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ORIGINAL PAPER

Association between reproductive factors and breast cancer survival in younger women

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Abstract This analysis investigated whether reproductive factors such as age at menarche, parity, and timing and outcomes of pregnancies were associated with survival among women with breast cancer younger than 55 years. Female residents of Atlanta, Georgia, and central New Jersey who were diagnosed with a primary, incident invasive breast cancer between 1990 and 1992 and enrolled in a population-based study (n = 1,264) were followed for 8–10 years. Detailed exposure and covariate information was collected via in-person interviews administered shortly after diagnosis. Vital status as of January 1, 2000 was ascertained through the National Death Index via the state cancer registries (n = 292 deaths). Cox regression methods were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) adjusted for confounders. Parity of 4 or more births, as compared with nulliparity, was positively associated with all-cause mortality, [HR (95% CI) = 1.71 (1.09–2.67)]. Increased mortality was associated with having given birth within 5 years prior to diagnosis (≤5 vs. >5 years) [1.78 (1.28–2.47)], and was more pronounced among women with a pre-diagnostic body mass index of <25 kg/m^2 [2.54 (1.61–4.00)]. Early age at menarche and early age at first birth also modestly increased mortality; history of miscarriage, induced abortion, and ever breastfeeding were not related to survival. These results may help

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elucidate breast cancer progression mechanisms and enable a better understanding of how reproductive characteristics influence breast cancer survival.

Keywords Breast cancer · Reproductive factors · Reproductive history · Survival

Abbreviations

AJCC	American Joint Committee on Cancer
BMI	Body mass index
CI	Confidence interval
ER+	Estrogen receptor positive
GA	Georgia
HR	Hazard ratio
NDI	National Death Index
NJ	New Jersey
SEER	Surveillance, Epidemiology, and End Results Program

Introduction

An estimated 212,920 new cases of breast cancer and 40,970 deaths from the disease will occur among American women in 2006 [1]. The prevalence of invasive female breast cancer was estimated to be 2.28 million in 2002 [2]. Despite the importance of tumor characteristics such as stage and molecular markers in determining survival [3], it has been estimated that prognostic classification schemes based on tumor size, grade, and receptor status in node-negative patients explain only a small fraction of the variation (~10%) in survival [4]. Adding lymph node status may raise this value to 20% [5]. Thus, other factors warrant investigation. In particular, there are few data on survival in younger women who usually experience higher mortality than older women [2].

Reproductive events result in life-long changes in the hormonal milieu. Pregnancy decreases circulating estradiol levels and increases sex hormone binding globulin levels, thus reducing bioavailable estradiol and permanently lowering prolactin levels [6]. Late age at menarche has also been correlated with lower urinary estrogen metabolite levels [7]. Reproductive factors such as early menarche, nulliparity, older age at first birth, and fewer births are well-established risk factors for breast cancer incidence [8], but their effect on survival is less well understood [9–30].

Hormonal influences are implicated in tumor progression since serum estrogen levels have been inversely correlated with disease-free survival [31]. Estrogen deprivation, through adjuvant systemic therapy or, in younger women, ovarian ablation, is effective in reducing tumor recurrence and death and is recommended for almost all women with estrogen receptor-positive (ER+) tumors [32].

Studies investigating the influence of reproductive history on breast cancer mortality may increase our understanding of possible reasons for decreased survival in certain groups of women in the United States. This research is timely given the secular changes in age at menarche and childbearing patterns in recent cohorts of women [33, 34]. For example, any effect of timing of pregnancies on survival after diagnosis may become increasingly relevant as women postpone childbearing into older ages.

This large, population-based study of younger breast cancer patients with carefully constructed reproductive history data was designed, first, to provide additional data on inconsistent and less well-studied reproductive characteristics and survival, including age at menarche, parity, age at first and last birth, pregnancy outcomes, and breastfeeding. Secondly, we sought to confirm the association of poor survival with recency of birth and to more precisely establish the length of time since a woman's last birth that is associated with increased mortality.

Methods

Study population

This follow-up study included eligible patients previously enrolled in a population-based case–control study of breast cancer (n = 1,283) [35]. Those eligible were women, aged 20–54 years, who resided in a 5-county area of central New Jersey (n = 452) or in the Atlanta, Georgia, metropolitan area (n = 831), and had received a diagnosis of primary, invasive breast cancer between May 1, 1990 and December 31, 1992. Cases were identified through population-based registries using rapid-ascertainment systems. Detailed baseline exposure and covariate information was collected in the original case–control study via structured in-person interviews administered by trained interviewers that lasted an average of 67 min. The interview was completed by 86% of eligible patients with in situ and invasive cancer and occurred a median 4.2 months after diagnosis [35]. Nineteen participants were missing vital status, leaving 1,264 subjects for analysis. Institutional Review Boards at collaborating institutions approved this study.

Exposure assessment

With the exception of clinical data relating to tumor characteristics, the exposure and covariate data used in this investigation came from the case–control interview, which included comprehensive questions on reproductive and menstrual history prior to diagnosis, all of which were captured on a reproductive history calendar. Participants were asked to recall their age at menarche, and number of pregnancies. For each pregnancy, the outcome (live birth, stillbirth, abortion, miscarriage, or ectopic pregnancy), dates and length, and breastfeeding after delivery were queried. Gravidity was defined as ever being pregnant and parity was defined as the number of still and live births prior to diagnosis. Pregnancies at the time of the interview ($n = 2$) or births after diagnosis ($n = 4$) were not counted in the gravidity or parity calculations. Age at each pregnancy, recency of last birth, and gestational length of each pregnancy were derived from the date and length data of the reported pregnancies. Lifetime breastfeeding duration until supplementation and until complete cessation was calculated.

All patients were asked about treatment received prior to interview and medical records were abstracted as part of the case–control study to ascertain clinical data such as Surveillance, Epidemiology, and End Results (SEER) Program summary stage (local, regional, or distant), tumor grade, and hormone receptor status. For the Atlanta participants only ($n = 831$), more detailed data on the first course of treatment (surgery, chemotherapy, radiation, and hormonal therapy) and American Joint Committee on Cancer (AJCC) stage (I, IIA, etc.) were available through the SEER program and re-abstraction of the medical records.

Outcome ascertainment

Eligible case participants diagnosed with invasive breast cancer were followed-up for a maximum of 118 months. Vital status and if deceased, date and cause of death were ascertained through the National Death Index via the cancer registries serving the two geographic locations. By the time of study truncation (January 1, 2000), there had been 292 deaths. Breast cancer was listed on the death certificate as the cause of death for 85% of deceased participants ($n = 248$ deaths).

Statistical analyses

Prediagnostic reproductive exposures and covariates of interest were initially examined using Kaplan–Meier plots. Follow-up time was calculated from the date of diagnosis to the date of death, last known follow-up or date of study truncation (January 1, 2000). The proportional hazards assumption was assessed by examining log(-log(survival)) plots and including interactions with follow-up time. The interaction term between continuous follow-up time and income was statistically significant; therefore all models include this term. Variables were categorized according to their association with mortality and modeled using indicator variables.

Bivariate analyses were conducted between all exposures and survival; and between reproductive exposures and other potential confounders. Multivariable models were subsequently built using Cox regression methods [36], to estimate hazard ratios (HR) and 95% confidence intervals (CI). All-cause mortality was the primary end-point of interest, and patients alive at the end of the study were censored. In models that considered breast cancer specific-mortality only, participants who died of causes other than breast cancer were censored. Each reproductive characteristic (age at menarche, gravidity, parity, spontaneous abortions, induced abortions, age at first birth, age at last birth, recency of last birth, and ever breastfeeding for ≥2 weeks) was modeled separately.

Potential confounders were initially included in multivariable models if they were associated with the specific reproductive characteristic and the outcome in bivariate analyses. Final models were built using backward elimination and variables were retained and considered as confounders if they produced more than a 10% change in the ln(HR) for the reproductive variable. Potential confounders included race, age at diagnosis, education, household income in the year before diagnosis, physical activity at age 20 and in the year before diagnosis, obesity as measured by body mass index (BMI) at age 20 and in the year before diagnosis, chemotherapy, radiation, cigarette smoking status, alcohol consumption, oral contraceptive use, study site, comorbidities (diabetes, thyroid disease, high blood pressure, high cholesterol, other cancers) and the number of Pap smears and clinical breast exams received in the 5 years before diagnosis. The latter two variables were considered as proxies for health care access; mammography was not considered as a proxy for health care access given that most women in our study would not have been of the age to be routinely recommended for mammographic screening. All results are adjusted for age (<35, 35–44, or 45–54 years) and income (<$15,000, $15,000–<$25,000, 25,000–<$90,000, or ≥$90,000) as these were consistent confounders of all of the reproductive exposures of

interest. Each reproductive exposure–mortality association is also adjusted for additional confounders specific to that association (these are listed in the footnotes to each table). In the Atlanta subgroup, the additional detailed treatment information did not confound any of the considered exposure–mortality associations. High parity and having a recent birth were positively associated with tumor characteristics such as stage (either summary or AJCC-derived stage) and grade in our data. As such, they may partially act as intermediates in the causal pathway between various reproductive variables and survival. Thus, these tumor characteristics were not considered as confounders or adjusted for in final models [37]. Instead, stage-stratified results are presented.

Several potential effect modifiers were evaluated including age (<45, ≥45), menopausal status (women were defined as postmenopausal if they had not menstruated for ≥6 months prior to diagnosis), ER status, SEER summary stage, family history, BMI in the year before diagnosis (<25 kg/m^2, ≥25 kg/m^2), and method of cancer detection (accidental, routine self-exam, screening mammogram, etc.). Effect modification was initially assessed by examining stratum-specific estimates, and further analyses explored the inclusion of product interaction terms. If the *P* value for the likelihood ratio test comparing models with and without the interaction term(s) was <0.05, then effect modification was considered significant on a multiplicative scale.

Results

At the time of diagnosis with a first primary breast cancer, the majority of patients were between 35 and 44 years of age, and approximately 78% were premenopausal (Table 1). Most were diagnosed with local stage disease and had ER+ tumors. Approximately 60% of women had at least graduated from college, and 19% had a yearly household income of $90,000 or more. About 10% made less than $15,000 per year. Twenty-two percent of women were nulliparous, and among parous women, about 7% first gave birth at <18 years of age and 18% gave birth within 5 years before diagnosis. Two hundred ninety-two deaths (23.1%) occurred by the end of follow-up.

Because results from Kaplan–Meier curves revealed similar predictors of survival as multivariable models, only the latter are presented (Table 2.). Women with an earlier age at menarche (<12 years) tended to have a small increase in mortality relative to women who underwent menarche at 12 or older [HR (95% CI) = 1.25 (0.97–1.62)]. Gravidity was not associated with mortality, but parity of ≥4 births remained associated with death [1.71 (1.09–2.67)].

Having ≥1 spontaneous or induced abortions was not associated with survival (Table 2). Results were similar when induced or spontaneous abortions among nulliparous and parous women were examined separately. Risk of death was not influenced by the number of induced abortions, nor did mortality vary among subgroups defined by characteristics of induced abortions, such as age at first abortion (<22 vs. ≥22 years of age), timing of abortion relative to first birth, or the gestational length of the first abortion (>8 vs. ≤8 weeks) (results not shown).

Young age at first birth (<18 years) appeared to modestly increase mortality [1.45 (0.91–2.31)], but mortality was not altered if a first birth was after age 18. After adjustment for recency of birth, age at last birth did not influence survival (results not shown).

Women with a recent birth (≤5 years before diagnosis) had a 78% increased risk of death [1.78 (1.28–2.47)]. Risk of death was similar for those giving birth within 5 years, i.e., when finer categorizations of recency within 5 years were used, little variation in mortality was observed. Survival for those with a birth >5 years before diagnosis was equivalent to survival among nulliparous women (results not shown). Ever breastfeeding was not associated with survival. Shorter durations of breastfeeding were associated with a decreased risk of death [e.g. HR ≤ 12 months = 0.71 (0.52–0.97)], but longer durations were not (Table 2).

Age at menarche and recency of birth were modified by menopausal status and BMI, respectively. The effect of young age at menarche on overall mortality appears stronger in premenopausal [1.42 (1.08–1.88)] than postmenopausal women [0.69 (0.34–1.38)] (*P* value = 0.04). The association between a recent birth and overall mortality was more pronounced in women with a BMI of <25 kg/m^2 [2.54 (1.61–4.00)] versus ≥25 kg/m^2 [1.34 (0.79–2.26)] (*P* value = 0.05). Parity and recency of birth stratified by summary stage are noted in Table 3. Some modest heterogeneity with stage was observed, but the differences were not statistically significant.

In general, analyses of breast cancer-specific mortality-yielded estimates that were typically stronger, although not considerably so, than those for overall mortality (results not shown). For example, the largest difference for all-cause versus breast cancer-specific mortality was for recency of birth, for which the HR rose from 1.78 to 1.89 (1.32–2.69).

Table 1 Distribution [*n* (%)] of baseline characteristics (at or before diagnosis) among breast cancer patients stratified by vital status, central New Jersey and metropolitan Atlanta, Georgia, 1990–1992

Characteristic	Total	Died	Alive
	Total study population		
	n = 1,264	*n* = 292	*n* = 972
Age at diagnosis (years)			
<35	154 (12.2)	47 (16.1)	107 (11.0)
35–44	705 (55.8)	167 (57.2)	538 (55.4)
45–54	405 (32.0)	78 (26.7)	327 (33.6)
Summary stage			
Local	721 (57.1)	76 (26.1)	645 (66.4)
Regional	510 (40.4)	188 (64.6)	322 (33.2)
Distant	31 (2.5)	27 (9.3)	4 (0.4)
Menopausal status			
Premenopausal	985 (78.1)	239 (81.9)	746 (77.0)
Postmenopausal	276 (21.9)	53 (18.2)	223 (23.0)
Estrogen receptor status			
Positive	706 (55.9)	143 (49.0)	563 (57.9)
Negative	446 (35.3)	128 (43.8)	318 (32.7)
Unknown/borderline	112 (8.9)	21 (7.2)	91 (9.4)
Education			
<College graduate	508 (40.2)	101 (34.6)	407 (41.9)
≥College graduate	756 (59.8)	191 (65.4)	565 (58.1)
Income ($ per year)			
<15,000	126 (10.2)	56 (19.6)	70 (7.4)
15,000–24,999	131 (10.6)	35 (12.2)	96 (10.2)
25,000–89,999	739 (60.0)	155 (54.2)	584 (61.7)
≥90,000	236 (19.2)	40 (14.0)	196 (20.7)
Age at menarche (years)			
<12	316 (25.0)	85 (29.2)	231 (23.8)
≥12	946 (75.0)	206 (70.8)	740 (76.2)
Parity			
Nulliparous	275 (21.8)	56 (19.2)	219 (22.5)
1–3	887 (70.2)	199 (68.2)	688 (70.8)
≥4	102 (8.1)	37 (12.7)	65 (6.7)
	Among parous women		
	n = 989	*n* = 236	*n* = 753
Age at first birth (years)			
<18	73 (7.4)	28 (11.9)	45 (6.0)
18–21	278 (28.1)	70 (29.7)	208 (27.6)
≥22	638 (64.5)	138 (58.5)	500 (66.4)
Recency of last birth (years)			
≤5	180 (18.2)	65 (27.5)	115 (15.3)
>5	808 (81.7)	171 (72.5)	637 (84.6)

Stratum-specific numbers may not add up to totals because of missing data

Discussion

In this cohort of younger women with breast cancer, increased mortality was associated with various aspects of prediagnostic reproductive history, particularly high parity and recent births. There was also evidence that the effect of recent births were stronger among women with a BMI < 25 kg/m^2. There was some suggestion of increased mortality for early age at menarche and early age at first birth, but the estimates were modest.

Most [9–18], but not all [19, 20], studies have observed that a recent birth (within approximately 1–5 years) is associated with an increased risk of death, but the extent to which death is influenced by the exact timing of the birth has remained unresolved. Estimates within fine categories of recency of birth are often imprecise, making time-specific results difficult to interpret in individual studies. However, many studies report the strongest effects for births within 1 or 2 years, with risk remaining elevated through 4 or

Table 2 Adjusted HR (95% CI) for all-cause mortality in relation to prediagnostic reproductive factors among breast cancer patients in central New Jersey and metropolitan Atlanta, Georgia (1990–1992 through 2000)

Characteristic	No. died	No. alive	HR[a] (95% CI)
Total study population			
Age at menarche (years)			
≥12	200	723	1.00
<12	85	222	1.25 (0.97–1.62)
Gravidity[b]			
Never pregnant	39	144	1.00
Ever pregnant	247	801	0.99 (0.70–1.40)
Parity[b]			
Nulliparous	55	217	1.00
1–3	195	665	1.01 (0.73–1.38)
≥4	36	63	1.71 (1.09–2.67)
Among gravid women			
Spontaneous abortions			
0	183	612	1.00
≥1	64	190	1.10 (0.83–1.46)
Induced abortions			
0	194	622	1.00
≥1	53	180	0.86 (0.63–1.17)
Number of induced abortions			
0	194	622	1.00
1	37	132	0.80 (0.56–1.15)
≥2	16	48	1.02 (0.61–1.71)
Among parous women			
Age at first birth (years)[c]			
<18	26	41	1.45 (0.91–2.31)
18–21	69	204	1.00
≥22	134	478	1.05 (0.76–1.44)
Recency of last birth (years)			
>5	168	617	1.00
≤5	63	111	1.78 (1.28–2.47)
Breastfeeding			
Never (<2 weeks)	125	359	1.00
Ever (≥2 weeks)	106	370	0.90 (0.69–1.18)
Total breastfeeding duration until cessation (months)			
Never (<2 weeks)	125	359	1.00
≤12	61	277	0.71 (0.52–0.97)
>12	41	91	1.36 (0.95–1.95)
Total breastfeeding duration until supplementation (months)			
Never/<2 weeks	125	359	1.00
≤3	40	200	0.67 (0.46–0.96)
>3	62	165	1.13 (0.83–1.54)

CI Confidence interval, *HR* hazard ratio

[a] Adjusted for age at diagnosis (<35, 35–44, 45–54), income (<$15,000, $15,000–$24,999, $25,000–$89,999, ≥$90,000) and includes an interaction term between income and continuous time

[b] Additionally adjusted for recency of birth (≤5 vs. >5 years/nulliparous)

[c] Additionally adjusted for parity (≥4 vs. 1–3) and the number of Pap smears (0–1, 2–4, ≥5) and clinical breast exams (0,1–5, >5) in the past 5 years

5 years and dropping off substantially in subsequent years [10, 12, 15–17]. In contrast, Rosenberg et al. [13] reported a slow decrease in the risk of death, over a 10-year period, for each year since last giving birth. Our results indicated consistently elevated mortality for women who last gave birth in the 5 years before diagnosis but no association for >5 years since last giving birth. Although this finding corroborates the basic pattern of results from previous studies, it does not necessarily support the notion of a strict linear relationship between time since last birth and mortality.

Similar to our findings, numerous investigators have also found an association with increased mortality for parous versus nulliparous women [10–12, 15, 25, 27–30], whereas others have reported null effects for

Table 3 Adjusted HR (95% CI) for all-cause mortality in relation to parity and recency of birth, stratified by summary stage, among breast cancer patients in central New Jersey and metropolitan Atlanta, Georgia (1990–1992 through 2000)

Characteristic	HR[a] (95% CI) local stage	HR[a] (95% CI) regional/distant stage	*P* value[b]
Parity			
Nulliparous	1.00	1.00	
1–3	0.71 (0.41–1.25)	1.01 (0.69–1.50)	0.670
≥4	1.42 (0.63–3.21)	1.85 (1.08–3.14)	
Recency of last birth among parous (years)			
>5	1.00	1.00	
≤5	1.88 (0.93–3.83)	1.38 (0.95–2.01)	0.308

CI Confidence interval, *HR* hazard ratio

[a] Adjusted for age at diagnosis (<35, 35–44, 45–54), income (<$15,000, $15,000–$24,999, $25,000–$89,999, ≥$90,000), and includes an interaction term between income and continuous time. Parity is additionally adjusted for recency of birth (≤5 vs. ≥5 years/nulliparous)

[b] *P* value of the likelihood ratio test comparing models with and without the interaction term(s) in model

parity [9, 16, 17, 19, 21–24]. Few previous studies have presented parity estimates adjusted for recency of last birth, but our results indicate that the relationship remained even after such adjustment. Whether this effect of high parity is a biological phenomenon or due to residual confounding by other variables (e.g., socioeconomic status) is unclear.

Age at menarche [9, 12, 19, 24, 26–28], age at first birth [9, 10, 12, 13, 16, 17, 19, 21, 22, 24, 26, 27], and breastfeeding [16, 23, 27, 29] have previously been inconsistently associated with survival. We found suggestive effects for age at menarche and age at first birth but little effect of ever breastfeeding. Shorter, but not longer, durations of breastfeeding were associated with decreased risk of death. The reasons for this association are unknown, and limited power prevented us from exploring it further.

Similar to our results, other studies have observed that a history of induced or spontaneous abortions did not influence survival [10, 26, 28]. Because of the postulated, yet unsubstantiated, link between age at first abortion, abortion timing relative to a first birth, gestational length at the time of the abortion and breast cancer incidence [38], we analyzed similar subgroups for differences in survival. None was associated with increased mortality. Likewise, the choice of referent groups (using nulligravid women as the reference group for nulliparous women with a history of an induced abortion and parous women without a history as the comparison group for parous women with a history) yielded no additional information.

The mechanisms of action of childbearing and other reproductive factors on prognosis are unknown. It is possible that associations between recent pregnancies and survival could be due, in part, to delays in diagnosis. Pregnancy-related changes in breast density and architecture make cancer detection and diagnosis more difficult in that breast changes might be ascribed to pregnancy rather than subclinical disease [39]. However, ours and another study [14] did observe lower survival for women with recent births at all tumor stages, providing evidence that even less advanced tumors are affected by a recent pregnancy. Also, since younger women do not routinely undergo mammography, systematic delays in diagnoses for women who recently gave birth versus women without a recent birth are minimized. Also, increases in mortality were observed for recent births across the entire 5-year range before diagnosis; stronger effects were not noted for births closest to diagnosis. This argues against changes in the breast due to pregnancy or breastfeeding delaying the diagnosis of cancer.

Previous studies suggest that high parity and recent births may exert their effects on survival through the production of tumors with more aggressive characteristics. In our data, high parity and having a recent birth were associated with both advanced stage disease and higher grade. Women with high parity or a recent birth are more likely to be diagnosed with later stage and node-positive disease and with ER–, p53+, high grade, highly mitotic, and high S phase fraction tumors [10, 14, 18, 25]. This is evidence that characteristics such as stage may be on the causal pathway of certain reproductive characteristics and mortality. The practice of adjusting for potential intermediates to test the degree to which an exposure is mediated by another variable has been shown to be invalid except in limited circumstances under stringent assumptions [40]. In our data, the adverse effects of high parity and recent births were evident at both local and regional/distant stages, and so the effects were not modified by stage. This finding suggests such variables exert effects on survival beyond their associations with advanced stage. Thus, the proposed biological mechanisms may be more complicated than previously considered.

Reproductive factors may also influence survival through hormonally mediated pathways. Estrogen is thought to promote human and rodent breast cancer cell growth [41]. Increased hormone levels in pregnancy could therefore increase cell division [42], and stimulate already initiated cancer cells [43]. The effect appears to be more than just growth promotion since parity, age at menarche, and age at first birth have not been found to be associated with measures of tumor

growth (Ki-67 and mitotic count) in one study [44]. Our result that recent births exert a stronger effect among leaner women is consistent with an estrogen-mediated pathway.

A limitation of this follow-up study is its reliance on prediagnostic exposure information that was collected shortly after diagnosis and it did not include information on nonclinical factors after diagnosis. This circumstance is likely not an issue for many of the reproductive exposures of interest (e.g., few women get pregnant after a diagnosis of breast cancer). However, potential confounders (e.g., socioeconomic position, employment) may have changed over time, leading to the potential for inadequate control for such factors, with any resultant bias difficult to predict. Other variables such as psychosocial support, stress, and insurance status were not collected as part of the baseline interview.

Although the validity of self-reported reproductive history, including parity and age at menarche, is high [45–47], recall of certain exposures such as induced and spontaneous abortions may be lower [48, 49]. We conducted a basic sensitivity analysis to explore the potential for recall bias in the association between induced abortion and survival. Two assumptions were made: (1) upwards of 50% of all study participants may have underestimated a history of an induced abortion [50] and (2) any bias would be non-differential by vital status. Under such conditions, the observed, crude association between induced abortions and vital status (0.92) did not differ from the estimate corrected for underreporting (0.93). In our study the percentage of women who reported having had an induced abortion (22%) is similar to estimates found in surveys that rely on more objective means of gathering abortion data (25%) [51]. Potential misclassification of outcome is minimal, given that survival was ascertained using the NDI [52]. However, any bias is likely nondifferential since a woman's reproductive history should not be correlated with the likelihood of being correctly classified in the NDI. All-cause mortality was the primary endpoint of interest since the accuracy of cause of death on death certificates has been questioned [53].

Because eligibility for this cohort study of breast cancer patients was contingent on participation in an earlier study, the identified reproductive predictors may not represent prognostic factors in all breast cancer patients. Of eligible patients in the parent case–control study, those who were most ill may not have been interviewed, thus they would not have been included in the subsequent follow-up study. Additionally, exposure status may have differed between patients who were interviewed and were eligible for the case–control study. However, participation was high (86% of breast cancer patients who were eligible were interviewed for the case–control study) and differences in exposure status were small, thus our results are likely generalizable. For example, common reasons why some breast cancer patients were not interviewed in the parent case–control study included refusal (5.4% physician's refusal and 6.4% patient's refusal), death (0.4%), and illness (0.6%). Responders to the case–control interview, as compared with non-responders, had an earlier age at menarche, and were slightly more likely to be parous [54].

This study is a comprehensive, population-based study of younger women with long-term follow-up, carefully assessed reproductive data, and detailed individual level data on covariates. In this analysis of a younger cohort, the prognostic factors of interest and the outcome were separated by a comparatively short time, thus preventing the dilution of effects observed in many epidemiological studies. This cohort was also relatively recently diagnosed and therefore more similar to current populations of breast cancer survivors than cohorts established more distantly. The breadth and detail of the reproductive data allowed us to examine less well-studied reproductive characteristics such as pregnancy outcomes and breastfeeding.

Results from studies such as this one can help elucidate the wide range of factors that influence all-cause mortality and enhance understanding of differences in mortality among subpopulations. In this cohort of younger breast cancer cases we observed an increased risk of death for parity of 4 or more births. We confirmed the association between having had a recent birth and poor survival. In our data, the risk of death remains consistently elevated for births within 5 years before diagnosis, beyond which the risk drops off substantially. Overall survival among younger patients with breast cancer appears to be influenced by some reproductive characteristics, possibly reflecting hormonal influences.

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