2] · Se Jeong Oh[3] · Han-Byoel Lee[4] · Min-Ki Seong[5] · Seokwon Lee[6] · Kyung Do Byun[7] · Seung Pil Jung[8] · Soo Youn Bae[8]

Received: 24 October 2018 / Accepted: 27 October 2018 / Published online: 2 November 2018

Abstract

Purpose We explored the association between parity and the risk of developing a specific subtype of breast cancer. We also assessed the association between parity and prognosis according to subtypes.

Methods A total of 158,189 patients were enrolled in the Korean Breast Cancer Society Registry database between 1996 and 2015 in Korea. The database provided information on sex, age, number of parity, surgical method, stage, histological findings, presence of biologic markers, adjuvant therapy, and date and cause of death.

Results The patients with higher parity showed a higher ratio of triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2) subtypes. In univariate analysis, women with TNBC who had more than three children had a worse prognosis compared to other groups (HR 1.83; 95% CI 1.34–2.49; $P<0.001$). This association was also observed in women younger than 50 years (HR 1.63; 95% CI 1.07–2.48; $P=0.021$). In multivariate analysis stratified by subtypes, women who had more than three children were associated with a worse prognosis in TNBC in the total population (HR 1.53; 95% CI 1.11–2.12; $P=0.011$). This association was also observed in patients younger than 50 years of age (HR 1.53; 95% CI 1.09–2.61; $P=0.017$).

Conclusion Women who had more than three children were more likely to develop hormone receptor-negative (HR−) subtypes. Women who had more than three children were associated with worse prognosis in patients younger than 50 years of age and in patients with TNBC.

Keywords Parity · Breast cancer · Subtype · Prognosis

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-018-5032-3) contains supplementary material, which is available to authorized users.

✉ Soo Youn Bae
baessu@gmail.com

[1] Department of Breast Surgery, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju-si, Republic of Korea

[2] Department of Breast Surgery, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea

[3] Department of Surgery, Incheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, Incheon-si, Republic of Korea

[4] Department of Breast Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

[5] Department of Surgery, Korea Cancer Center Hospital, Korea Institute of Radiological & Medical Sciences, Seoul, Republic of Korea

[6] Department of Surgery, Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea

[7] Department of Surgery, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Republic of Korea

[8] Division of Breast and Endocrine Surgery, Department of Surgery, Korea University Anam Hospital, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, 02841 Seoul, Republic of Korea

Introduction

Several studies have thoroughly investigated an association between the risk of developing breast cancer and reproductive profiles [1]. Reproductive factors, such as early age at menarche, nulliparity, and late age at first birth, are believed to be associated with breast cancer risk through hormonal mechanisms [2]. Nulliparity is a risk factor for breast cancer compared with the risk among parous women [3], and pregnancy transiently increases the risk after childbirth [4]. Use of oral contraceptives is associated with an increased risk of breast cancer [5, 6], and combined postmenopausal hormone therapy (estrogen and progesterone) increases the risk of breast cancer as well [7]. However, breast cancer consists of several molecular subtypes that have very different prognoses [8]. Prior research has been conducted to show whether different reproductive factors predispose to or protect against certain subtype of breast cancer, with conflicting results to date.

It is widely accepted that risk factors vary by the subtype of breast cancer [defined by estrogen receptor (ER) and progesterone receptor (PR) expression] [9], and that breast cancer risk factors are more strongly associated with hormone receptor (HR)-positive cancers. High parity, early age at first birth, and late age at menarche have been associated with a reduced risk of HR-positive cancers [10]. In contrast, HR-negative cancers are not associated with reproductive and hormonal risk factors in the same way as HR-positive cancers [11]. Recent studies have addressed this question, evaluating the impact of reproductive profiles on breast cancer subtypes that are defined by HR and human epidermal growth factor receptor 2 (HER2) expression [12].

We explored the association between parity and the risk of developing a specific subtype of breast cancer. We also assessed the association between parity and prognosis according to cancer subtype.

Methods

Study population

All patient data of those diagnosed with breast cancer were collected by the Korean Breast Cancer Society (KBCS) online breast cancer registry (http://registry.kbcs.or.kr/ecrf/login.php). Thirty-eight of the 41 medical schools in Korea, as well as 24 general hospitals and six private hospitals and special clinics, participated in the survey. The database provided information about sex, age, number of parity, surgical method, stage according to the American Joint Committee on Cancer (AJCC) classification, histological findings, and presence of biologic markers, adjuvant therapy, and date and cause of death [13].

This was a retrospective study of 158,189 patients who were surgically treated for primary breast cancer between January 1, 1996, and December 31, 2015 in Korea. A nationwide questionnaire survey was used to determine the total number of patients newly diagnosed with breast cancer (including ductal carcinoma in situ [DCIS] and invasive breast cancer) and the age of these patients. Patients with unknown age, unknown ER, PR and HER2 status, and unknown parity were excluded. Patients who had been diagnosed with breast cancer during pregnancy or within 1 year after delivery were excluded, and male patients were excluded.

Patient survival data, including dates and causes of death, were obtained from the Korean Central Cancer Registry, Ministry of Health and Welfare, Korea. The Korean Central Cancer Registry is linked to the Korea National Statistical Office, which has complete death statistics recorded by a unique identification number assigned to each Korean resident. The last follow-up time for surviving patients was December 31, 2015.

Definition of breast cancer subtypes

ER and PR expression were recorded as negative or positive, whereas 0 or 1 + was considered to be negative for HER2 status, and 3 + was considered to be positive [14]. HER2 expression status was determined at each laboratory with immunohistochemistry (IHC) staining and/or in situ hybridization. Cases with no (0) or weak (1 +) immunostaining were defined as HER2-negative, while cases with moderate (2 +) or strong immunostaining (3 +) were defined as HER2-positive. In situ hybridization (fluorescence [FISH] or silver [SISH] in situ hybridization methods) was usually used to confirm HER2 status if IHC yielded a 2 + result. If IHC was 2 + and FISH or SISH were missing, or if IHC was missing but FISH or SISH were positive, the tumor was classified as HER2-positive. If IHC was 2 + and FISH and SISH were negative, the tumor was regarded as HER2-negative. The breast cancer samples were categorized into breast cancer subtypes on the basis of their immunohistochemical ER, PR, and HER2 status as follows. Patients were classified into five groups according to tumor subtype. (1) Luminal A: HR-positive (ER and/or PR), HER2-negative and Ki67 < 14.0%; (2) luminal B (with high Ki67): HR-positive and HER2-negative and Ki67 ≥ 14.0%; (3) luminal B (with HER2): HR-positive and HER2-positive; (4) triple-negative breast cancer (TNBC): ER-negative, PR-negative, and HER2-negative; and (5) HER2 subtype: ER-negative, PR-negative, and HER2-positive.

Statistical analyses

The associations among the five breast cancer subtypes (luminal A, luminal B (with high Ki67), luminal B (with HER2+), TNBC and HER2 subtypes) and patient characteristics and tumor characteristics were determined using the Chi-square test. We used the Kaplan–Meier method to draw survival curves, and multivariate Cox proportional hazard models were used to determine the effects of parity, stage, and age at diagnosis on the overall survival (OS) (deaths from any cause) rates as dependent variables, adjusting for both age and subtypes. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the following study factors: age at diagnosis, number of children (0, 1, 2 and ≥ 3) and pathological stage. All analyses were performed using SPSS, version 24 (IBM Corp., Armonk, NY, USA).

This study was approved by the institutional review board of Chungbuk National University Hospital (approval numbers: 2018-10-002).

Results

Clinicopathologic characteristics of patients

The median age was 49 years (range 18–99 years), and the median follow-up period was 58 months (range 1–311 months). Descriptive statistics for parity, age at menarche, age at first birth, tumor size, nodal status, and stage stratified by molecular subtypes are presented in Table 1. Nulliparous patients had a higher proportion of stage 0 tumors, and patients with higher parity had a higher percentage of stage II and III tumors (nulliparous vs. ≥ 3 children, stage 0: 14.3% vs. 10.2%, stage III: 10.5% vs. 12.5%, $P < 0.001$). Women with higher parity had tumors with a higher nuclear grade (nulliparous vs. ≥ 3 children, 36.4 vs. 38.5%, $P = 0.037$). Women with higher parity had more ER- and PR-negative tumors, and they had more HER2-positive tumor (nulliparous vs. ≥ 3 children; ER+, 74.3% vs.63.7%, $P < 0.001$; PR+, 63.0% vs. 53.2%, $P < 0.001$; HER2 subtype, 22.1% vs. 26.0%, $P < 0.001$).

The differences in clinicopathologic characteristics were also determined according to age group. Patients with more than three children had a higher percentage of stage II and III tumors, and they had more ER- and PR-negative tumors among all women (Supplement Table 1).

Association between the number of parity and breast cancer subtypes

Patients with higher parity had a higher ratio of TNBC and HER2 subtypes (nulliparous vs. ≥ 3 children; TNBC 14.8% vs. 18.6%; HER2 9.6% vs. 14.4%, $P < 0.001$) and a lower ratio of the luminal subtypes (Table 2). This association was also observed by age. Patients 50 years of age or older with more than three children were more likely to develop TNBC/ HER2 subtype (nulliparous vs. ≥ 3 children; TNBC 13.27% vs. 18.9%; HER2 12.3% vs. 15.5%, $P < 0.001$) and lower luminal subtypes. However, patients under 50 years of age with more than three children had only a lower ratio of luminal B with high Ki67 level (nulliparous vs. ≥ 3 children, 16.8% vs. 10.3%, $P < 0.001$).

Survival analysis according to the number of parity and breast cancer subtypes

Women who had more than three children had a worse prognosis compared to other groups (HR 1.52; 95% CI 1.35–1.71; $P < 0.001$). This association was also observed by age. Patients with more than three children were associated with worse prognosis in both women younger than 50 years and women at 50 years of age or older (age < 50: HR 1.29; 95% CI 1.09–1.54; $P = 0.003$. age ≥ 50: HR 1.28; 95% CI 1.08–1.53; $P = 0.004$) (Table 3; Fig. 1).

In univariate analysis according to breast cancer subtypes, women who had more than three children had a worse prognosis compared to other groups in patients with TNBC (HR 1.83; 95% CI 1.34–2.49; $P < 0.001$, Table 4). This association was also perceived in women younger than 50 years (HR 1.63; 95% CI 1.07–2.48; $P = 0.021$). However, there was no correlation between parity and prognosis in patients older than 50 years.

Prognosis according to the number of parity and breast cancer subtypes

In multivariate analysis, women who had more than three children were associated with a worse prognosis in the total population (HR 1.22; 95% CI 1.08–1.38; $P = 0.001$). This association was also observed in patients younger than 50 years of age. However, we did not observe a significant difference in patients at 50 years of age or older (Supplement Table 2).

In multivariate analysis stratified by subtypes, women who had more than three children were associated with worse prognosis in TNBC in the total population (HR 1.53; 95% CI 1.10–2.12; $P = 0.011$). This association was also observed in patients younger than 50 years of age (HR 1.69; 95% CI 1.09–2.61; $P = 0.017$). However, we did not observe significance in patients at 50 years of age or older (Supplement Table 3).

Discussion

This study shows that women who had more than three children were more likely to develop HR-negative cancer than HR+ cancer. This association was also observed in

Table 1 Clinicopathologic characteristics of patients

	Number of parity	Total				
		0	1	2	≥3	*P*
Age	< 50	4390	10,426	31,871	6011	< 0.001
		61.1%	65.2%	59.4%	25.1%	
	≥ 50	2792	5555	21,812	17,944	
		38.9%	34.85	40.6%	74.9%	
Family history	Yes	513	1345	4232	1677	< 0.001
		10.3%	9.3%	8.7%	7.9%	
	No	4456	13,158	44,550	19,601	
		89.7%	90.7%	91.3%	92.1%	
	Unknown	2213	1478	4901	2677	
Menarche	≤ 13 years	4166	3490	9942	2501	< 0.001
		62.1%	24.6%	20.8%	12.3%	
	> 13 years	2539	10,673	37,893	17,778	
		37.9%	75.4%	79.2%	87.7%	
	Unknown	477	1818	5848	3676	
First delivery	≥ 30 years		5123	6607	971	< 0.001
			38.8%	14.8%	5.1%	
	< 30 years		8073	38,026	18,219	
			61.2%	85.2%	94.9%	
	Unknown		2785	9050	4765	
Operation (breast)	Mastectomy	3097	7075	23,279	12,447	< 0.001
		43.4%	44.6%	43.7%	52.5%	
	BCS	3982	8662	29,658	11,119	
		55.8%	54.6%	55.7%	46.9%	
	No operation	52	115	290	160	
		0.7%	0.7%	0.5%	0.7%	
	Unknown	51	129	456	229	
Operation (axillary)	ALND	2145	6360	21,721	11,214	< 0.001
		30.0%	40.3%	41.0%	47.4%	
	SLN biopsy	4257	7973	26,643	10,326	
		59.6%	50.5%	50.3%	43.6%	
	No op	737	1443	4656	2138	
		10.3%	9.1%	8.8%	9.0%	
	Unknown	43	205	663	277	
T	T0	1101	2019	6728	2597	< 0.001
		15.8%	12.8%	12.7%	11.0%	
	T1	3377	7825	27,200	11,570	
		48.4%	49.6%	51.3%	48.8%	
	T2	2122	5042	16,793	8374	
		30.4%	32.0%	31.6%	35.3%	
	T3	291	655	1843	829	
		4.2%	4.2%	3.5%	3.5%	
	T4	85	221	504	334	
		1.2%	1.4%	0.9%	1.4%	
	Unknown	206	219	615	251	
N	N0	4925	10,658	35,530	15,469	< 0.001
		70.5%	67.6%	67.0%	65.4%	
	N1	1438	3640	12,685	5697	
		20.6%	23.1%	23.9%	24.1%	

Table 1 (continued)

	Number of parity	Total				
		0	1	2	≥3	*P*
	N2	386	971	3188	1629	
		5.5%	6.2%	6.0%	6.9%	
	N3	235	499	1613	860	
		3.4%	3.2%	3.0%	3.6%	
	Unknown	198	213	667	300	
T	ypT0	134	160	452	179	0.023
		18.2%	16.1%	15.6%	18.4%	
	ypT1	296	392	1127	367	
		40.3%	39.6%	38.8%	37.6%	
	ypT2	212	277	900	272	
		28.8%	28.0%	31.0%	27.9%	
	ypT3	65	104	277	85	
		8.8%	10.5%	9.5%	8.7%	
	ypT4	28	58	145	72	
		3.8%	5.9%	5.0%	7.4%	
	Unknown	12	16	61	13	
N	ypN0	375	460	1215	391	< 0.001
		50.5%	46.0%	41.6%	40.0%	
	ypN1	242	354	1060	346	
		32.6%	35.4%	36.3%	35.4%	
	ypN2	83	119	443	164	
		11.2%	11.9%	15.2%	16.8%	
	ypN3	42	66	206	77	
		5.7%	6.6%	7.0%	7.9%	
	Unknown	5	8	38	10	
Stage	O	980	1853	6202	2383	< 0.001
		14.3%	11.9%	11.8%	10.2%	
	I	2661	6018	20,742	8725	
		38.8%	38.7%	39.6%	37.3%	
	II	2366	5638	19,048	9072	
		34.5%	36.3%	36.4%	38.7%	
	III	720	1793	5785	2926	
		10.5%	11.5%	11.0%	12.5%	
	IV	124	243	617	306	
		1.8%	1.6%	1.2%	1.3%	
	Unknown	331	436	1289	543	
ypStage	ypO	50	56	171	60	< 0.001
		7.5%	6.2%	6.4%	6.7%	
	ypI	182	191	555	184	
		27.2%	21.0%	20.7%	20.4%	
	ypII	250	359	993	319	
		37.4%	39.5%	37.0%	35.4%	
	ypIII	149	243	853	285	
		22.3%	26.8%	31.8%	31.6%	
	ypIV	37	59	114	54	
		5.5%	6.5%	4.2%	6.0%	
	Unknown	79	99	276	86	

Table 1 (continued)

	Number of parity	Total				
		0	1	2	≥3	*P*
Nuclear grade	Low/intermediate	3384	7063	23,960	10,186	0.037
		63.6%	62.3%	61.8%	61.5%	
	High	1937	4275	14,793	6382	
		36.4%	37.7%	38.2%	38.5%	
	Unknown	1861	4643	14,930	7387	
Histology	IDC	5422	12,642	42,897	19,492	< 0.001
		82.4%	84.6%	84.8%	86.6%	
	ILC	209	516	1617	630	
		3.2%	3.5%	3.2%	2.8%	
	DCIS	941	1771	5999	2318	
		14.3%	11.9%	11.9%	10.3%	
	etc.	7	15	65	60	
		0.1%	0.1%	0.1%	0.3%	
	Unknown	603	1037	3104	1455	
ER	Positive	4941	10,410	34,477	14,180	< 0.001
		74.3%	69.7%	68.4%	63.7%	
	Negative	1707	4527	15,928	8066	
		25.7%	30.3%	31.6%	36.3%	
	Unknown	534	1044	3278	1709	
PR	Positive	3865	9054	30,130	11,741	< 0.001
		63.0%	61.2%	60.4%	53.2%	
	Negative	2274	5731	19,782	10,347	
		37.0%	38.8%	39.6%	46.8%	
	Unknown	1043	1196	3771	1867	
HER2	Positive	1272	2918	10,653	4732	< 0.001
		22.1%	23.2%	25.2%	26.0%	
	Negative	4489	9646	31,659	13,477	
		77.9%	76.8%	74.8%	74.0%	
	Unknown	1421	3417	11,371	5746	
Chemotherapy	Yes	4024	9708	33,003	13,539	< 0.001
		59.7%	66.4%	67.2%	63.1%	
	No	2718	4906	16,097	7932	
		40.3%	33.6%	32.8%	36.9%	
	Unknown	440	1367	4583	2484	
Chemotherapy	Neoadjuvant	747	1007	2962	988	< 0.001
		18.6%	10.4%	9.0%	7.4%	
	Adjuvant	3209	8493	29,458	12,265	
		80.0%	88.1%	89.8%	91.3%	
	Palliative	55	144	384	185	
		1.4%	1.5%	1.2%	1.4%	
	Unknown	3171	6337	20,879	10,517	
Radiotherapy	Yes	4351	9009	30,871	11,561	< 0.001
		65.6%	64.1%	64.9%	55.6%	
	No	2282	5044	16,718	9250	
		34.4%	35.9%	35.1%	44.4%	
	Unknown	549	1928	6094	3144	

HER2 human epidermal growth factor 2, *TNBC* triple-negative breast cancer, *BCS* breast conserving surgery, *ALND* axillary lymph node dissection, *SLN* sentinel lymph node, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ

Table 2 Distribution (*n*, %) of breast cancer subtypes according to number of parity

	Subtype	Number of parity				
		0	1	2	≥3	*P*
Total	Luminal A	2531	6030	19,976	8341	< 0.001
		47.2%	48.6%	47.8%	46.2%	
	Luminal B (HER2+)	669	1575	5517	2101	
		12.5%	12.7%	13.2%	11.6%	
	TNBC	791	2043	6893	3360	
		14.8%	16.4%	16.5%	18.6%	
	HER2	514	1325	5031	2592	
		9.6%	10.7%	12.0%	14.4%	
	Luminal B (high Ki67)	855	1447	4406	1655	
		16.0%	11.7%	10.5%	9.2%	
	Unknown	1822	3561	11,860	5906	
Age < 50	Luminal A	1567	3996	12,158	2109	< 0.001
		47.7%	49.9%	50.1%	47.9%	
	Luminal B (HER2+)	391	1040	3320	580	
		11.9%	13.0%	13.7%	13.2%	
	TNBC	516	1305	4006	775	
		15.7%	16.3%	16.5%	17.6%	
	HER2	258	703	2234	481	
		7.9%	8.8%	9.2%	10.9%	
	Luminal B (high Ki67)	551	962	2551	455	
		16.8%	12.0%	10.5%	10.3%	
	Unknown	1107	2420	7602	1611	
Age ≥ 50	Luminal A	964	2034	7818	6232	< 0.001
		46.4%	46.1%	44.5%	45.7%	
	Luminal B (HER2+)	278	535	2197	1521	
		13.4%	12.1%	12.5%	11.1%	
	TNBC	275	738	2887	2585	
		13.2%	16.7%	16.4%	18.9%	
	HER2	256	622	2797	2111	
		12.3%	14.1%	15.9%	15.5%	
	Luminal B (high Ki67)	304	485	1855	1200	
		14.6%	11.0%	10.6%	8.8%	
	Unknown	715	1141	4258	4295	

HER2 human epidermal growth factor 2, *TNBC* triple-negative breast cancer

women younger than 50 years of age. In univariate and multivariate analysis, women who had more than three children were associated with worse prognosis. This association was also observed in patients younger than 50 years of age and in patients with TNBC.

Number of parity is associated with risk of breast cancer, and it varies in different breast cancer subtypes. In this study, patients who had more than three children were more likely to develop TNBC and the HER2 subtype cancer. This is consistent with a recent study which showed that parous women were more likely to develop TNBC relative to luminal A breast cancer around age 55 years [15]. Another study also suggested that parity was associated with an increased risk of the HER2 subtype [16]. Multiparity combined with no breastfeeding was associated with an increased risk of HR-neagitve cancer and TNBC [16], and similar findings were suggested among studies that examined TNBC [17]. However, one study suggested that parity was associated with a decreased risk of TNBC and HER2-positive breast cancer [18].

The protective effect of parity against HR-negative subtypes but not against HR-postive subtypes suggests that hormonal mechanisms involving estrogen and progesterone might have an effect on breast cancer risk. The systemic hormonal changes that occur during pregnancy seem to be a major influence in protecting against mammary cancer [19].

Table 3 Hazard ratio (HRs) and 95% confidence intervals (CI) for number of parity

	B	Standard error	Wald	*P*	HR	95.0% CI	
						Lower	Upper
Total							
Parity							
0	(Ref)						
1	0.178	0.064	7.734	0.005	1.194	1.054	1.354
2	−0.015	0.060	0.067	0.796	0.985	0.876	1.107
≥3	0.420	0.060	48.207	0.000	1.522	1.352	1.713
Age < 50							
Parity							
0	(Ref)						
1	0.219	0.085	6.681	0.010	1.245	1.054	1.469
2	0.107	0.080	1.806	0.179	1.113	0.952	1.301
≥3	0.261	0.088	8.868	0.003	1.299	1.093	1.543
Age ≥ 50							
Parity							
0	(Ref)						
1	0.167	0.098	2.937	0.087	1.182	0.976	1.431
2	−0.187	0.091	4.270	0.039	0.829	0.694	0.990
≥3	0.254	0.089	8.164	0.004	1.289	1.083	1.535

In the presence of estrogen, HR+ progenitor cells produce paracrine signals that stimulate the proliferation of nearby populations of HR− cells [20]. This suggests a possible influence on the risk of developing TNBC. A molecular "involution signature" regulated by STAT3 signaling seems to be the key mediator of the involution process occurring in the mammary gland during breastfeeding [21]. The lack of involution might be associated with a risk of developing basal-like breast cancers [22]. A previous study suggested that higher parity and the absence or short duration of breastfeeding were independently associated with TNBC [23]. A recent meta-analysis showed a protective effect of ever breastfeeding against HR− breast cancers [24], and another meta-analysis showed that ever breastfeeding was associated with a reduced risk of developing both luminal and triple-negative subtypes [25]. We were unable to determine any association with breastfeeding because lack of information from our database.

Few studies have investigated the association between parity and breast cancer prognosis. Some studies report no association between number of births and prognosis [26, 27], while other studies report that multiple births are associated with a poorer prognosis [28, 29]. In this study, women who had more than three children were associated with worse prognosis. Pregnancy has a dual effect on the risk of developing breast cancer: pregnancy transiently increases breast cancer risk after childbirth but reduces the risk in later years [4]. In women with two or more pregnancies, the short-term adverse effect might be masked by the long-term protection afforded by the first pregnancy [4]. The proposed biologic mechanisms associated with parity and the transiently increased risk of breast cancer are increased hormonal stimulation, expansion of stem/progenitor cells, growth stimuli, and proinflammatory and wound-healing changes in the microenvironment [30, 31].

In this study, women who had more than three children were associated with worse prognosis, and this association was consistent in patients with TNBC. Whether the prognostic value of parity with breast cancer across intrinsic subtypes is independent of established clinical variables is still under debate. Recent studies have shown that luminal B cancer is less dependent on the estrogen pathway, which acts as an alternative pathway EGFR [32] and PI3K/Akt/mTOR in advanced ER+ cancer [33]. TNBC has a heterogeneous clinical behavior and no known targetable biomarkers, and patients with this disease frequently have a poor prognosis. Several pathways, including PI3K/mTOR or RAS/RAF/MEK, have been found to be affected in TNBC [34].

In this study, women who had more than three children were associated with worse prognosis in patients younger than 50 years of age. This is consistent with a previous study that revealed a positive association between high parity and mortality from breast cancer in premenopausal women [35]. In general, younger age correlates with a worse clinical outcome compared to older age [8]. In a previous study, premenopausal women had higher breast cancer risk factors

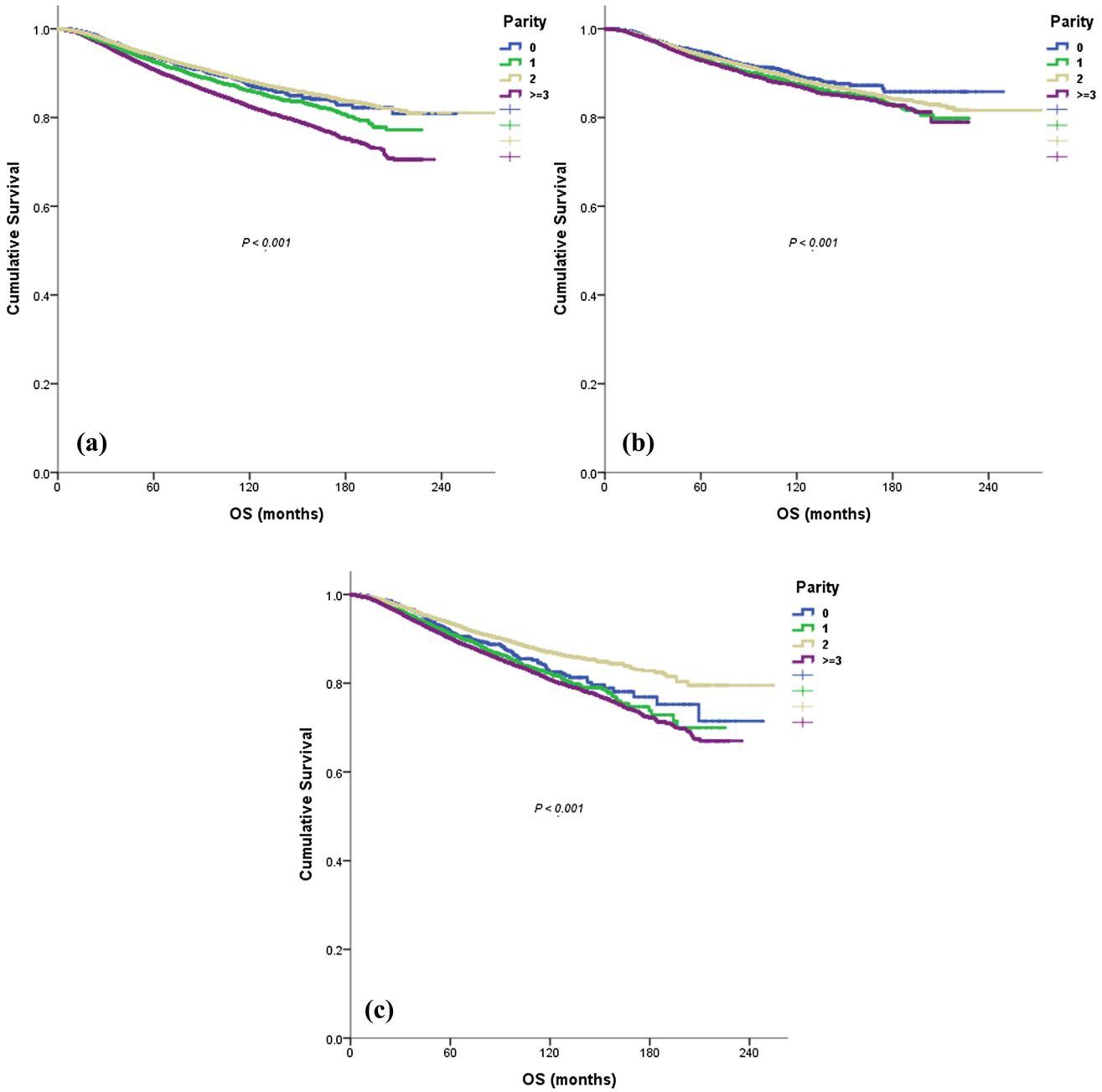

Fig. 1 Kaplan–Meier survival curves for overall survival rate by parity: **a** total, **b** age < 50 and **c** age ≥ 50

at baseline than postmenopausal women as reflected by younger age and more frequent node-positive disease [36]. We could not ascertain patient's menopausal status from our database, which is a limitation of this study. In the absence of detailed information, we consider age alone as a crude proxy for menopausal status based on an epidemiologic study [37].

This study suggests that high parity is associated with the risk of developing specific subtypes of breast cancer and poor prognosis, especially in women younger than 50 years of age. Women who had more than three children were more likely to develop HR− subtypes. In univariate and multivariate analyses, women who had more than three children were associated with worse prognosis in patients younger than 50 years of age and in patients with TNBC.

Table 4 Hazard ratio (HRs) and 95% confidence intervals (CI) for association between number of parity and breast cancer subtypes

	B	Standard error	Wald	*P*	HR	95.0% CI	
						Lower	Upper
Total							
Luminal A							
Parity							
0	(Ref)						
1	0.111	0.133	0.704	0.401	1.118	0.862	1.450
2	−0.138	0.125	1.228	0.268	0.871	0.682	1.112
≥3	0.415	0.126	10.902	0.001	1.514	1.184	1.938
Luminal B (HER2+)							
Parity							
0	(Ref)						
1	−0.072	0.186	0.149	0.699	0.931	0.647	1.340
2	−0.419	0.173	5.881	0.015	0.658	0.469	0.923
≥3	−0.027	0.177	0.023	0.879	0.973	0.687	1.378
TNBC							
Parity							
0	(Ref)						
1	0.371	0.166	4.998	0.025	1.449	1.047	2.006
2	0.353	0.157	5.066	0.024	1.423	1.047	1.934
≥3	0.604	0.159	14.483	0.000	1.830	1.341	2.498
HER2							
Parity							
0	(Ref)						
1	0.432	0.220	3.841	0.050	1.540	1.000	2.370
2	0.140	0.210	0.444	0.505	1.150	0.762	1.734
≥3	0.359	0.212	2.867	0.090	1.432	0.945	2.169
Luminal B (high Ki67)							
Parity							
0	(Ref)						
1	0.669	0.314	4.542	0.033	1.952	1.055	3.610
2	0.435	0.299	2.123	0.145	1.545	0.861	2.776
≥3	0.915	0.304	9.074	0.003	2.496	1.376	4.525
Age < 50							
Luminal A							
Parity							
0	(Ref)						
1	0.047	0.175	0.071	0.790	1.048	0.743	1.478
2	−0.077	0.164	0.219	0.640	0.926	0.671	1.278
≥3	0.167	0.182	0.847	0.358	1.182	0.828	1.688
Luminal B (HER2+)							
Parity							
0	(Ref)						
1	−0.068	0.229	0.089	0.765	0.934	0.596	1.462
2	−0.435	0.214	4.126	0.042	0.647	0.425	0.985
≥3	−0.442	0.252	3.076	0.079	0.643	0.392	1.053
TNBC							
Parity							
0	(Ref)						
1	0.363	0.206	3.099	0.078	1.437	0.960	2.153
2	0.421	0.194	4.701	0.030	1.524	1.041	2.231

Table 4 (continued)

	B	Standard error	Wald	*P*	HR	95.0% CI	
						Lower	Upper
≥ 3	0.490	0.213	5.318	0.021	1.633	1.076	2.478
HER2							
Parity							
0	(Ref)						
1	0.397	0.299	1.761	0.184	1.487	0.828	2.670
2	0.286	0.285	1.008	0.315	1.331	0.762	2.325
≥ 3	0.277	0.310	0.802	0.371	1.320	0.719	2.422
Luminal B (high Ki67)							
Parity							
0	(Ref)						
1	1.113	0.525	4.499	0.034	3.043	1.088	8.511
2	0.933	0.511	3.338	0.068	2.543	0.934	6.923
≥ 3	1.021	0.547	3.485	0.062	2.776	0.950	8.111
Age ≥ 50							
Luminal A							
Parity							
0	(Ref)						
1	0.248	0.203	1.501	0.221	1.282	0.862	1.908
2	− 0.233	0.191	1.482	0.223	0.792	0.545	1.153
≥ 3	0.263	0.188	1.961	0.161	1.301	0.900	1.880
Luminal B (HER2+)							
Parity							
0	(Ref)						
1	− 0.076	0.320	0.057	0.812	0.927	0.495	1.734
2	− 0.392	0.292	1.802	0.179	0.676	0.381	1.197
≥ 3	0.059	0.288	0.042	0.838	1.060	0.603	1.864
TNBC							
Parity							
0	(Ref)						
1	0.406	0.280	2.109	0.146	1.501	0.868	2.598
2	0.234	0.265	0.781	0.377	1.264	0.752	2.124
≥ 3	0.506	0.263	3.697	0.055	1.658	0.990	2.777
HER2							
Parity							
0	(Ref)						
1	0.496	0.326	2.318	0.128	1.642	0.867	3.110
2	− 0.018	0.310	0.003	0.955	0.983	0.535	1.804
≥ 3	0.344	0.308	1.245	0.264	1.410	0.771	2.579
Luminal B (high Ki67)							
Parity							
0	(Ref)						
1	0.470	0.405	1.345	0.246	1.600	0.723	3.538
2	0.055	0.372	0.022	0.883	1.056	0.509	2.192
≥ 3	0.466	0.368	1.597	0.206	1.593	0.774	3.280

Acknowledgements This work was supported by the research grant of the Korean Breast Cancer Society and the Chungbuk National University Hospital in 2018.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Azim HA Jr, Partridge AH (2014) Biology of breast cancer in young women. Breast Cancer Res 16(4):427. https://doi.org/10.1186/s13058-014-0427-5
2. Beral V (2002) Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 360(9328):187–195. https://doi.org/10.1016/s0140-6736(02)09454-0
3. MacMahon B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, Salber EJ, Valaoras VG, Yuasa S (1970) Age at first birth and breast cancer risk. Bull World Health Organ 43(2):209–221
4. Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO (1994) Transient increase in the risk of breast cancer after giving birth. N Engl J Med 331(1):5–9. https://doi.org/10.1056/nejm199407073310102
5. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O (2017) Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med 377(23):2228–2239. https://doi.org/10.1056/NEJMoa1700732
6. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER (2013) Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev 22(11):1931–1943. https://doi.org/10.1158/1055-9965.epi-13-0298
7. Ambrosone CB, Zirpoli G, Ruszczyk M, Shankar J, Hong CC, McIlwain D, Roberts M, Yao S, McCann SE, Ciupak G, Hwang H, Khoury T, Jandorf L, Bovbjerg DH, Pawlish K, Bandera EV (2014) Parity and breastfeeding among African-American women: differential effects on breast cancer risk by estrogen receptor status in the Women's Circle of Health Study. Cancer Causes Control 25(2):259–265. https://doi.org/10.1007/s10552-013-0323-9
8. de la Rochefordiere A, Asselain B, Campana F, Scholl SM, Fenton J, Vilcoq JR, Durand JC, Pouillart P, Magdelenat H, Fourquet A (1993) Age as prognostic factor in premenopausal breast carcinoma. Lancet 341(8852):1039–1043
9. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, Gaudet M, Schmidt MK, Broeks A, Cox A, Fasching PA, Hein R, Spurdle AB, Blows F, Driver K, Flesch-Janys D, Heinz J, Sinn P, Vrieling A, Heikkinen T, Aittomaki K, Heikkila P, Blomqvist C, Lissowska J, Peplonska B, Chanock S, Figueroa J, Brinton L, Hall P, Czene K, Humphreys K, Darabi H, Liu J, Van 't Veer LJ, van Leeuwen FE, Andrulis IL, Glendon G, Knight JA, Mulligan AM, O'Malley FP, Weerasooriya N, John EM, Beckmann MW, Hartmann A, Weihbrecht SB, Wachter DL, Jud SM, Loehberg CR, Baglietto L, English DR, Giles GG, McLean CA, Severi G, Lambrechts D, Vandorpe T, Weltens C, Paridaens R, Smeets A, Neven P, Wildiers H, Wang X, Olson JE, Cafourek V, Fredericksen Z, Kosel M, Vachon C, Cramp HE, Connley D, Cross SS, Balasubramanian SP, Reed MW, Dork T, Bremer M, Meyer A, Karstens JH, Ay A, Park-Simon TW, Hillemanns P, Arias Perez JI, Menendez Rodriguez P, Zamora P, Benitez J, Ko YD, Fischer HP, Hamann U, Pesch B, Bruning T, Justenhoven C, Brauch H, Eccles DM, Tapper WJ, Gerty SM, Sawyer EJ, Tomlinson IP, Jones A, Kerin M, Miller N, McInerney N, Anton-Culver H, Ziogas A, Shen CY, Hsiung CN, Wu PE, Yang SL, Yu JC, Chen ST, Hsu GC, Haiman CA, Henderson BE, Le Marchand L, Kolonel LN, Lindblom A, Margolin S, Jakubowska A, Lubinski J, Huzarski T, Byrski T, Gorski B, Gronwald J, Hooning MJ, Hollestelle A, van den Ouweland AM, Jager A, Kriege M, Tilanus-Linthorst MM, Collee M, Wang-Gohrke S, Pylkas K, Jukkola-Vuorinen A, Mononen K, Grip M, Hirvikoski P, Winqvist R, Mannermaa A, Kosma VM, Kauppinen J, Kataja V, Auvinen P, Soini Y, Sironen R, Bojesen SE, Orsted DD, Kaur-Knudsen D, Flyger H, Nordestgaard BG, Holland H, Chenevix-Trench G, Manoukian S, Barile M, Radice P, Hankinson SE, Hunter DJ, Tamimi R, Sangrajrang S, Brennan P, McKay J, Odefrey F, Gaborieau V, Devilee P, Huijts PE, Tollenaar RA, Seynaeve C, Dite GS, Apicella C, Hopper JL, Hammet F, Tsimiklis H, Smith LD, Southey MC, Humphreys MK, Easton D, Pharoah P, Sherman ME, Garcia-Closas M (2011) Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst 103(3):250–263. https://doi.org/10.1093/jnci/djq526
10. Ma H, Bernstein L, Pike MC, Ursin G (2006) Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. Breast Cancer Res 8(4):R43. https://doi.org/10.1186/bcr1525
11. Setiawan VW, Monroe KR, Wilkens LR, Kolonel LN, Pike MC, Henderson BE (2009) Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. Am J Epidemiol 169(10):1251–1259. https://doi.org/10.1093/aje/kwp036
12. Anderson KN, Schwab RB, Martinez ME (2014) Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat 144(1):1–10. https://doi.org/10.1007/s10549-014-2852-7
13. Park B, Choi KS, Lee YY, Jun JK, Seo HG (2012) Trends in Cancer Screening Rates among Korean Men and Women: Results from the Korean National Cancer Screening Survey (KNCSS), 2004–2011. Cancer Res Treat 44(2):113–120. https://doi.org/10.4143/crt.2012.44.2.113
14. Hammond ME, Hayes DF, Wolff AC (2011) Clinical notice for American Society of Clinical Oncology-College of American Pathologists guideline recommendations on ER/PgR and HER2 testing in breast cancer. J Clin Oncol 29(15):e458. https://doi.org/10.1200/jco.2011.35.2245
15. Brouckaert O, Rudolph A, Laenen A, Keeman R, Bolla MK, Wang Q, Soubry A, Wildiers H, Andrulis IL, Arndt V, Beckmann MW, Benitez J, Blomqvist C, Bojesen SE, Brauch H, Brennan P, Brenner H, Chenevix-Trench G, Choi JY, Cornelissen S, Couch FJ, Cox A, Cross SS, Czene K, Eriksson M, Fasching PA, Figueroa J, Flyger H, Giles GG, Gonzalez-Neira A, Guenel P, Hall P, Hollestelle A, Hopper JL, Ito H, Jones M, Kang D, kConFab KJA, Kosma VM, Li J, Lindblom A, Lilyquist J, Lophatananon A, Mannermaa A, Manoukian S, Margolin S, Matsuo K, Muir K, Nevanlinna H, Peterlongo P, Pylkas K, Saajrang S, Seynaeve C, Shen CY, Shu XO, Southey MC, Swerdlow A, Teo SH, Tollenaar R, Truong T, Tseng CC, van den Broek AJ, van Deurzen CHM, Winqvist R, Wu AH, Yip CH, Yu JC, Zheng W, Milne RL, Pharoah PDP, Easton DF, Schmidt MK, Garcia-Closas M, Chang-Claude J, Lambrechts D, Neven P (2017) Reproductive profiles and risk of breast cancer subtypes: a multi-center case-only study. Breast Cancer Res 19(1):119. https://doi.org/10.1186/s13058-017-0909-3
16. Work ME, John EM, Andrulis IL, Knight JA, Liao Y, Mulligan AM, Southey MC, Giles GG, Dite GS, Apicella C, Hibshoosh H,

Hopper JL, Terry MB (2014) Reproductive risk factors and oestrogen/progesterone receptor-negative breast cancer in the Breast Cancer Family Registry. Br J Cancer 110(5):1367–1377. https://doi.org/10.1038/bjc.2013.807

17. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Stefanick ML, Vitolins M, Kabat GC, Rohan TE, Li CI (2011) Reproductive history and oral contraceptive use in relation to risk of triple-negative breast cancer. J Natl Cancer Inst 103(6):470–477. https://doi.org/10.1093/jnci/djr030
18. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G (2017) Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. Breast Cancer Res 19(1):10. https://doi.org/10.1186/s13058-016-0798-x
19. Rajkumar L, Guzman RC, Yang J, Thordarson G, Talamantes F, Nandi S (2004) Prevention of mammary carcinogenesis by short-term estrogen and progestin treatments. Breast Cancer Res 6(1):R31–R37. https://doi.org/10.1186/bcr734
20. Dontu G, El-Ashry D, Wicha MS (2004) Breast cancer, stem/progenitor cells and the estrogen receptor. Trends Endocrinol Metab 15(5):193–197. https://doi.org/10.1016/j.tem.2004.05.011
21. Faupel-Badger JM, Arcaro KF, Balkam JJ, Eliassen AH, Hassiotou F, Lebrilla CB, Michels KB, Palmer JR, Schedin P, Stuebe AM, Watson CJ, Sherman ME (2013) Postpartum remodeling, lactation, and breast cancer risk: summary of a National Cancer Institute-sponsored workshop. J Natl Cancer Inst 105(3):166–174. https://doi.org/10.1093/jnci/djs505
22. Yang XR, Figueroa JD, Falk RT, Zhang H, Pfeiffer RM, Hewitt SM, Lissowska J, Peplonska B, Brinton L, Garcia-Closas M, Sherman ME (2012) Analysis of terminal duct lobular unit involution in luminal A and basal breast cancers. Breast Cancer Res 14(2):R64. https://doi.org/10.1186/bcr3170
23. Shinde SS, Forman MR, Kuerer HM, Yan K, Peintinger F, Hunt KK, Hortobagyi GN, Pusztai L, Symmans WF (2010) Higher parity and shorter breastfeeding duration: association with triple-negative phenotype of breast cancer. Cancer 116(21):4933–4943. https://doi.org/10.1002/cncr.25443
24. Islami F, Liu Y, Jemal A, Zhou J, Weiderpass E, Colditz G, Boffetta P, Weiss M (2015) Breastfeeding and breast cancer risk by receptor status—a systematic review and meta-analysis. Ann Oncol 26(12):2398–2407. https://doi.org/10.1093/annonc/mdv379
25. Lambertini M, Santoro L, Del Mastro L, Nguyen B, Livraghi L, Ugolini D, Peccatori FA, Azim HA Jr (2016) Reproductive behaviors and risk of developing breast cancer according to tumor subtype: a systematic review and meta-analysis of epidemiological studies. Cancer Treat Rev 49:65–76. https://doi.org/10.1016/j.ctrv.2016.07.006
26. Rosenberg L, Thalib L, Adami HO, Hall P (2004) Childbirth and breast cancer prognosis. Int J Cancer 111(5):772–776. https://doi.org/10.1002/ijc.20323
27. Barnett GC, Shah M, Redman K, Easton DF, Ponder BA, Pharoah PD (2008) Risk factors for the incidence of breast cancer: do they affect survival from the disease? J Clin Oncol 26(20):3310–3316. https://doi.org/10.1200/jco.2006.10.3168
28. Alsaker MD, Opdahl S, Romundstad PR, Vatten LJ (2013) Association of time since last birth, age at first birth and parity with breast cancer survival among parous women: a register-based study from Norway. Int J Cancer 132(1):174–181. https://doi.org/10.1002/ijc.27593
29. Halmin M, Bellocco R, Lagerlund M, Karlsson P, Tejler G, Lambe M (2008) Long-term inequalities in breast cancer survival—a ten year follow-up study of patients managed within a National Health Care System (Sweden). Acta Oncologica 47(2):216–224. https://doi.org/10.1080/02841860701769768
30. Lyons TR, O'Brien J, Borges VF, Conklin MW, Keely PJ, Eliceiri KW, Marusyk A, Tan AC, Schedin P (2011) Postpartum mammary gland involution drives progression of ductal carcinoma in situ through collagen and COX-2. Nat Med 17(9):1109–1115. https://doi.org/10.1038/nm.2416
31. O'Brien J, Lyons T, Monks J, Lucia MS, Wilson RS, Hines L, Man YG, Borges V, Schedin P (2010) Alternatively activated macrophages and collagen remodeling characterize the postpartum involuting mammary gland across species. Am J Pathol 176(3):1241–1255. https://doi.org/10.2353/ajpath.2010.090735
32. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H (2009) Breast cancer in young women: poor survival despite intensive treatment. PLoS ONE 4(11):e7695. https://doi.org/10.1371/journal.pone.0007695
33. Baselga J, Campone M, Piccart M, Burris HA III, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366(6):520–529. https://doi.org/10.1056/NEJMoa1109653
34. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L (2016) Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol 13(11):674–690. https://doi.org/10.1038/nrclinonc.2016.66
35. Butt S, Borgquist S, Garne JP, Landberg G, Tengrup I, Olsson A, Manjer J (2009) Parity in relation to survival following breast cancer. Eur J Surg Oncol 35(7):702–708. https://doi.org/10.1016/j.ejso.2008.03.017
36. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Livingston RB, Davidson NE, Perez EA, Chavarri-Guerra Y, Cameron DA, Pritchard KI, Whelan T, Shepherd LE, Tu D (2013) Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole. Ann Oncol 24(2):355–361. https://doi.org/10.1093/annonc/mds330
37. Hill K (1996) The demography of menopause. Maturitas 23(2):113–127