



Parity Differently Affects the Breast Cancer Specific Survival from Ductal Carcinoma In Situ to Invasive Cancer: A Registry-Based Retrospective Study from Korea

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ABSTRACT

PURPOSE: Multiparity might increase general mortality for women, but has inconclusive in patients with breast cancer. Here, we aim to discover their effect in terms of the breast cancer development hypothesis: from ductal carcinoma in situ to invasive carcinoma.

METHODS: We included 37 947 patients from the web-based breast cancer registration program of the Korean Breast Cancer Society and analyzed survivals using multivariate Cox regression analysis and whether the associations of these factors displayed linear trends. They were divided into the following groups: (1) pure ductal carcinoma in situ (DCIS), (2) invasive ductal carcinoma (IDC) mixed with intraductal component (DCIS-IDC), and (3) node negative pure IDC.

RESULTS: The mean age was 48.9 ± 9.9 years including premenopausal women was 61.8%. Although patients with parities of 1-3 had better prognosis compared with patients with nulliparous women, high parity (≥ 4) increased the hazard ratio (HR) of overall survival (OS) (DCIS: HR, 1.52; 95% confidence interval [CI] 0.62-3.78; IDC: HR, 1.43, 95% CI 0.89-2.31; and DCIS-IDC: HR, 1.44, 95% CI 0.45-4.59) during 84.2 (± 10.7) months. For breast cancer specific survival (BCSS), the HR of the IDC group (*P-value for trend* = .04) increased along with increasing parity and was worse than nulliparous patients, and the HR of the DCIS-IDC group increased but was better than nulliparous patients (*P-value for trend* = .02). Compared with nulliparous patients, any age at first birth (AFB) decreased HR of OS in the DCIS and IDC groups (DCIS: *P* = .01; IDC: *P* = .04).

CONCLUSIONS: Parity show dual effects on OS of women with all ductal typed breast cancer but show different effects on BCSS in Korea.

KEYWORDS: Parity, breast cancer, age at first birth, survival

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Introduction

Women who have not given birth are known to be at higher risk for all-cause mortality, and moderate-level parity is inversely associated with all-cause mortality.^{1,2} High parity-related all-cause death risk is proposed to be related to an increased risk of cardiovascular diseases among women. In addition, physical and psychological stress arising from pregnancy and childbearing may also increase the risk of death, especially among people with high parity (e.g. six or more live births).²

On the other hand, the physical changes related to reproduction may also play an important role in reducing all-cause

mortality. Both in vitro and in vivo studies have suggested that endogenous estrogens may protect women from pancreatic cancer, which is one of the leading causes of cancer-related deaths.^{3,4} In addition, while parity is inversely associated with the risk of breast cancer among women, others have reported that high parity can promote aggressive tumors, as there have been positive associations between a high parity and invasive breast cancer.^{5,6}

Invasive ductal carcinoma (IDC) is assumed to arise from a pre-existing ductal carcinoma in situ (DCIS) lesion, which is a recognized precursor for IDC.⁷ However, much epidemiological evidence shows that atypical ductal hyperplasia (ADH) and



DCIS often never progress to IDC,^{8,9} and DCIS is therefore termed a non-obligatory precursor to IDC.^{10,11} Furthermore, experimental data have shown that carcinoma precursor cells in DCIS lesions, suggesting that the aggressive phenotype of breast cancer is predetermined early at the premalignant stage. Cowell et al¹² suggested hypothetical models of progression from in situ to invasive breast cancer. First is progression from DCIS to IDC as a convergent phenotype, where several combinations of somatic genetic and/or epigenetic aberrations result in the acquisition of the biological properties required for cancer cells to progress from in situ to invasive cancer. Second progression model is as an evolutionary bottleneck. As DCIS develops, cells accumulate somatic mutations and copy number aberrations to generate a heterogeneous lesion with distinct subclones harboring private mutations in addition to the founder genetic aberrations present in all neoplastic cells. Only subclones harboring a specific repertoire of genetic aberrations are selected and pass through the evolutionary bottleneck of progression to IDC. Currently, it is not possible to predict accurately which DCIS would be more likely to progress to invasive breast cancer as neither the significant drivers of the invasive transition have been identified. Therefore, synchronous DCIS and invasive breast cancers (DCIS-IDC) are one of attractive phenotype to recapitulating this hypothesis.

Reproductive factors could make epigenetic aberrations on mammary carcinogenesis. If reproductive factors of DCIS-IDCs present similar to DCIS, then they are likely to play early step carcinogenic roles from DCIS to DCIS-IDC, and while the reproductive factors of DCIS-IDC may be similar to IDC, they could be likely to play late step carcinogenesis. There is a lack of trials that investigate this topic.

Information from the Korean Breast Cancer Society showed that reproductive factors, including early menarche, late menopause, late first birth, and no breastfeeding increased steadily in Korean women with breast cancer from 1996 to 2004.¹³ Reproductive events associated with tumor initiation or progression mostly occurred in the premenopausal period. Furthermore, the proportion of premenopausal breast cancer in Korea was higher than in Western countries.¹⁴ Therefore, we aimed to explore the reproductive factors of IDC, DCIS, and DCIS-IDC, and to determine how they affect the clinical outcomes of each carcinoma.

Methods and Materials

Study population

A total of 66 472 patients who were diagnosed with breast cancer were registered in the Korean Breast Cancer Society Registry between January 1993 and December 2011. The Korean Breast Cancer Society Registry has been described in detail elsewhere.¹⁵ Patients with clinically node-positive breast cancer, metastatic breast cancer, and unknown reproductive data were excluded for including early premalignant or

malignant breast cancers. After which, a total of 37 947 patients were included for final analysis. The total study cohort was divided into three sets: (1) pure DCIS (11 404 patients; DCIS group, ICD-10 (Version 2010), D05), (2) IDC mixed with an intraductal component (DCIS-IDC) (3328 patients; DCIS-IDC group), and (3) pure IDC (23 215 patients; IDC group; ICD-10, C50). DCIS-IDC was defined as IDC with an intraductal component that was >80% of the entire tumor size because we focused to early developed breast cancers according to previous hypothesis.^{12,16} Patients with both DCIS and microinvasion (T1 mic) were included in the DCIS-IDC group because American Joint Committee on Cancer. When multifocal primary lesions were found, we mainly evaluated invasive cancers. Personal interviews were conducted with each patient at the time of diagnosis to generate information about each subject, including demographic information, reproductive variables (age at menarche, pregnancy, childbirth, and age at first birth [AFB]) after informed consent. The tumor characteristics were obtained from pathology reports registered in the cancer registry database. The proportion of missing reproductive data in the DCIS, IDC, and DCIS-IDC groups were 40.6%, 27.4%, and 21.2%, respectively, because some women expressed private freedom of disclosure personal information.

Reliable Ki-67 labeling index assessment was not available in this period. The breast cancer sample were categorized into breast cancer sub-types based on immunohistochemical estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status as follows; Luminal A tumors were ER+ and/or PR+ and HER2-; luminal B tumors were ER+ and/or PR+ and HER2+; HER2-overexpressing tumors were ER-, PR-, and HER2+; and triple-negative breast cancer (TNBC) were ER-, PR-, and HER2-.

Patient survival data, including date 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 Korean National Statistical Office, which had complete death statistics recorded by a unique identification number assigned to each Korean resident. Overall survival (OS) was defined as survival without any cause death and breast cancer specific survival (BCSS) as survival without recurrence or distant metastasis of primary breast cancer.

The last follow-up time for surviving patients was December 31, 2012. Mean duration of follow-up was 84.2 ± 10.7 months (range 1-302 months). The mean age was 48.9 ± 9.9 years (range 18-98 years) including patients less than 50 years was 55.57% (n=21 089) and patients more than 50 years was 44.43% (n=16 858) of all study population.

Statistical analyses

The associations among the three cohorts and patient characteristics and tumor characteristics were determined using the

Table 1. Baseline characteristics of patients in the DCIS, IDC, and DCIS-IDC groups.

	DCIS GROUP (N=11 404)	IDC GROUP (N=23215)	DCIS-IDC GROUP (N=3328)
Mean age at diagnosis, years	48.8 ± 9.9	49.8 ± 10.2	48.4 ± 9.7
Mean BMI (kg/m ²)	23.0 ± 6.9	23.5 ± 9.4	23.1 ± 3.2
Mean tumor size, cm	2.3	1.4	1.2
	N (%)	N (%)	N (%)
Intrinsic subtype			
Luminal A	5549 (66.5)	13219 (64.7)	1377 (46.9)
Luminal B	981 (11.7)	1840 (9.0)	396 (13.5)
HER2/neu	1108 (13.3)	1695 (8.3)	792 (27.0)
TNBC	708 (8.5)	3673 (18.0)	373 (12.7)
Type of treatment			
BCS	6340 (57.8)	15 111 (66.2)	1309 (40.2)
MRM	4424 (40.4)	7684 (33.7)	1944 (59.7)
RT (+)	4648 (51.7)	13 513 (67.4)	1220 (39.6)
Chemotherapy (+)	541 (6.2)	11 694 (57.2)	1017 (32.8)
ET (+)	5784 (64.7)	14 180 (72.7)	1870 (61.8)

Abbreviations: BCS, breast cancer surgery; BMI, body mass index; DCIS, ductal carcinoma in situ; DCIS-IDC, invasive ductal carcinoma with predominant intraductal component; ET, endocrine therapy; HER2/neu, human epidermal growth factor receptor 2/neu; HG, histologic grade; IDC, invasive ductal carcinoma; MRM, modified radical mastectomy; NG, nuclear grade; RT, radiation therapy; TNBC, triple-negative breast cancer.

chi-square test and Analysis of Variance (ANOVA) test. Associations between each group (IDC vs DCIS, DCIS vs DCIS-IDC, and DCIS-IDC vs IDC) and patients' reproductive events were determined using the chi-square test. Multivariate Cox proportional hazard models were used to determine the effect of reproductive factors on BCSS and OS rates according to three cohorts. Hazard ratio (HR) and 95% confidence interval (CI) were calculated for the following study factors: Age at first pregnancy (AFP) (<20 years, 20-24, 25-29 years, ≥30 years) and number of children (nulliparous, 1, 2, 3, 4, ≥5). All analyses were adjusted for age at diagnosis. We also assessed whether the associations of parity or AFB displayed linear trends in relation to breast cancer, as expressed by *P*-values for the trends. All analyses were performed using SAS EG, version 5.1 (SAS Institute, Inc., Cary, NC, USA). Alpha for all statistical tests was 0.05. Statistical significance was assumed for *P* < .05.

Results

Patients' characteristics

Among the 37 947 patients with breast cancer, the mean age was 48.9 ± 9.9 years, and 61.8% of the patients were premenopausal women. The DCIS-IDC group had lower proportion of luminal A (46.7%) but higher proportion of HER2

expression (27.0%) and luminal B (13.5%) type cancer. The IDC group had higher proportion of TNBC (18.0%), and the DCIS group had higher proportion of luminal A type breast cancer (66.5%).

Local treatments differed according to the histologic type of breast cancer. Mastectomy was performed in the DCIS-IDC group, and breast cancer surgery (BCS) was performed in the IDC group. Patients in the IDC group mostly received radiation therapy, because BCS was recommended for their disease stage. Chemotherapy was performed in 57% of the patients in the IDC group and 32.8% of those in the IDC-DCIS group. The clinicopathologic factors of the three groups are summarized in Table 1.

DCIS (58.4%) and DCIS-IDC (58.3%) groups had higher proportions of patient diagnosed before 50 years of age compared with IDC group, respectively, and the IDC group had more married patients (94.8%) than other groups. Except for nulliparous women, the DCIS group had more patients with an AFB <20 years (50.3%) and less patients with an AFB ≥30 (7.6%) compared with each DCIS or IDC groups. The DCIS-IDC group had more patients with an AFB ≥30 (13.4%) compared with each DCIS or IDC groups, and the IDC group had more patient with more than three births compared with each DCIS or IDC groups. Reproductive characteristics of the three groups are summarized in Table 2.

Table 2. Reproductive characteristics at diagnosis in the DCIS, IDC, and DCIS-IDC groups.

	DCIS GROUP		IDC GROUP		DCIS-IDC GROUP		DCIS VS IDC	DCIS VS DCIS-IDC	IDC VS DCIS-IDC
	N	%	N	%	N	%			
Age at diagnosis, years									
	(n=11 404)		(n=23 215)		(n=3328)				
<50	6668	58.4	12 479	53.8	1942	58.3	<0.05	0.90	<0.001
≥50	4736	41.6	10 736	46.2	1386	41.7			
Married									
	(n=7641)		(n=18 444)		(n=2905)				
No	527	6.9	955	5.2	185	6.4	<0.05	0.33	0.007
Yes	7114	93.1	17 489	94.8	2720	93.6			
Age at first birth among parous women, years									
	(n=11 169)		(n=22 786)		(n=3273)				
<20	5737	50.3	8801	37.9	1105	33.2	<0.001	<0.001	<0.001
20-24	1535	13.5	4288	18.5	621	16.5			
25-29	3018	26.5	7649	32.9	1176	35.3			
≥30	879	7.6	2048	8.9	371	13.4			
Number of children among parous women									
	(n=6536)		(n=16 418)		(n=2566)				
1	1120	17.1	2602	15.8	449	17.5	<0.001	0.89	0.007
2	3825	58.5	9416	57.4	1508	58.8			
3	1142	17.5	2969	18.1	427	16.6			
4	287	4.4	892	5.4	114	4.4			
≥5	162	2.5	539	3.3	68	2.7			
Breast-feeding among parous women									
	(n=6596)		(n=16 036)		(n=2659)				
Never	2233	33.9	4705	29.3	794	29.9	<0.05	0.0002	0.58
Ever	4363	66.1	11 331	70.7	1865	70.1			

Abbreviations: DCIS, ductal carcinoma in situ; DCIS-IDC, invasive ductal carcinoma with predominant intraductal component; IDC, invasive ductal carcinoma.

Relationship between reproductive factors and survival according to the histologic type of breast cancer

In terms of OS, three groups showed significantly different results (DCIS-IDC, HR=1.0 [ref]; IDC, 1.24 [95% CI 1.02-1.52]; DCIS, HR=0.63 [95% CI 0.50-0.80]) (Table 3). In terms of BCSS, DCIS-IDC showed significantly different results from DCIS (HR=0.38 [95% CI 0.26-0.54], $P<.0001$), and DCIS-IDC showed different results from IDC groups (HR=1.18 [95% CI 0.89-1.56], $P=.25$), but this is insignificant (Table 3).

The HR of all groups gradually decreased with increasing parity, but increased when patients with more than four births, and the associations of parity with OS significantly displayed linear trends (DCIS; P -value for trend $<.0001$, IDC; P -value for trend $<.0001$, DCIS-IDC; P -value for trend $=.005$) (Table 4). In terms of BCSS, the HR of the IDC group gradually increased with increasing parity (P -value for trend $=.04$) compared with nulliparous women with breast cancer. Although the HRs of the DCIS-IDC group were less than nulliparous patients, the higher the number of children, the greater the risk of BCSS (P -value for trend $=.02$) (Table 4)

Table 3. Hazard ratio (HR) and 95% confidence interval (CI) for association between survival and breast cancer type from DCIS to IDC.

	B	STANDARD ERROR	WALD	P	HR	95%	
						LOWER	UPPER
OS	DCIS-IDC	ref					
	DCIS	-0.45	0.12	14.4	.0001	0.63	0.50 0.80
	IDC	0.21	0.10	4.4	.035	1.24	1.02 1.52
BCSS	DCIS-IDC	ref					
	DCIS	-0.97	0.18	27.2	<.0001	0.38	0.26 0.54
	IDC	0.16	0.14	1.2	.25	1.18	0.89 1.56

Abbreviations: BCSS, breast cancer specific survival; CI, confidence interval; DCIS, ductal carcinoma in situ; DCIS-IDC, invasive ductal carcinoma with intraductal component; HR, hazard ratio; IDC, invasive ductal carcinoma; OS, overall survival.

Table 4. Trends between parity and prognosis of patients with breast cancer in the DCIS, IDC, and DCIS-IDC groups.

PARITY	OS							
	DCIS GROUP			IDC GROUP			DCIS-IDC GROUP	
	HR	95% CI		HR	95% CI		HR	95% CI
Nulliparous	1.00	ref		1.00	ref		1.00	ref
1	0.73	0.31	1.72	0.66	0.41	1.06	0.321	0.09 1.10
2	0.58	0.26	1.28	0.69	0.45	1.08	0.454	0.16 1.28
3	0.38	0.15	0.95	1.00	0.64	1.58	0.729	0.25 2.16
4	1.52	0.62	3.78	1.43	0.89	2.31	1.44	0.45 4.59
≥5	3.41	1.41	8.22	2.02	1.23	3.29	1.118	0.30 4.16
P-value for trend	<.0001			<.0001			.005	
PARITY	BCSS							
	DCIS GROUP			IDC GROUP			DCIS-IDC GROUP	
	HR	95% CI		HR	95% CI		HR	95% CI
Nulliparous	1.00	ref		1.00	ref		1.00	ref
1 child	2.09	0.26	16.73	1.66	0.66	4.21	0.12	0.02 0.72
2 children	1.22	0.16	9.25	1.71	0.70	4.17	0.32	0.09 1.07
3 children	0.84	0.09	7.47	2.07	0.83	5.13	0.48	0.13 1.78
4 children	2.36	0.25	22.72	2.76	1.07	7.12	1.163	0.29 4.65
≥5 children	4.44	0.46	42.69	2.75	1.02	7.42	0.61	0.10 3.63
P-value for trend	.20			.04			.02	

Abbreviations: BCSS, breast cancer specific survival; CI, confidence interval; DCIS, ductal carcinoma in situ; DCIS-IDC, invasive ductal carcinoma with intraductal component; HR, hazard ratio; IDC, invasive ductal carcinoma; OS, overall survival.

Any AFB increased HR of BCSS in both DCIS groups and IDC groups, and decreased HR of BCSS in DCIS-IDC group. But they did not show linear trends. However, the HR of OS decreased with older AFB in both the DCIS and IDC groups and show significant linear trends (DCIS, $P = .01$; IDC, $P = .04$) (Table 5).

Discussion

In general, parity in women has been known to have a dual, non-linear effect on life span, and less than three births is associated with a higher survival than more than three births or nulliparous status. Women with a higher parity would be considered to have the physical, physiologic, and financial

Table 5. Trends between AFB and prognosis of patients with breast cancer in the DCIS, IDC, and DCIS-IDC groups.

AFB	OS								
	DCIS GROUP			IDC GROUP			DCIS-IDC GROUP		
	HR	95% CI		HR	95% CI		HR	95% CI	
Nulliparous	1.00	ref		1.00	ref		1.00	ref	
<20 years	0.66	0.31	1.42	0.89	0.58	1.37	0.72	0.26	1.99
20-24 years	1.09	0.49	2.46	0.96	0.62	1.50	0.79	0.28	2.28
25-29 years	0.49	0.22	1.12	0.73	0.47	1.14	0.54	0.19	1.53
≥30 years	0.77	0.31	1.89	0.77	0.47	1.13	0.17	0.04	0.76
P-value for trend	0.01			0.04			0.07		
AFB	BCSS								
	DCIS GROUP			IDC GROUP			DCIS-IDC GROUP		
	HR	95% CI		HR	95% CI		HR	95% CI	
Nulliparous	1.00	ref		1.00	ref		1.00	ref	
<20 years	1.47	0.20	10.81	1.85	0.76	4.51	0.44	0.13	1.48
20-24 years	2.02	0.26	15.61	2.16	0.88	5.32	0.55	0.16	1.92
25-29 years	1.42	0.19	10.76	1.59	0.65	3.91	0.37	0.12	1.26
≥30 years	1.43	0.16	12.81	1.88	0.73	4.81	0.15	0.03	0.91
P-value for trend	0.88			0.15			0.24		

Abbreviations: IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; DCIS-IDC, invasive ductal carcinoma with intraductal component; HR, hazard ratio; CI, confidence interval; AFB, age at first birth.

stress of a larger family unit.^{2,17} During pregnancy and lactation, women would be exposed to a transiently different gestational hormonal environment such as increased estrogen, progesterone, prolactin, and growth hormone concentrations, which were known as stimulating breast tumor cells.¹⁸ A higher expression of prolactin levels tended to be associated with increasing parity and worse survival among perimenopausal or postmenopausal women.¹⁹

Several studies have shown the association between reproductive and hormonal factors and mortality among women with other cancers.²⁰⁻²⁸ Most studies have found that giving birth at an early age may confer a protective effect on the risk of death from pancreatic, ovarian, colon, Non Hodgkin Lymphoma (NHL), kidney, brain, and liver cancer.²⁰⁻²⁶ However, premenopausal women who are of higher parity may experience increased risks of death from gallbladder or gastric cancers.^{27,28}

The effect of estrogen on cancer survival has not been clearly concluded, although related factors to prolonged estrogen exposure, including early menarche and late menopause, are well-known risk factors of breast cancer.^{29,30} Similar results which a high parity (≥4 births) was related to poorer breast cancer survival compared with nulliparity or 1-3 births have also been reported in several previous studies.³¹⁻³⁷

However, in the current study, we also found dual effect of parity on all cohorts, which agrees with the results of a previous prospective, large-scale study.³⁸ Contrary to the effects on OS, high parity did not show this dual effect, and increasing parity linearly increased the HR of BCSS in the IDC cohort. However, in the DCIS-IDC cohort, parity showed a dual effect, and these findings were not consistent with other Korean cohorts.³⁹ Although certain risk factors for breast cancer incidence may also affect survival, findings have been inconsistent and the long-term role of childbirth remains unknown.^{31,33,36} Differences between studies could occur, including distinct patient populations (including advanced breast cancer or excluding in situ), different subgroup analyses, and duration of observation, and such variables could relate to differential findings.

Although parity is a well-known preventive factor, higher parity could be associated with worse prognosis. Such paradoxes generally tend to bias studies toward the null and cause associated contributions to be substantially overestimated, due to the general congruence between risk factors for the index and recurrent events, such as breast cancer.^{40,41}

If synchronous DCIS-IDC is similar to DCIS in group of age, marriage status, and parity according to the hypothesis of breast cancer development from in situ cancer to invasive

cancer sequentially, these factors would be suggested to play a role in the early developmental processes of breast cancer. However, experience of breastfeeding is similar between DCIS-IDC and IDC; they would likely play a role of in late developmental process.

An evolutionary bottleneck model has been supported by several reports that have identified additional copy number alterations and mutations in IDC regions of patients with synchronous DCIS that were absent in DCIS regions.^{42,43} Such data are consistent with the selection of a minor subclone in the ductal regions that expands during invasion. Other genomic studies^{44,45} have reported cases of patients with synchronous DCIS-IDC with high concordance of CNAs between DCIS and IDC regions, which is consistent with convergent phenotype. With the development of next-generation sequencing technologies, many of these studies have identified concordant and discordant mutations in patients with synchronous DCIS-IDC.⁴⁶ The current study supports this evolutionary bottleneck model. Our study has several limitations that should be addressed. First, we did not adjust for important confounding factors such as socioeconomic status, alcohol intake, smoking, education, chronic condition, and AFB, because only the relevant data were collected through a registry. Other information on quality of life, delayed treatment, and complications after the breast cancer diagnosis were not collected and could not be considered in the analyses. Second, the statistical power of the analysis was limited due to further stratification by histologic groups (IDC, DCIS, and DCIS-IDC). Finally, it is another limitation that compared with other population-based studies, this population is young and high missing information. In addition, an 84-month follow-up duration did not show association between parity and risk of death with DCIS.

In conclusion, known reproductive risk factors of breast cancer, specifically the number of children and AFB, may be contributable to survival of patient with breast cancer from DCIS to IDC. In addition, its role may depend on status of breast cancer development from DCIS and DCIS-IDC to IDC, suggesting that hormone-related biological behavior may play heterogeneous roles at each step of breast cancer development.

Author Contributions

JL: conception and design, data interpretation manuscript writing, and final approval of manuscript; MH: data analysis and interpretation and final approval of manuscript; SK, CP, EL, HK, YJ, and KK: data collection and final approval of manuscript.

Availability of Data and Materials

Korean Breast Cancer Registry restricted their dataset by an internal regulation of the Korean Breast Cancer Society. This article was permitted to access the registry by the Korean Breast Cancer Society (approval no: WA 419-20160126-01).

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