Short Communication

Prediagnosis Reproductive Factors and All-Cause Mortality for Women with Breast Cancer in the Breast Cancer Family Registry

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Abstract

Studies have examined the prognostic relevance of reproductive factors before breast cancer diagnosis, but most have been small and their overall findings inconclusive. Associations between reproductive risk factors and all-cause mortality after breast cancer diagnosis were assessed with the use of a population-based cohort of 3,107 women of White European ancestry with invasive breast cancer (1,130 from Melbourne and Sydney, Australia; 1,441 from Ontario, Canada; and 536 from Northern California, United States). During follow-up with a median of 8.5 years, 567 deaths occurred. At recruitment, questionnaire data were collected on oral contraceptive use, number of full-term pregnancies, age at first full-term pregnancy, time from last full-term pregnancy to breast cancer diagnosis, breastfeeding, age at menarche, and menopause and menopausal status at breast cancer diagnosis. Hazard ratios for all-cause mortality were estimated with the use of Cox proportional hazards models with and without adjustment for age at diagnosis, study center, education, and body mass index. Compared with nulliparous women, those who had a child up to 2 years, or between 2 and 5 years, before their breast cancer diagnosis were more likely to die. The unadjusted hazard ratio estimates were 2.75 [95% confidence interval (95% CI), 1.98-3.83; $P < 0.001$] and 2.20 (95% CI, 1.65-2.94; $P < 0.001$), respectively, and the adjusted estimates were 2.25 (95% CI, 1.59-3.18; $P < 0.001$) and 1.82 (95% CI, 1.35-2.46; $P < 0.001$), respectively. When evaluating the prognosis of women recently diagnosed with breast cancer, the time since last full-term pregnancy should be routinely considered along with other established host and tumor prognostic factors, but consideration of other reproductive factors may not be warranted. (Cancer Epidemiol Biomarkers Prev 2009;18(6):1792–7)

Introduction

Reproductive factors have a clear role in the etiology of breast cancer (1). It is therefore plausible that they might also influence the course of the disease. The time between last full-term pregnancy and subsequent breast cancer diagnosis has recently emerged as an independent predictor of survival (2-7). The influences of exposure to other reproductive factors before breast cancer diagnosis, such as oral contraceptive (OC) use, breastfeeding, parity

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(number of full-term pregnancies), age at menarche, and menopause and menopausal status, on breast cancer prognosis remain uncertain (6, 8-16). These factors are highly interrelated and might be confounded with established prognostic factors, such as age at diagnosis, body mass index, and education. The aim of the current study was to examine the potential impact of prediagnosis reproductive factors on all-cause mortality after breast cancer with the use of a large, international, multicenter, population-based cohort.

Materials and Methods

Subjects were from population-based samples of women recently diagnosed with invasive breast cancer recruited by the Australian (Melbourne and Sydney), Canadian (Ontario), and U.S. (Northern California) registries of the Breast Cancer Family Registry (17). The Breast Cancer Family Registry was established in 1995 with support from the National Cancer Institute (United States) and is a collaboration of six academic and research institutions. Details of sampling strategies, and data and biospecimen collection relevant to this study, have been described elsewhere (18). For the current study, women reporting ethnicity other than White European, as well as women who had been found to carry a germline mutation in *BRCA1* or *BRCA2* (19), were excluded.

A core epidemiology questionnaire was administered at enrolment in the Breast Cancer Family Registry to collect information on demographics, race/ethnicity, personal cancer history, reproductive history, and other factors (18). Information on broad categories of treatment received (e.g., type of chemotherapy and hormonal therapy) within the 1st year after diagnosis was obtained with the use of a validated self-reported treatment questionnaire (20). Detailed information on duration and dose of therapies was not available. Tumor pathology data were obtained by central review or abstracted from the diagnostic report. Vital status of cases was ascertained through various complementary follow-up activities. All three registries contacted treating physicians, reviewed hospital medical records, and did checks by linkage to their local cancer registry and death registry. Information was also obtained directly from the cases or their relatives. In Northern California, cases or their relatives were contacted on an annual basis by phone. In Ontario, information was collected on an annual basis via mailed self-completed questionnaires. In Australia between 2005 and 2006, cases and their relatives were mailed and, if necessary phoned, to complete an extensive follow-up epidemiologic and family history questionnaire. Approval from the appropriate Institutional Review Board was obtained at each participating registry, and all study participants provided written informed consent.

Statistical Methods. The prediagnosis reproductive variables considered as potential prognostic factors in this study were: OC use, defined as use for at least 12 mo (ever, duration, years since last use, use before first pregnancy, and use before age 20 y), parity (number of full-term pregnancies), age at first full-term pregnancy, time from last full-term pregnancy to breast cancer diagnosis, breastfeeding (ever and duration), age at menarche, age at menopause, and menopausal status at breast cancer diagnosis. Reproductive factors were categorized as presented in Table 1. Hazard ratios (HR) and 95% confidence intervals (95% CI) for all-cause mortality associated with each reproductive factor were estimated with the use of multivariate Cox proportional hazards models. Women were censored at the date they were last known to be alive. Time to death was measured from the date of diagnosis. Subjects' person-years were left-truncated at the date of interview. Fitted models initially included age at diagnosis (continuous), study center (Australia, Ontario, Northern California), education (university degree, high school certificate, lower), and body mass index (continuous) as covariates. Further sensitivity analyses also included tumor characteristics (size, grade, number of involved axillary nodes, and hormone receptor status), each categorized as presented in Table 1, and hormonal therapy (yes, no), chemotherapy (yes, no), and radiation treatment (yes, no) within the 1st year after diagnosis as independent covariates. Additional sensitivity analyses were conducted, excluding subjects not known to be free of metastases at diagnosis and/or those with missing information on tumor characteristics.

Schoenfeld residuals were used to test the proportional hazards assumption. There was evidence of deviation for age at diagnosis, tumor grade, and chemotherapy treatment. The final multivariate models therefore included these factors as stratifying variables (age at diagnosis in the categories presented in Table 1) rather than covariates.

HR estimates with floating CIs (21, 22) were generated by including eight dummy variables in Cox regression with the use of "deviation from means coding" (23). The ln(HR) for nulliparity (and its corresponding SE) was estimated as the negative sum of these eight ln(HR)s with the use of the "lincom" command in Stata. These nine ln(HR)s were then rescaled by subtracting the ln(HR) for nulliparity from each, thereby setting the HR to 1.0 for nulliparity.

All statistical analyses were performed with the use of Stata 10.0 (24), and all hypothesis tests and P values were two-tailed.

Results

Follow-up subsequent to the date of initial interview and covariate data (age at diagnosis, study center, education level, body mass index, and months since last full-term pregnancy) were available for 3,107 (98%) of 3,159 eligible women, and of these, 567 (18%) had died. Median follow-up was 8.5 years. Subject and tumor characteristics are described in Table 1. Table 2 presents estimated HRs and 95% CIs for the associations between prediagnosis reproductive variables and all-cause mortality from both unadjusted and adjusted analyses.

Based on unadjusted analyses, having had a recent full-term pregnancy before breast cancer diagnosis was associated with poorer survival. Compared with nulliparous women, those who had had a full-term pregnancy within 2 years before their breast cancer diagnosis, or within 2 to 5 years before, were more likely to die (HR, 2.75; 95% CI, 1.98-3.83; $P < 0.001$ and HR, 2.20; 95% CI, 1.65-2.94; $P < 0.001$, respectively). Mortality was also associated with shorter time since last OC use (HR, 0.71 per decade; 95% CI, 0.62-0.80; $P < 0.001$) and OC use before age 20 years (HR, 1.27; 95% CI, 1.02-1.58; $P = 0.03$).

From adjusted analyses, poorer survival was associated only with time from last full-term pregnancy to diagnosis

Table 1. Distribution of patients according to both established prognostic factors (personal and tumor characteristics) and prediagnosis reproductive factors considered in the current study

Factor	*N*	%
Age at diagnosis (y)		
<35	398	13
35-59	462	15
40-44	397	13
45-49	578	19
50-54	616	20
55-59	358	12
≥60	298	10
Education (highest level)		
University degree	834	32
High school certificate	1,274	41
Lower	999	27
Body mass index (kg/m^2)		
<18.5; underweight	95	3
18.5-24.9; normal	1,656	53
25.0-29.9; overweight	780	25
≥30.0; obese	576	19
Tumor grade		
1	595	19
2	1,150	37
3	1,155	37
Unknown	207	7
Tumor size (mm)		
≤20	1,967	63
21-50	820	26
≥51	110	4
Unknown	210	7
No. of affected axillary nodes		
None	1,662	53
1-3	737	24
4-9	256	8
≥10	116	4
Unknown	336	11
Metastatic disease at diagnosis		
Absent	2,404	77
Present	41	1
Unknown	662	21
Estrogen receptor status		
Negative	748	24
Positive	2,045	66
Unknown	314	10
Progesterone receptor status		
Negative	792	25
Positive	1,989	64
Unknown	326	10
Radiation treatment*		
No	964	31
Yes	1,427	46
Unknown	716	23
Other treatment*		
Chemotherapy	1,425	46
Hormonal therapy	690	22
Both	301	10
Neither	750	24
Both unknown	111	4
Ever OC use		
No	830	27
Yes	2,267	73
Unknown	10	0
Duration of OC use (y)		
0	830	27
1-4	740	24
5-9	757	24
≥10	754	24
Unknown	26	1
Time since last OC use (y; OC users only)		
<10	528	23
10-17	484	21
18-23	522	23
≥24	330	14
Unknown	413	18
OC use before age 20 y		
Never used OCs	830	27
Yes	907	29
No	1,361	44
Unknown	9	0
OC use before first full-term pregnancy		
Never used OCs	830	27
Yes	1,274	41
No	523	17
Used OCs but nulliparous	465	15
Unknown	15	0
Time from last full-term pregnancy to diagnosis (y)		
Nulliparous	676	22
<2	133	4
2-5	231	7
≥6	2,067	67
No. of full-term pregnancies (parous women only)		
1	412	17
2	1,149	48
3	599	25
≥4	271	11
Age at first full-term pregnancy (y; parous women only)		
<20	314	13
20-24	867	36
25-29	804	33
30-34	339	14
≥35	98	4
Unknown	9	0
Ever breastfed (parous women only)		
No	848	35
Yes	1,548	64
Unknown	35	1
Duration of breastfeeding† (mo; parous women only)		
Never breastfed	848	35
1-6	580	24
7-12	328	13
≥13	604	25
Unknown	71	3
Age at menarche (y)		
<12	611	20
12	753	24
13	932	30
14	423	14
≥15	340	11
Unknown	48	2
Menopausal status		
Premenopausal	1,724	55
Postmenopausal	994	32
Unknown	389	13
Age at menopause (y; postmenopausal women only)		
<48	261	26
48-50	281	28
≥51	267	27
Unknown	185	19

*Within the 1st year after diagnosis.
†Trend was not assessed for duration of breastfeeding because this information was collected in categories of months.

(Table 2). Compared with nulliparous women, those who had had a child within 2 years before their breast cancer diagnosis, or within 2 to 5 years before, were more likely to die (HR, 2.25; 95% CI, 1.59-3.18; $P < 0.001$ and HR, 1.82; 95% CI, 1.35-2.46; $P < 0.001$, respectively). This association was further examined by plotting HR estimates and their floating 95% CIs in smaller categories of time from last full-term pregnancy to diagnosis (Fig. 1). This confirmed that most of the excess mortality above that for nulliparous

Table 2. HR estimates and 95% CIs for death (all causes) after breast cancer diagnosis associated with reproductive factors before diagnosis in unadjusted and adjusted analyses

Reproductive factor	Person-years*	No. of deaths*	Unadjusted analysis		Adjusted analysis†	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Ever OC use						
No	5,117.4	139	1.00		1.00	
Yes	14,382.8	428	1.10 (0.91-1.33)	0.3	0.98 (0.80-1.21)	0.9
Duration of OC use (y)						
0	5,117.4	139	1.00	0.8	1.00	0.9
1-4	4,614.8	129	1.03 (0.81-1.30)	0.1	1.02 (0.79-1.30)	0.7
5-9	4,768.4	154	1.19 (0.95-1.50)	0.5	1.05 (0.82-1.34)	0.4
≥10	4,908.0	143	1.08 (0.86-1.37)	0.7	0.91 (0.71-1.16)	0.3
Trend (per 5 y)			1.01 (0.94-1.09)		0.96 (0.89-1.04)	
Time since last OC use (y; OC users only)						
<10	3,516.3	148	1.00	0.002	1.00	
10-17	2,990.2	85	0.66 (0.50-0.86)	<0.001	0.90 (0.65-1.24)	0.5
18-23	3,337.2	72	0.49 (0.37-0.66)	<0.001	0.79 (0.53-1.16)	0.2
≥24	2,043.2	50	0.56 (0.40-0.77)	<0.001	1.00 (0.63-1.59)	0.9
Trend (per 10 y)			0.71 (0.62-0.80)		0.94 (0.76-1.14)	0.5
OC use before age 20 y						
Never used OCs	5,117.4	139	1.00		1.00	
Yes	5,856.7	200	1.27 (1.02-1.58)	0.03	0.93 (0.73-1.19)	0.6
No	8,534.0	226	0.98 (0.79-1.20)	0.8	0.99 (0.80-1.24)	0.9
OC use before first full-term pregnancy						
Never used OCs	5,117.4	139	1.00		1.00	
Yes	8,108.4	265	1.21 (0.98-1.48)	0.07	0.93 (0.72-1.19)	0.6
No	3,281.1	83	0.93 (0.71-1.22)	0.6	0.98 (0.73-1.31)	0.9
Used OCs but nulliparous	2,961.4	79	0.99 (0.75-1.30)	0.9	1.12 (0.73-1.73)	0.6
Time from last full-term pregnancy to diagnosis (y)						
Nulliparous	4,298.8	109	1.00		1.00	
<2	746.8	52	2.75 (1.98-3.83)	<0.001	2.25 (1.59-3.18)	<0.001
2-5	1,445.4	80	2.20 (1.65-2.94)	<0.001	1.82 (1.35-2.46)	<0.001
≥6	13,065.5	326	0.98 (0.79-1.22)	0.8	1.04 (0.83-1.32)	0.7
No. of full-term pregnancies (parous women only)						
1	2,562.0	80	1.00		1.00	
2	7,268.5	206	0.91 (0.70-1.18)	0.5	1.03 (0.79-1.34)	0.8
3	3,739.5	117	1.00 (0.76-1.33)	0.9	1.15 (0.86-1.53)	0.4
≥4	1,687.7	55	1.04 (0.74-1.47)	0.8	1.28 (0.89-1.84)	0.2
Trend (per full-term pregnancy)			1.03 (0.95-1.13)	0.5	1.08 (0.98-1.19)	0.1
Trend (per full-term pregnancy; all women)			1.05 (0.99-1.12)	0.1	1.08 (0.98-1.18)	0.1
Age at first full-term pregnancy (y; parous women only)						
<20	1,969.3	51	1.00		1.00	
20-24	5,392.3	156	1.12 (0.82-1.54)	0.5	1.06 (0.77-1.46)	0.7
25-29	5,119.0	161	1.21 (0.89-1.66)	0.2	0.97 (0.70-1.36)	0.9
30-34	2,155.0	67	1.20 (0.84-1.73)	0.3	0.81 (0.54-1.21)	0.3
≥35	567.0	22	1.47 (0.89-2.42)	0.1	1.06 (0.62-1.84)	0.8
Trend (per 5 y)			1.09 (1.00-1.20)	0.06	0.97 (0.86-1.08)	0.6
Ever breastfed (parous women only)						
No	5,100.7	147	1.00		1.00	
Yes	9,958.7	304	1.07 (0.88-1.30)	0.5	0.94 (0.76-1.16)	0.6
Duration of breastfeeding‡ (mo; parous women only)						
Never breastfed	5,100.7	147	1.00		1.00	
1-6	3,729.3	115	1.08 (0.85-1.38)	0.5	0.97 (0.76-1.25)	0.8
7-12	2,083.1	54	0.91 (0.67-1.24)	0.6	0.83 (0.60-1.15)	0.3
≥13	3,909.2	128	1.15 (0.91-1.46)	0.2	0.95 (0.73-1.23)	0.7
Age at menarche (y)						
<12	3,876.1	110	1.00		1.00	
12	4,656.0	138	1.04 (0.81-1.34)	0.8	1.07 (0.83-1.37)	0.6
13	5,843.5	164	0.98 (0.77-1.25)	0.9	1.05 (0.82-1.34)	0.7
14	2,793.1	75	0.95 (0.71-1.27)	0.7	1.02 (0.75-1.37)	0.9
≥15	2,127.1	73	1.21 (0.90-1.62)	0.2	1.34 (0.99-1.81)	0.06
Trend (per y)			1.01 (0.96-1.07)	0.6	1.04 (0.98-1.10)	0.2
Menopausal status						
Premenopausal	10,534.8	312	1.00		1.00	
Postmenopausal	6,612.0	195	1.01 (0.84-1.21)	0.9	1.36 (1.08-1.71)	0.01
Age at menopause (y; postmenopausal women only)						
<48	1,659.0	37	1.00		1.00	
48-50	1,725.0	46	1.24 (0.80-1.91)	0.3	1.41 (0.86-2.31)	0.2
≥51	1,715.6	40	1.08 (0.69-1.69)	0.7	1.23 (0.72-2.10)	0.4
Trend (per y)			0.99 (0.95-1.02)	0.4	1.00 (0.97-1.04)	0.8

*Totals across categories do not always coincide due to missing data for reproductive factors (see Table 1).
†Adjusted for study center, education, body mass index, and time since last full-term pregnancy as categorical covariates and stratified on age at diagnosis.
‡Trend was not assessed for duration of breastfeeding because this information was collected in categories of months.

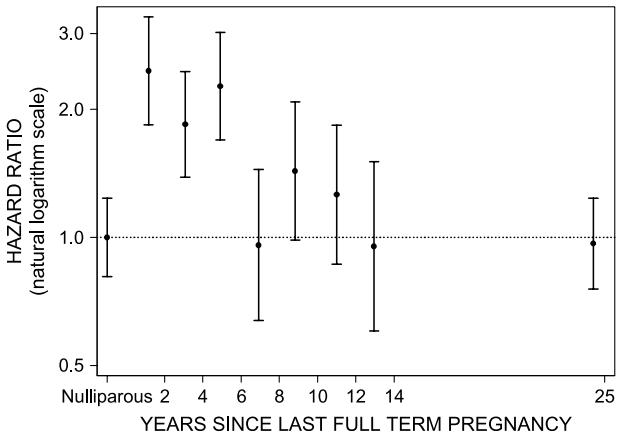

Figure 1. Adjusted HR estimates with floating 95% CIs relative to nulliparous women by categories of time between last full-term pregnancy and breast cancer diagnosis. Categories considered are defined by the values labeled on the x-axis, with lower bounds included in all categories except the first. HR estimates are plotted at the median number of years in each category.

women was for parous women who developed breast cancer within 6 years of their last full-term pregnancy, with the highest risk seen for those who developed breast cancer within 2 years of their last full-term pregnancy, and there was virtually no excess risk beyond 6 years.

Sensitivity analyses showed that the association between all-cause mortality and time between last full-term pregnancy and breast cancer diagnosis became slightly stronger when restricted to the 2,404 women who tested negative for metastases at diagnosis, with adjusted HR estimates of 2.39 ($P < 0.001$) and 2.11 ($P < 0.001$) for <2 years and 2 to 5 years since last full-term pregnancy, respectively. The same pattern of risk was also observed after including tumor characteristics and treatment within the 1st year after diagnosis in the adjusted analyses based on the 1,826 women with complete data (HR, 1.97; $P = 0.04$ and HR, 2.55; $P = 0.001$, respectively).

The statistically significant unadjusted associations between OC use variables and mortality were no longer evident after adjustment for established determinants of mortality. The apparent association seemed to be due to confounding of OC use with age and time since last full-term pregnancy. After adjustment, the HR per decade for time since last OC use became 0.91 (95% CI, 0.74-1.11; $P = 0.3$), and the HR for OC use before age 20 years became 1.04 (95% CI, 0.81-1.33; $P = 0.7$). There were no statistically significant associations between all-cause mortality and any of the other prediagnosis reproductive factors from either the unadjusted or adjusted analyses, although for menopausal status there was a nominally significant association, but only after adjustment for age, and this disappeared once an additional adjustment was made for treatment, in particular chemotherapy. This may therefore represent a false positive association.

Discussion

From this large, international population-based study, we confirmed the previous observation made by us based on a subset of the current study (5) and by others (2-4, 6, 7, 25) that recent childbirth before diagnosis of breast cancer was associated with increased all-cause mortality, and this association was highly statistically significant. Furthermore, by using floating CIs, we were able to show graphically (see Fig. 1) that this association steadily decreases with time since childbirth to become negligible after about 6 years. After adjusting for the known prognostic factors that we had measured, there was no compelling evidence of any prognostic associations with other measured reproductive factors.

The present study has a number of strengths, including the relatively large sample size, long follow-up period, and population-based sampling. In particular, our deliberate oversampling of women with an early age at diagnosis resulted in increased power to study the prognostic associations of pregnancies within a few years before diagnosis. Details on prediagnosis exposures to reproductive factors were collected uniformly across the three study centers with the use of a standard questionnaire. Previous studies have shown that self-reports of reproductive history have high validity (26, 27). We also adjusted for potentially important prognostic factors, including tumor characteristics, treatment, and host factors (such as age at diagnosis and body mass index; ref. 28).

There have been several other large studies of the influence of prediagnosis reproductive factors on survival after a breast cancer diagnosis (6-10, 12, 13, 25). Most studies found associations with some reproductive factors, but the findings have not been consistent.

A population-based study of >1,000 women with breast cancer found that women who had four or more children had worse survival, only partly accounted for by confounding due to an association with having given birth within 5 years before diagnosis (6). In the current study, there was no evidence for an association between high parity and all-cause mortality. As the other published large studies of parity and survival have not adjusted, as we have, for recency of last birth (8, 10, 13), further examination of this issue is warranted.

Another study of >10,000 women with breast cancer found that women who had their first child at ages 20 to 24 years or 25 to 29 years had a marginally significantly reduced risk of death compared with those who had their first child before the age of 20 years, after adjustment for age at diagnosis, tumor size, nodal status, tumor grade, treatment, year of diagnosis, and parity (relative risk, 0.88; 95% CI, 0.78-0.99 and relative risk, 0.80; 95% CI, 0.70-0.91, respectively; ref. 12). The current study did not confirm that finding. Like other studies (6, 7), ours did not confirm the finding of Lees et al. that women who had breastfed had worse survival after a breast cancer diagnosis than those who had never breastfed (13).

Most recently, Barnett et al. (25) showed that there was an association between survival after breast cancer diagnosis and proximity of last full-term pregnancy to study entry, but no association with other reproductive factors, such as age at menarche, age at menopause, menopausal status at diagnosis, or prior OC use. Although a large study ($n = 4,560$), their results are difficult to compare with ours given that it included both prevalent and incident breast cancers, and did not analyze time between last full-term pregnancy and breast cancer diagnosis. Other large recent studies have also found no association between survival and menopausal status, age at menarche,

parity, age at first birth (9), or OC use (9, 16); recency of last childbirth before breast cancer diagnosis was not examined in these studies.

Our study provides further confirmation that having had a full-term pregnancy within 5 years before a breast cancer diagnosis is associated with an adverse prognosis, which is not fully explained by other measured prognostic factors. Unmeasured factors that might be mediating this association include effects of the hormonal milieu of pregnancy, such as relative insulin resistance, hyperprolactinemia, or reduced melatonin levels in the postnatal period (5). These issues need further research. In the meantime, clinicians should be aware that women diagnosed with breast cancer within 5 years after childbirth tend to have a worse outcome than might be suggested just by assessing the standard histopathologic and host prognostic factors. Whether more intensive adjuvant treatment would improve their prognosis is not known. The present and other studies suggest that, when evaluating the prognosis of women recently diagnosed with breast cancer, the poorer survival of women who have recently given birth should be considered, in addition to their tumor and other established prognostic factors. Consideration of other reproductive factors does not seem to be warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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