Association of Parity and Time since Last Birth with Breast Cancer Prognosis by Intrinsic Subtype

Xuezheng Sun[1], **Hazel B. Nichols**[1,2], **Chiu-Kit Tse**[1], **Mary B. Bell**[2], **Whitney R. Robinson**[1], **Mark E. Sherman**[3,4], **Andrew F. Olshan**[1,2], and **Melissa A. Troester**[1,2,*]

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[3]Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

[4]Breast and Gynecologic Cancer Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA

Abstract

Background—Parity and time since last birth influence breast cancer risk and vary by intrinsic tumor subtype, but the independent effects of these factors on prognosis has received limited attention.

Methods—Study participants were 1,140 invasive breast cancer patients from Phases I and II of the population-based Carolina Breast Cancer Study, with tissue blocks available for subtyping using immunohistochemical markers. Breast cancer risk factors, including pregnancy history, were collected via in-person interviews administered shortly after diagnosis. Vital status was determined using the National Death Index. The association of parity and birth recency with breast cancer (BC)-specific and overall survival was assessed using Cox proportional hazards models.

Results—During follow-up (median =13.5 years), 450 patients died, 61% due to breast cancer (n=276). High parity (3+ births) and recent birth (< 5 years before diagnosis) were positively associated with BC-specific mortality, independent of age, race, and selected socioeconomic factors (parity, reference=nulliparous, adjusted hazard ratio [HR]=1.76, 95% confidence interval [CI]=1.13-2.73; birth recency, reference=10+ years, adjusted HR=1.29, 95% CI=0.79, 2.11). The associations were stronger among patients with luminal tumors and those surviving longer than 5 years.

Conclusions—Parity and recent birth are associated with worse survival among breast cancer patients, particularly among luminal breast cancers and long-term survivors.

Impact—The biological effects of parity and birth recency may extend from etiology to tumor promotion and progression.

*Correspondence to: Melissa A. Troester, Ph.D., Department of Epidemiology, CB 7435, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, (919) 966-7408, troester@unc.edu.

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Keywords

parity; time since last birth; breast cancer subtype; prognosis; survival

Introduction

Reproductive history is an important determinant of breast cancer risk, with a transiently increased risk in the first 5-7 years after last child birth, followed by a long-term risk reduction (1, 2). Increased appreciation of etiologic heterogeneity in breast cancer has added complexity to our current understanding of reproductive risk factors. Risk of basal-like breast cancer/triple-negative breast cancer increases with multiple births and recency of last birth/pregnancy , particularly among young women (3-6), while risk of luminal tumors follows patterns established for breast cancer overall. These findings suggest that pregnancy and the associated events may have mechanistic effects that vary by subtype. The proposed biological mechanisms linking parity and the transiently increased risk of breast cancer include increased hormonal stimulation, expansion of stem/progenitor cells, growth stimuli, and pro-inflammatory and wound-healing changes in microenvironment (7-11). Although the role of these mechanisms in breast cancer heterogeneity is still under investigation, these mechanisms could influence both risk and prognosis.

Parity variables, including number and recency of birth, have had limited study in the association with breast cancer prognosis. While some studies report no association between number of births and prognosis (12-16), other studies report that multiple births are associated with a poorer prognosis (16-19), and still others show improved prognosis among multiparous women (13, 20, 21). These discrepancies may be attributed to different distributions of potential effect measure modifiers such as race and menopausal status, and a different profile of intrinsic subtypes across study populations. In comparison with multiparity, time since last birth shows relatively consistent patterns with survival in previous literature. Recent birth appears to be associated with poor outcome among breast cancers overall (17, 22-24), but associations by breast cancer intrinsic subtype are poorly understood. Using data from the Carolina Breast Cancer Study (CBCS), a large population-based case-control study, we assessed the impact of multiparity and birth recency on overall and breast cancer (BC)-specific survival. These associations were evaluated among breast cancers as a whole and in strata defined by specific breast cancer subtypes (basal-like and luminal).

Materials and Methods

Study Population

The CBCS is a population-based case-control study, the details of which have been described previously (3, 25). Briefly, a total of 1,808 patients aged 20-74 years diagnosed with primary invasive breast cancer during 1993-1996 (Phase I) and 1996-2001 (Phase II) were identified using rapid case ascertainment from NC Central Cancer Registry, with African American and young cases (aged 20-49 years) oversampled using randomized recruitment (25). Participants were interviewed in person within 1 year of diagnosis by

trained nurses who collected anthropometric measurements and questionnaire responses. Clinicopathological information was abstracted from clinical records and pathological reports. All study participants gave written informed consent. The study was approved by the Institutional Review Board of the University of North Carolina (UNC).

Breast cancer subtype classification

The details of breast cancer subtyping have been published previously (3, 26). Briefly, whole, formalin-fixed paraffin-embedded tumor tissues were sectioned and stained for a panel of immunohistochemical (IHC) markers in the IHC Core Laboratory at UNC. The following markers were used to determine breast cancer intrinsic subtypes: luminal A (ER+ and/or PR+, HER2-), luminal B (ER+ and/or PR+, HER 2+), basal-like (ER-, PR-. HER2-, HER1+ and/or cytokeratin 5/6+), HER2-enriched (ER-, PR-, HER2+), and unclassified (negative for all five markers). We combined luminal A and luminal B as luminal tumors due to the small number of luminal B tumors (n=111) and, more importantly, recent revisions to the IHC definition of luminal B (27, 28). Luminal A and B tumors cannot be reliably distinguished without additional markers (such as Ki-67) or RNA expression data (29). Although the information on tumor grade and mitotic index collected in Phase I of the CBCS may help classify luminal B and luminal A, the resulting number of luminal B tumors was too small to generate reliable estimation in survival analyses. In the CBCS, the demographic and tumor characteristics in patients with luminal A and B tumors were comparable except luminal B tumors more likely to be lymph node positive (p=0.01).

Exposure and Outcome Assessment

Parity status was evaluated as number of full-term births. Recency of last birth was calculated as the year of diagnosis minus the year of the last full-term birth. Their values were 0 for nulliparous women. Linkage with the National Death Index provided vital status, dates of deaths, and cause of death on the CBCS cases through December 31, 2011. The detailed description of linking method has been published previously (30). Briefly, deaths among cases were determined using weighted probabilistic scores and predetermined matching cutoffs to establish a maximum of 1 match per individual. International Classification of Diseases (ICD) breast cancer codes 174.9 (ICD-9) or C50.9 (ICD-10) were used to identify deaths due to breast cancer on death certificate.

Statistical Analysis

The current analysis was limited to 1,140 African American or White patients (9 other race cases excluded) with available information on intrinsic subtype, parity, and birth recency. The demographic and tumor characteristics of the excluded cases (n=668) were compared with those of the included cases. No significant differences were detected, except that the excluded cases were less aggressive (more likely to be negative lymph node status, tumor size 2 cm, and stage I). Considering categories used in previous studies (3) and the distribution of patients in the CBCS, the number of full-term live births was grouped into three categories: nulliparous, 1-2 births, and 3 births. Birth recency was evaluated among parous women, and grouped into three categories: <5 years, 5-<10 years, and 10 years. To describe the characteristics of the study population, the distribution of age at diagnosis, menopausal status, race, body mass index (BMI), waist hip ratio (WHR), family history of

breast cancer, education, family income, smoking, alcohol intake, physical activity, the usage of hormone replacement therapy (HRT) and oral conceptive (OC), lymph node status, intrinsic subtype, tumor size, tumor stage, histology group, nuclear grade, histological grade, and mitotic index, were evaluated by multiparity and birth recency categories using Chi-square test or Student's t-test. The assessment and definition of these variables have been described previously (3). Patients living as of December 31, 2011 were censored at the end of follow-up, and those who died of causes other than breast cancer were censored at the time of event for BC-specific analysis. Kaplan-Meier survival curves and log-rank tests were used to compare the difference in overall and BC-specific survivals by multiparity and birth recency.

Cox regression analysis was used to estimate hazard ratio (HR) and 95% confidence interval (CI) for overall and BC-specific death, with nulliparous as reference in multiparity analyses and patients with last birth 10 years as reference in recency analyses. A model adjusted for study design factors (including age, race, and study phase) was considered as the initial model. Potential confounders were selected based on *a priori* knowledge, associations in this particular study, and directed acyclic graphs (DAG). Although obesity, alcohol abstainers, OC usage, smoking, and HRT were suggested to be associated with parity/recency, they were not included in the multivariate analysis considering their weak relationship with mortality based in previously literature and in the present study. Age, race, education, and family income were adjusted as minimally sufficient adjustment set based on DAG (31). Lastly, tumor characteristics, including tumor stage, tumor size, lymph node status, and histology group, were adjusted to evaluate the influence of other prognostic factors. The categorization of covariates is shown in Table 1 and Supplementary Table S1 and S2. Stratified analyses were performed to evaluate effect modification by intrinsic subtype. Only basal-like and luminal strata are presented because unclassified tumors are of biologically uncertain subtype, and because too few patients (n=73) are HER2-enriched for stable estimation. The proportional hazards assumption in each Cox model was assessed using log-log plots of survival and time-dependent cross-product terms of the survival time (years) and the variables of interest, and showed no violation of the assumptions. All statistical tests were two sided with $\alpha=0.05$, all analyses were performed using SAS version 9.2 (SAS Institute), and all figures were generated using R 3.0.0.

Differences in HRs by race and menopausal status within luminal and basal-like tumors were explored. In the analysis by menopausal status, perimenopausal women were excluded to avoid misclassification (n=95). In addition, because studies have suggested that factors predicting survival in early years after diagnosis may differ from those in later years (e.g. with tumor biological and pathologic characteristics dominant in early years and lifestyles dominant in later years) (32), analyses were conducted conditional on follow-up length: data were truncated at five years to evaluate five-year mortality and then survival was assessed conditional upon surviving the first five years. Exploratory analyses were conducted to characterize the dose-response relationship of multiparity and birth recency with mortality. To assess the potential interactions of multiparity-breastfeeding or multiparity-birth recency, compound variables were created and their corresponding HRs were calculated (multiparity-breastfeeding: nulliparous, 1-2 births and ever breastfed, 1-2 births and never breastfed, 3+

births and ever breastfed, and 3+ births and never breastfed; multiparity-birth recency: nulliparous, 1-2 births and last birth <10 years, 1-2 births and last birth 10 years, 3+ births and last birth <10 years, and 3+ births and last birth 10 years). To evaluate the influence of reference selection on estimates for birth recency, we did sensitivity analyses using nulliparous women as reference. In addition, we performed sensitivity analyses 1) including age at first birth and number of birth in the models, and 2) modeling age at diagnosis as an eight-level categorical variable (five-year intervals) and as a quadratic continuous variable.

Results

Patient and tumor characteristics

Among 1,140 breast cancer patients in this study, the average age at diagnosis was 51 years (SD=11.5 years, range=23-74 years). Approximately half of patients were African American (45%) and premenopausal (49%) per the sampling strategy of the CBCS. A total of 967 (85%) women were parous, among which 416 (43%) had 3 or more births. 165 (17% of parous patients) had last full-term birth within 10 years of breast cancer diagnosis. The selected patient demographics by multiparity and by birth recency are shown in Table 1 and detailed in Supplementary Table S1 and S2, respectively. Compared with nulliparous patients, patients with high parity (3+ births) were significantly older, and were more likely to be African American, obese (BMI 30 kg/m^2), lower socioeconomic status (SES) (measured by education and family income), alcohol abstainers, and non-OC users. Patients with high parity also tended to have last birth more than 10 years prior to diagnosis. Consequently, birth recency and multiparity were associated with similar characteristics. Additionally, patients who had given birth 10 years more before breast cancer diagnosis were more likely to be smokers and HRT users than patients with last birth within 5 years.

Luminal tumors comprised the majority of breast cancers (n=731, 64%), followed by basal-like tumors (n=205, 18%), unclassified (n=131, 11%), and HER2-enriched tumors (n=73, 6%). Compared with nulliparous patients, parous patients were more likely to have basal-like breast cancer (frequency was highest in women with birth within 5-<10 years) and lymph node positive tumors (Supplementary Table S1 and S2). Among parous patients, lymph node positive and poorly differentiated tumors were more frequent in women with recent birth (<5 years).

Associations of multiparity and birth recency with prognosis

The median follow-up time was 13.5 years, ranging from 0.2 years to 18.7 years. By the end of follow-up (December 31, 2011), there were 450 deaths, 61% due to breast cancer (n=276). Among breast cancer deaths, 159 (58%) had occurred within 5 years of diagnosis, and 78 (28%) occurred between 5 and 10 years. Patients with higher parity tended to have poorer overall and BC-specific survival (overall, Supplementary Fig. S1; BC-specific, Figure 1). Comparing patients with three or more births to nulliparous patients, the age- and race-adjusted HR was 1.77 (95% CI=1.18-2.66) for BC-specific mortality (Table 2). Parous women with recent birth (<5 years) tended to have an increased risk for BC-specific mortality (adjusted HR=1.28, 95% CI=0.80-2.06, reference=10+ years). Neither multiparity nor birth recency were significantly associated with all-cause mortality (parity 3, adjusted

HR=1.03, 95% CI=0.76-1.39; recency <5 years, adjusted HR=1.31, 95% CI=0.81-2.12; Supplementary Table S3).

The association of multiparity with BC-specific survival remained after adjusting for SES factors (parity 3+, adjusted HR=1.76, 95% CI=1.13-2.73), but were attenuated after further adjustment for tumor characteristics (parity 3, adjusted HR=1.42, 95% CI=0.91-2.23). The association with birth recency was suggested, but statistically insignificant (recency <5 years, adjusted HR=1.29, 95% CI=0.79-2.11). The recency analyses were repeated when including all women and using nulliparous women parous women as reference, and a significantly increased risk for BC-specific mortality in patients with more recent birth was observed (adjusted HR=1.90, 95% CI=1.10-3.34, adjusted for age, race, study phase, and selected SES factors). Dose-response relationships were evaluated without significant results detected (multiparity, p trend=0.40; birth recency, p trend =0.76; adjusted for age, race, study phase, and selected SES factors).

In stratified analyses, multiparity and birth recency showed distinct associations by intrinsic subtype (Figure 1). Compared with luminal tumors, basal-like tumors had a worse survival across different exposure levels, particularly in the first five years of follow-up. Higher parity and more recent birth predicted poorer BC-specific survival, with a stronger association observed in luminal tumors than in basal-like tumors (p-value of the interaction term was 0.09 and 0.11 for multiparity and recency, respectively), although the HR estimates in basal-like tumors were imprecise. As shown in Table 2, the associations of BC-specific mortality with multiparity and recency in women with luminal tumor were independent of age, race, and SES factors (parity 3, adjusted HR=2.34, 95% CI=1.22-4.47, reference=nulliparous; last birth < 5 years, adjusted HR=2.03, 95% CI=1.09-3.81, reference= 10+ years), but was attenuated after adjustment for tumor characteristics. Our sensitivity analysis demonstrated that this increased risk for BC-specific mortality in luminal cases with more recent birth was not confounded by multiparity or age at first birth, nor influenced by the way modeling age at diagnosis (data not shown). Consistent with results among all cases, no association of multiparity or birth recency with overall survival was detected in either luminal or basal-like tumors, except that birth within 10 years was associated with poor outcome in patients with luminal tumors (Supplementary Table S3).

Exploratory analyses

To explore potential temporal difference in the influence of multiparity and recency on survival, we stratified analyses on survival time (5 years), although no statistically significant violation of proportional hazards assumptions were detected. Compared with effect estimates for the first five years, HRs for BC-specific mortality were greater after conditioning on survival to 5 years, particularly among patients with luminal tumors (Table 3). The 5-year conditional associations of multiparity and birth recency in luminal tumors were independent of the tumor characteristics (parity 3, adjusted HR = 2.68, 95% CI=1.02-7.05, reference=nulliparous; last birth < 5 years, adjusted HR = 2.74, 95% CI=1.25-6.00, reference=10+ years). No significant differences were detected by menopausal status, younger age (<40 years) or race, although a stronger effect of birth recency was suggested in White women and younger women with luminal tumors.

We explored the combined effect of multiparity and birth recency on breast cancer prognosis. As presented in Figure 2, parous patients with parity 3 births and recency < 10 years had the worst prognosis after adjustment for age, race, study phase, and SES factors (adjusted HR=2.02, 95% CI=1.09-3.73; reference=nulliparous). Reduced survival was also observed among patients with 1-2 births and recency < 10 years (adjusted HR=1.69, 95% CI=1.06-2.67). No significant association with survival was observed among parous patients with recency 10 years (parity 3 birth and recency 10 years: adjusted HR=1.47, 95% CI=0.87-2.50; parity 1-2 birth and recency 10 years, adjusted HR=1.42, 95% CI=0.92-2.21). Nulliparous patients had the best prognosis. No significant modification of hazard ratios by breastfeeding status was detected. We also evaluated possible immune time bias (due to time elapsed between diagnosis and enrollment) and found that time-to-enrollment did not differ by parity/recency (multiparity, p=0.83; recency, p=0.68).

Discussion

In this study, patients with high parity or recent birth had worse BC-specific survival compared to nulliparous patients or compared to patients who gave birth more than 10 years prior. These associations were independent of age, race, and SES factors, and were attenuated, but not fully explained by tumor characteristics. Stronger effects of parity and birth recency were observed in long-term survivors (i.e. those with survival 5 years) and in patients with luminal tumors.

Birth recency, defined as time interval from last birth until diagnosis, has consistently been related to deleterious tumor characteristics (e.g. advanced stage, high histological grade, and high proportion of hormone receptor-negative tumors) (5, 19, 24), and consequently poor prognosis (19, 22-24). Multiparity has also been associated with higher mortality, particularly BC-specific mortality (20, 33). Our findings are in line with these previous studies. While effects of multiparity and recency of birth are most often considered as separate dimensions of exposure, we considered the joint effects of these two variables. Women with high parity and short time since last birth had the highest BC-specific mortality, while nulliparous women had the lowest BC-specific mortality. These findings indicate that multiparity and recency, as quantitative and temporal measures of pregnancy, may influence the natural history of breast cancer through distinct pathways. Survivorship of nulliparous women relative to parous women has been controversial in previous studies (23, 33-36), with differences in age being one possible explanation for between-study differences. However, in our analysis, flexible modeling of age reduced concerns about possible residual confounding by age and our findings support better prognosis in nulliparous women relative to parous women. The inconsistent findings in previous studies may result from distributional differences in other effect modifiers. Indeed, pregnancy is a complex biological exposure and epidemiologic variable. While we were underpowered to address all parity-related variables (37, 38), other factors beyond number and recency of births (e.g. breastfeeding, age at first birth, and interval between births), may modify the effect of pregnancy in breast cancer development and progression.

Most previous studies of parity and survival considered subtype (usually defined by hormone receptor status) as a confounder (36, 39). However, the heterogeneous association

of parity with breast cancer risk across intrinsic subtype indicates that the underlying mechanisms may be different for each subtype (3-6, 40-42). As a result, we considered subtype as an effect modifier in this study. We found that multiparity and birth recency had weaker effects among patients with basal-like tumors than among patients with luminal tumors. The trend of decreased mortality risk with time since last birth has been reported previously (12, 24, 43), but in our study was confined to luminal tumors. Thus far, there are very few studies examining the influence of multiparity and birth recency on mortality by breast cancer intrinsic/molecular subtype (23, 44). One study was based on 526 young patients (20-44 years) with invasive breast cancer in Japan. Although no association between multiparity and mortality was detected, worse prognosis was observed in patients with more recent birth. Similar to our results, this association was stronger in luminal tumor patients than in all breast cancer patients (HR for 2 years group=3.07 vs 2.19, reference=nulliparous). However, the very small sample size of triple-negative tumors (n=79) and lack of subtype-specific markers for basal-like breast cancer prevented inferences about basal-like breast cancer in that study. In another Israeli study among triple negative breast cancer patients with family history prevalence of 35% (compared with 16% among basal-like tumors in the present study), a significantly poorer survival among women with high parity (4+ children) was observed (HR of survival for nulliparous=0.31, 95% CI=0.10-0.95, reference = 4+) (44). Thus, effect modification by subtype is supported by previous literature as well as our own findings.

Whether the prognostic value of parity is independent of established clinical variables is still under debate. If parity shifts tumors toward more aggressive characteristics at diagnosis, then the effect of parity variables on survival should be diminished upon adjustment for tumor characteristics. In this study, we adjusted for tumor characteristics and found that the adjustment only modestly influenced the effect of parity, consistent with previous studies (23, 36, 39, 45). Furthermore, if parity does not act primarily by altering tumor clinical factors, but through influencing host factors, then likely its effect would be more pronounced in the later survival when the influence of tumor characteristics has decreased. Therefore, we conducted survival analyses conditioning upon the survival of the first five years, and observed a stronger effect of parity among patients surviving longer than five years. How parity, as a host factor, influences BC-specific survival requires better understanding of the long-term biological consequences of pregnancy.

There are many biological mechanisms that have been proposed for pregnancy-associated breast cancer progression. High levels of pregnancy hormones is a plausible mechanism, given the influence of estrogen in breast cancer progression (11, 46-48). Considering the relatively long latent period of breast tumors, the hormonal milieu of pregnancy may stimulate growth and promotion of occult tumor cells. This pathway is expected to specifically influence ER-positive tumors. Alternatively, the post-partum /post-lactation involution hypothesis is also widely accepted, wherein inflammatory changes that accompany involution may promote tumor progression (11). Our previous research showed parity-induced changes in microenvironment gene expression that differed by ER status (49), consistent with the observation in the current investigation that pregnancy may have strongest effects on ER-positive/luminal tumor progression (50).

Our study should be interpreted in light of some limitations. First, as a survival cohort, our study is subjective to immortal person-time bias because participants have to survive to time of enrollment (51). To minimize the impact of this issue, the CBCS used the rapid identification system from NC Central Cancer Registry (25), with the average time interval between interview and diagnosis of 145 days (SD=123). In addition, we evaluated whether time-to-enrollment differed by parity/recency, and concluded that our findings were not substantially affected by immune time bias. Second, while the CBCS oversampled young and African American patients and therefore had a higher proportion of basal-like patients, stratified analyses by subtype still suffered from small sample size and imprecise estimates. For instance, our results demonstrated an effect modification by follow-up period that interestingly showed different patterns by intrinsic subtype, but we were underpowered to detect significant statistical interactions. Analyses among HER2-enriched tumors were also underpowered. Third, we adjusted for several key determinants of therapy (e.g. age, lymph node status, and SES) (52, 53), however treatment data was not collected. Treatment heterogeneity has undoubtedly increased variability in our study, but by controlling for tumor characteristics we have decreased bias due to differences in treatment. Finally, classification of luminal A and B in epidemiologic studies remains problematic. Recent data show that stratification of Luminal A vs. B using HER2 status (as has been done previously in the CBCS) results in substantial misclassification (29). We combined luminal A and B in this analysis, which prevented analysis of luminal A versus B progression.

In summary, our study identified multiparity and birth recency as predictors of breast cancer outcome, deepening the understanding of parity-associated survival. Given that the effect of parity may vary by intrinsic subtype, it may be important to consider reproductive history as a prognostic variable in clinical settings. Studies with large sample size and endocrine treatment data are needed to validate our findings and to further investigate the mechanisms and significance of parity in ER-positive and luminal breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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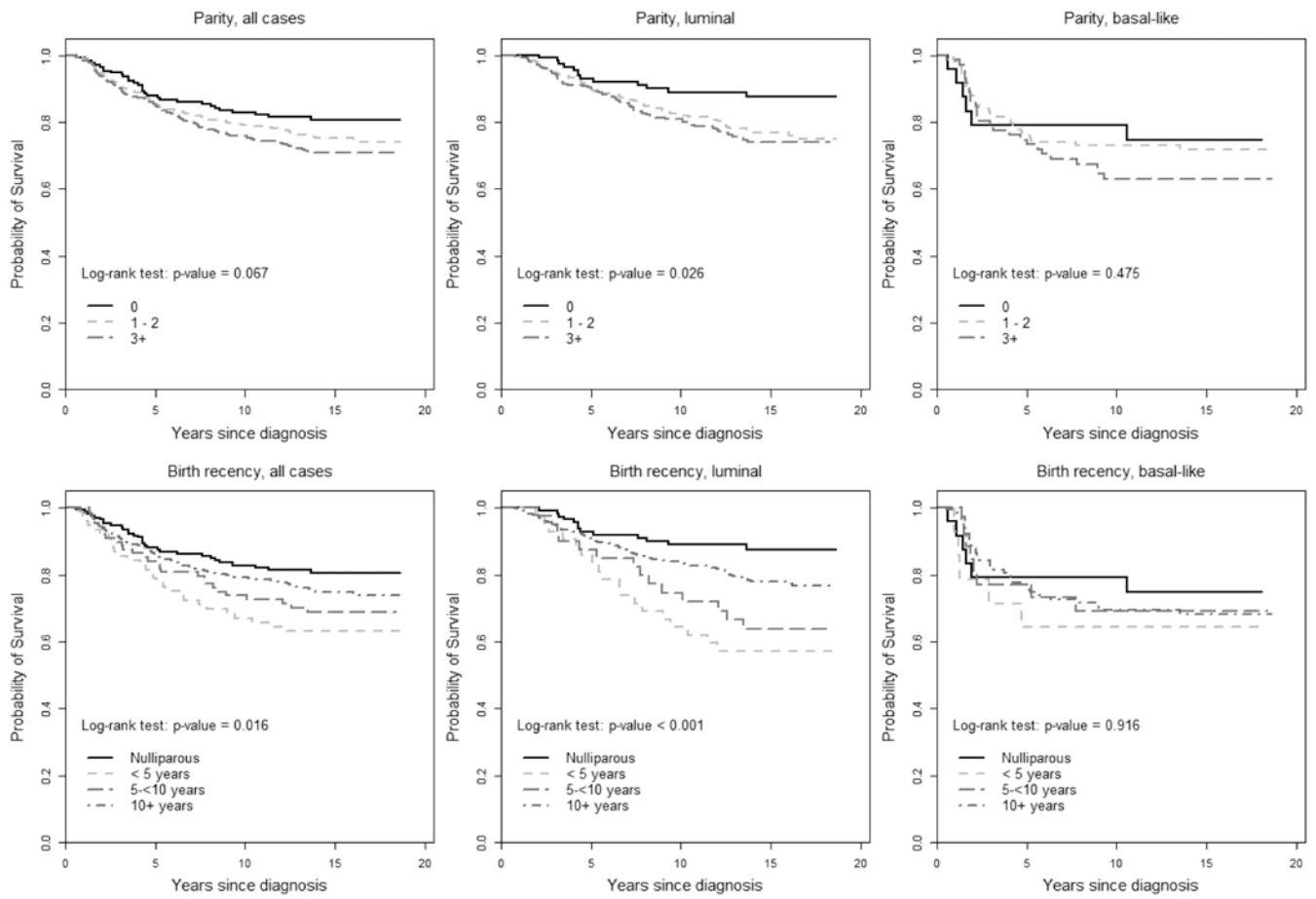
Figure 1.
BC-specific survival by parity and last birth recency, overall, among luminal tumors, and basal- tumors.
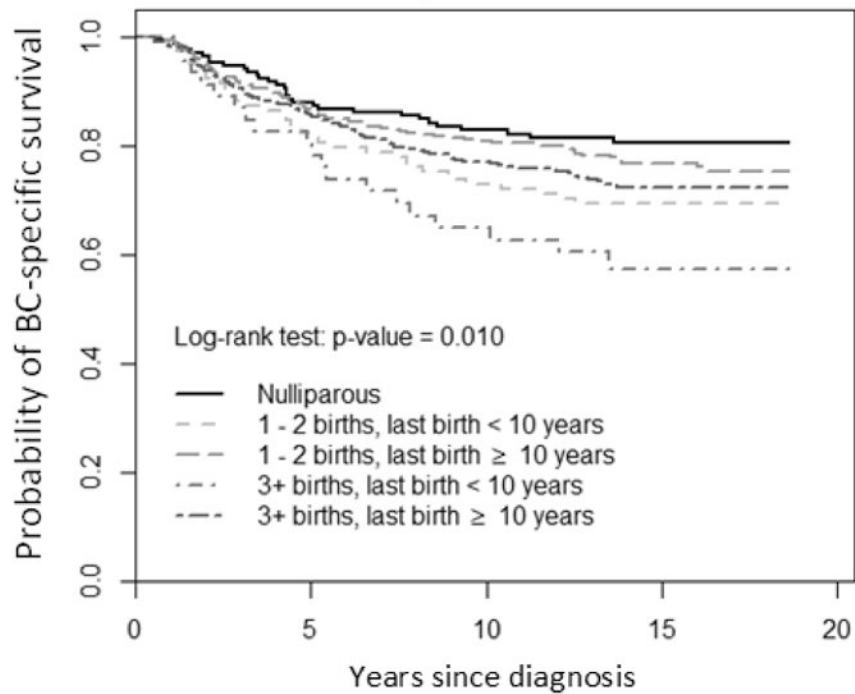
HRs of BC-specific mortality associated with parity and birth recency[a].

Nulliparous (reference, HR=1)	1-2	3+	HRs regardless parity
Time since last birth =10 years	1.42 (0.92, 2.21)	1.47 (0.87, 2.50)	1.51 (1.00, 2.30)
Time since last birth <10 years	1.69 (1.06, 2.67)	2.02 (1.09, 3.73)	1.65 (1.01, 2.68)
HRs regardless recency	1.44 (0.94, 2.19)	1.76 (1.13, 2.73)	

[a]HRs were adjusted for age, race, study phase, income and education.

Figure 2.
BC-specific survival by multiparity-recency groups.

Table 1

The distribution of the selected characteristics, overall and by parity and recency [a].

Characteristics	Overall (n=1140)	Nulliparous (n=173)	Parous (n=967)				
			Parity		Recency		
			1-2 (n=551)	3 (n=416)	<5 years (n=76)	5-<10 years (n=89)	10 years (n=801)
Age (years)							
Mean (SD)	50.64 (12)	49.07 (12.40)	47.91 (10.63)	54.92 (10.98)	35.43 (5.03)	39.46 (5.23)	53.64 (10.20)
<40	194 (17)	40 (23)	114 (21)	40 (10)	59 (78)	44 (49)	51 (6)
40-49	436 (38)	68 (39)	256 (46)	112 (27)	17 (22)	44 (49)	307 (38)
50-59	227 (20)	28 (16)	91 (17)	108 (26)	0 (0)	1 (1)	198 (25)
60	283 (25)	37 (21)	90 (16)	156 (38)	0 (0)	0 (0)	245 (31)
P-value				<0.01		<0.01	
Race							
White	622 (55)	99 (57)	348 (63)	175 (42)	50 (66)	52 (58)	421 (53)
AA	518 (45)	74 (43)	203 (37)	241 (58)	26 (34)	37 (42)	380 (47)
P-value				<0.01		0.10	
Education							
< high school	199 (17)	18 (10)	58 (11)	123 (30)	4 (5)	6 (7)	170 (21)
High school	627 (55)	84 (49)	317 (58)	226 (54)	35 (46)	45 (51)	463 (58)
College	314 (28)	71 (41)	176 (32)	67 (16)	37 (49)	38 (43)	168 (21)
P-value				<0.01		<0.01	
Family income (thousands US dollar)							
<15	244 (23)	32 (20)	78 (15)	134 (35)	14 (19)	9 (11)	188 (26)
15-<30	259 (25)	45 (28)	117 (23)	97 (26)	11 (15)	22 (27)	181 (25)
30-<50	258 (24)	37 (23)	139 (27)	82 (22)	19 (25)	19 (23)	183 (25)
50	293 (28)	44 (28)	183 (35)	66 (17)	31 (41)	33 (40)	185 (25)
P-value				<0.01		<0.01	
Intrinsic subtype							
Luminal	731 (64)	118 (68)	349 (63)	264 (63)	42 (55)	41 (46)	529 (66)
Basal-like	205 (18)	24 (14)	109 (20)	72 (17)	14 (18)	26 (29)	141 (18)

Characteristics	Overall(n=1140)	Nulliparous(n=173)	Parity		Parous (n=967) Recency		
			1-2 (n=551)	3 (n=416)	<5 years (n=76)	5-<10 years (n=89)	10 years (n=801)
Her2-positive	73 (6)	13 (8)	31 (6)	29 (7)	7 (9)	7 (8)	46 (6)
Normal-like	131 (11)	18 (10)	62 (11)	51 (12)	13 (17)	15 (17)	85 (11)
P-value			0.58			0.01	

[a] P-values for the comparisons across parity/recency groups were calculated by Chi-square test for categorical variables except that when expected cell count was less than 5, they were calculated by Fisher exact test. Missing values were excluded from percentage calculations.

Table 2

HRs of BC-specific mortality associated with parity and birth recency, in the CBCS Phases I and II[a].

Variable	Deaths/N	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)
		Parity		
All BC patients				
nulliparous	31/173	1	1	1
1-2	132/551	1.32 (0.89, 1.95)	1.44 (0.94, 2.21)	1.16 (0.76, 1.78)
3+	113/416	1.77 (1.18, 2.66)	1.76 (1.13, 2.73)	1.42 (0.91, 2.23)
Basal-like				
nulliparous	6/24	1	1	1
1-2	30/109	1.05 (0.43, 2.56)	1.28 (0.49, 3.39)	1.44 (0.52, 4.03)
3+	26/72	1.52 (0.61, 3.82)	1.56 (0.58, 4.21)	1.45 (0.52, 4.05)
Luminal				
nulliparous	13/118	1	1	1
1-2	78/349	2.02 (1.12, 3.64)	2.12 (1.14, 3.91)	1.46 (0.78, 2.75)
3+	62/264	2.54 (1.38, 4.68)	2.34 (1.22, 4.47)	1.56 (0.81, 3.03)
		Birth recency		
All BC patients				
10+ years	190/801	1	1	1
5-<10 years	27/89	0.99 (0.63, 1.54)	0.98 (0.61, 1.57)	0.87 (0.53, 1.44)
<5 years	28/76	1.28 (0.80, 2.06)	1.29 (0.79, 2.11)	1.10 (0.64, 1.86)
Basal-like				
10+ years	43/141	1	1	1
5-<10 years	8/26	1.89 (1.03, 3.46)	0.88 (0.37, 2.10)	0.49 (0.19, 1.26)
<5 years	5/14	1.51 (0.83, 2.75)	1.11 (0.39, 3.16)	0.81 (0.29, 2.30)
Luminal				
10+ years	108/529	1	1	1
5-<10 years	14/41	0.86 (0.36, 2.04)	1.51 (0.76, 3.03)	1.66 (0.82, 3.35)
<5 years	18/42	1.13 (0.40, 3.14)	2.03 (1.09, 3.81)	1.85 (0.93, 3.69)

[a]Model 1 was adjusted for age, race, and study phase; model 2 was additionally adjusted for income and education; model 3 was additionally adjusted for tumor stage, tumor size, lymph node status, and histological group.

Table 3

HRs of BC-specific mortality associated with parity and birth recency, by follow-up length, in the CBCS Phases I and II[a].

Variable	5 years		> 5 years	
	Deaths/N	HR (95%CI)	Deaths/N	HR (95%CI)
Parity				
All BC patients				
nulliparous	20/173	1	11/143	1
1-2	78/551	1.26 (0.75, 2.10)	54/459	1.70 (0.84, 3.47)
3+	61/416	1.31 (0.76, 2.24)	52/341	2.51 (1.22, 5.16)
Luminal				
nulliparous	8/118	1	5/102	1
1-2	34/349	1.59 (0.70, 3.61)	44/306	2.87 (1.13, 7.28)
3+	25/264	1.49 (0.63, 3.51)	37/229	3.40 (1.31, 8.82)
Birth recency				
All BC patients				
10+ years	109/801	1	81/665	1
<5 years	16/76	1.20 (0.65, 2.22)	12/60	1.40 (0.72, 2.75)
5-<10 years	14/89	0.86 (0.46, 1.61)	13/74	1.14 (0.60, 2.16)
Luminal				
10+ years	48/529	1	60/463	1
<5 years	6/42	1.38 (0.54, 3.51)	12/36	2.62 (1.27, 5.40)
5-<10 years	5/41	0.89 (0.27, 2.98)	9/35	2.03 (0.91, 4.51)

[a]HRs were adjusted for age, race, study phase, income and education. The data of basal-like tumors is not shown because of no reliable 5-year conditional HRs generated due to small sample size.