Published in final edited form as:
Breast Cancer Res Treat. 2011 December ; 130(3): 975–980. doi:10.1007/s10549-011-1666-0.

Reproductive factors and histologic subtype in relation to mortality after a breast cancer diagnosis

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Abstract

Evidence suggests that certain reproductive factors are more strongly associated with the incidence of lobular than of ductal breast cancer. The mechanisms influencing breast cancer incidence histology may also affect survival. Women with invasive breast cancer (N = 22,302) diagnosed during 1986–2005 were enrolled in a series of population-based studies in three US states. Participants completed telephone interviews regarding reproductive exposures and other breast cancer risk factors. Histologic subtype was obtained from state cancer registries. Vital status and cause of death were determined through December 2006 using the National Death Index. Women were followed for 9.8 years on average with 3,050 breast cancer deaths documented. Adjusted hazard rate ratios (HR) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards regression models for breast cancer-specific and all-cause mortality. Parity was inversely associated with breast cancer-specific mortality (P_{Trend} = 0.002). Associations were similar though attenuated for all-cause mortality. In women diagnosed with ductal breast cancer, a 15% reduction in breast cancer-specific mortality was observed in women with five or more children when compared to those with no children (HR = 0.85, 95% CI: 0.73–1.00). A similar inverse though non-significant association was observed in women with lobular subtype (HR = 0.70, 95% CI: 0.43–1.14). The trend did not extend to mixed ductal–lobular breast cancer. Age at first birth had no consistent relationship with breast cancer-specific or all-cause mortality. We found increasing parity reduced mortality in ductal and lobular breast cancer. The number of full-term births, rather than age at first birth, has an effect on both breast cancer-specific and overall mortality.

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Keywords

Epidemiology; reproduction; lobular breast cancer; ductal breast cancer; mortality

INTRODUCTION

Reproductive factors such as nulliparity and age at first birth (AFB) are important risk factors for breast cancer with varying strengths of association by tumor histologic subtype [1]. Due to reproductive risk factors' strong associations with incidence, it is possible that these patterns also contribute to breast cancer-specific and all-cause mortality. Previous investigations into risk factors' associations with mortality after breast cancer have been inconclusive.

There is some evidence that childbirth reproductive factors may have a stronger effect on survival after a breast cancer diagnosis in premenopausal women due to the recency of increased endogenous hormones associated with pregnancy [2-4]. Studies focused primarily on premenopausal or postmenopausal women have found conflicting association between parity and mortality. Premenopausal women with high parity have been shown to have worse mortality outcomes [3] whereas postmenopausal women with increased parity fared better than their nulliparous counterparts [4]. The majority of other epidemiologic studies that have investigated the influence of parity on mortality have not stratified by menopausal status and have found no difference in breast cancer-specific or all-cause mortality by parity [5-9], although other studies have found marginal increased [10,11] or decreased [2,4] all-cause mortality rates in parous women.

The age of the mother at childbirth may also have a role in mortality after breast cancer. Early AFB (approximately less than 20 years) has been associated with borderline significant decreased survival in comparison to women with later first childbirth [5,9,2]. One small study by Greenberg et al. [12] demonstrated a linear trend of higher breast cancer mortality risk in women with earlier AFB (P <0.01). Most frequently, a null association between AFB and breast cancer prognosis has been found [6,10,7,8,11]. However, previous studies have not consider the joint effects of reproductive exposures and tumor characteristics, such as histologic subtype, on breast cancer prognosis and as a result the combined influences of reproductive factors and histologic subtype on mortality after a breast cancer diagnosis are not known.

The strength of the association between hormonal factors and mortality may vary by breast cancer histologic subtype as it does with breast cancer incidence. The stronger relationship between combined hormone therapy use and lobular breast cancer than other subtypes suggests that lobular breast cancer may be a more hormonally related subtypes [13]. A better understanding of how reproductive factors relate to breast cancer histologic subtypes will provide insight into how tumor differences influence mortality after breast cancer. We evaluated the associations between reproductive factors and breast cancer-specific and all-cause mortality and considered whether these relationships varied by histologic subtype using data from a cohort of over 22,000 breast cancer survivors.

METHODS

The data used for this analysis are from the Collaborative Breast Cancer Study, a series of population-based case-control studies conducted in successive phases with details previously published [14]. Briefly, participants were women with an incident diagnosis of invasive breast cancer between the years of 1986-2005, reported to tumor registries in New Hampshire, Massachusetts (excluding metropolitan Boston) or Wisconsin, aged 20-79 with a listed telephone number. Participants under age 65 must have had a self-reported driver's license due to the recruitment methods used in the original Collaborative Breast Cancer case-control studies. All subjects participated in a structured telephone interview to obtain information on traditional breast cancer risk factors. A total of 22,302 women (approximately 80% of eligible participants) diagnosed with invasive breast cancer were enrolled in the study.

Exposure assessment

The telephone interview elicited information on breast cancer risk factors exposures that occurred at least one year prior to diagnosis. A complete reproductive history was obtained including the number of pregnancies, each pregnancy outcome and date of birth. The interview also covered medical history, use of exogenous hormones, smoking status, cancer screening and demographics.

Additionally, clinical information such as tumor staging and histologic tumor subtype was available through the tumor registry for each state. Histology was defined using International Classification of Disease-Oncology (ICD-O) codes [15-17]. Cases were grouped by histology as follows: ductal (code 8010, 8012, 8021, 8140, 8310, 8323, 8410, 8500, 8502, 8530, 8560, 8571), lobular (code 8520) and mixed ductal-lobular (code 8521, 8522, 8523) [18]. The other individual histological groups each contributed less than 2% of deaths over the study period and were not included in the analysis of histologic subtypes.

Outcome assessment

Information on vital status was ascertained using automated searches of the National Death Index (NDI). Underlying causes of death were coded using the ICD-9 until 1998 and ICD-10 throughout the rest of the follow-up period [19,18]. The outcome of this analysis was death with breast cancer reported as the underlying cause (ICD-9 code 174; ICD-10 codes C50) and secondarily, all-cause mortality. Women in the cohort were followed a mean of 9.8 years (standard deviation 5.2 years) after breast cancer diagnosis with a median survival time of 9.3 years.

Statistical analysis

Survival time was calculated from the date of diagnosis until date of death provided by the NDI or December 31, 2006, whichever occurred first. Hazard rate ratios (HR) and 95% confidence intervals were calculated according to breast cancer histology using multivariate Cox proportional hazard models for the association between reproductive factors and the outcomes of interest with parity and AFB were modeled categorically. To assess the Cox proportionality assumption, a separate model was analyzed with the inclusion of a time-

dependent cross- product term for the natural log of survival time (days) and the covariate of interest. The assumption held for all models as the interaction terms was not significant at $P<0.05$.

All regression models were stratified by state of residence, year of interview and age at diagnosis. Confounders included in the multivariable models, defined *a priori*, were menopausal status, body mass index (BMI, kg/m^2), hormone therapy use, mammography use, smoking status at diagnosis, time from date of diagnosis to interview and stage of disease using Surveillance Epidemiology and End Results Summary Staging method. Participants were considered postmenopausal if they reported permanently stopped menstrual cycles for at least the last 6 months prior to their breast cancer diagnosis. BMI was calculated using weight at diagnosis and reported maximum height. Hormone therapy and smoking status were defined as never, former or current use. Women were considered mammography users if they had a mammogram within 5 years of diagnosis.

Potential effect modifications of the relationships between reproductive factors and mortality by histologic subtype were examined. Effect modification was also explored for the possibility that parity and AFB would have differing effects on mortality by menopausal status. Interactions were measured by including a cross-product term between the reproductive exposure of interest and an ordinal variable representing histologic subtype or menopausal status. Log likelihood values were measured to determine whether the cross-product term contributed significantly to the model. Parity and AFB P_{Trend} values were calculated by including an ordinal variable in the statistical model. All analyses were conducted using SAS Statistical Software (Version 9; SAS Institute, Cary, NC).

RESULTS

Of the 22,302 participant, 14% (N = 3,050) of the cohort died of breast cancer and 15% (N=3,360) died of other causes. In general, deceased participants were more likely to be older, current smokers at diagnosis and have more extensive disease than participants that were alive at the end of follow-up (Table 1). Breast cancer-specific and all-cause mortality rates were similar for all histologic subtypes. Women diagnosed with ductal breast cancer had a 5-year breast cancer-specific survival rate of 92%; likewise women with lobular and mixed ductallobular breast cancer had a 5-year survival rate of 94%, respectively. Evaluations of effect modification of the associations between breast cancer subtypes and breast cancer-specific or all-cause mortality by reproductive factors were not statistically significant (all $P>0.2$). Results are presented separately for ductal, lobular and mixed ductal-lobular histologies due to potential biological differences between subtypes.

Analysis of all cases combined showed significant inverse associations between parity and breast cancer-specific mortality ($P_{Trend}=0.002$) and all-cause mortality ($P_{Trend}=0.002$), although the HRs did not indicate a continuous decline in risk beyond two pregnancies, particularly for all-cause mortality (Table 2). Similarly, among participants diagnosed with ductal breast cancer, higher parity was inversely related to breast cancer-specific ($P_{Trend}=0.002$) and all-cause mortality ($P_{Trend}=0.004$), although the association was not entirely consistent. A similar trend in decreased risk to parous women was observed in

participants diagnosed with lobular disease however results were not statistically significant. Confidence intervals were wide in the analyses restricted to mixed ductal-lobular participants but parity appeared to increase risk of breast cancer-specific mortality in this subtype. The relationship between parity and mortality after breast cancer was similar irrespective of menopausal status (not shown).

In the analyses of all cases combined or by individual histologic subtypes, AFB was not associated with significant trends in relation to breast cancer mortality or all-cause mortality (Table 3). Breast cancer-specific mortality was slightly decreased in women with lobular disease who had an AFB between the ages of 25-29 (HR=0.63; 95%CI: 0.40-0.98). Similarly, in all histologies combined, women in the same 25-29 age group had a decreased risk of all-cause mortality. Null associations were seen between all other age groups and breast cancer-specific or all-cause mortality. The interaction term evaluating the interaction between menopausal status and AFB was not statistically significant in relation to breast cancer-specific or all-cause mortality.

DISCUSSION

In this large study of breast cancer survivors, we found increasing number of births reduced the risk for mortality. When all histologies were combined, there was a decreased risk of breast cancer-specific mortality similar in magnitude to previous studies [20,4]. Anderson et al. [4] found an increased 10-year survival rate in their participants who had ever experienced childbirth compared to nulliparous women (92% survival vs. 76%; *P*=0.002).

We found women diagnosed with ductal breast cancer with high parity were at a decreased risk of breast cancer mortality compared to nulliparous women diagnosed with the same subtype. This tendency also applied to lobular cases although it was not statistically significant. The association was null in cases diagnosed with mixed ductal-lobular breast cancer, but confidence intervals were wide and statistical power may have been inadequate in some of the analyses. Laboratory evidence suggests parous women with an early AFB compared to nulliparous women have long-term changes in the expression of genes that may be involved in the pathway to breast cancer, such as genes involved in cell proliferation and DNA repair [21]. Parity and AFB's effects on gene expression may result in less aggressive tumors and better survival for parous women.

Nonetheless, there was no evidence of a trend between AFB and breast cancer or all-cause mortality for any of the histologies studied. However, there was a hint of a decreased mortality risk in women with an AFB between the ages of 25-29 although this result may be spurious. Other studies have not looked specifically at histologic subtypes; however, another study found an inverse association with mortality limited to the AFB category of 25-29 years of age. In a study conducted by Kroman et al. [9], breast cancer survivors who were age 25 to 29 at first childbirth had a 20% reduced risk of all-cause mortality. One potential explanation for the reduced mortality risk observed in this subgroup may be differences in socioeconomic status. Women with higher socioeconomic status have been shown to delay childbirth [22] and additionally may have better access to healthcare and cancer treatment providing the foundation for better breast cancer outcomes.

Independent of parity and AFB, breast cancer-specific and all-cause mortality rates did not differ between subtypes which is in agreement with previous studies [7]. In addition to replication of earlier results, there are several strengths to the study. The mortality outcomes were obtained through the NDI which is a standardized and complete data source [23]. To our knowledge, this is the largest study to examine the associations between childbirth, maternal age and mortality, stratified by specific histologic subtypes. Most notably, we evaluated mixed ductal-lobular breast cancer associations with mortality separately from other subtypes.

Nevertheless, there are certain limitations to the present study. We have limited information on variables important to breast cancer survival such as treatment or tumor hormone receptor status and did not statistically control for these potential confounders. A recent study found that hormone receptor status did not vary by parity, but women with AFB>20 were more likely to have hormone receptor-positive breast tumors than women with early AFB [24]. As we are unable to account for receptor status, there is the potential that this mediating factor may partially explain our AFB results. Moreover, positive receptor status has shown to be more strongly tied to lobular and mixed ductal-lobular breast cancers than ductal subtype [25] thus the potential for confounding may be greater in some of the stratified analyses. Additionally, we were unable to account for study participants' medical treatment. However, adjustment for tumor stage may partially account for treatment's effect, as treatment is predicted by stage.

Our results do not lend support to the hypothesis that breast cancer-specific or all-cause mortality is affected by the age at childbirth or independently, by histologic subtype. This study shows that the number of full-term births rather than age at first birth, has an effect on both breast cancer-specific and overall mortality.

ACKNOWLEDGMENTS

Supported in part by grants from the National Institutes of Health Cancer Institute Grants CA47147, CA47305, CA69664, CA82004 and by the Avon Foundation.

Table of Abbreviations

AFB	Age at First Birth
CI	Confidence Interval
BMI	Body Mass Index
HR	Hazard rate Ratios
ICD-O	International Classification of Disease-Oncology
NDI	National Death Index

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Table 1

Selected baseline characteristics of breast cancer cases by histology (%)

	All women		Ductal		Lobular		Mixed ductal-lobular	
	Alive (N=15884)	**Deceased (N=6418)**	**Alive (N=12507)**	**Deceased (N=5189)**	**Alive (N=1373)**	**Deceased (N=581)**	**Alive (N=683)**	**Deceased (N=166)**
Mean age at diagnosis (y)	56.3	62.8	56.1	62.5	57.9	64.3	55.7	60.6
Postmenopausal	64.0	83.0	63.6	82.5	68.0	87.6	60.9	75.3
Hormone user[a] (% current)	34.2	13.2	33.5	12.3	38.9	18.2	38.6	22.6
Smoker (% current)	17.9	24.4	18.2	25.1	16.4	21.2	18.2	24.1
Body Mass Index[a] (kg/m^2)								
Underweight (< 18.5)	1.5	2.4	1.5	2.3	1.6	2.4	1.5	1.2
Average (18.5-24.9)	47.9	44.3	47.1	44.5	47.1	45.6	48.0	45.2
Overweight (25.0-29.9)	30.2	30.1	30.5	30.7	30.2	30.0	28.3	28.3
Obese (≥ 30.0)	19.0	19.7	18.9	19.7	20.0	19.1	20.6	22.3
Mammography screening[b]								
Never	16.7	27.2	17.3	27.4	12.9	23.9	13.3	29.5
Ever	72.8	48.6	71.8	47.4	80.2	57.3	79.7	51.8
Unknown	10.5	24.2	10.9	25.2	6.9	18.8	7.0	18.7
Stage of disease								
Local	65.6	47.2	65.3	47.0	62.6	41.8	66.2	45.8
Regional	24.9	37.7	25.6	38.5	30.0	42.5	27.2	36.1
Distant	0.8	6.4	0.8	6.4	1.5	8.1	0.7	8.4
Unknown	8.6	8.6	8.3	8.1	6.0	7.6	5.9	9.6
Parity (% nulliparous)	13.4	14.2	13.8	14.0	11.3	13.8	12.6	13.2
Age at first birth[c]								
< 20	15.9	15.3	16.3	15.2	13.1	13.2	15.1	13.9
20-24	46.5	45.4	46.5	46.1	45.6	42.8	41.7	43.8
25-29	26.3	26.5	26.0	26.4	27.4	28.0	30.8	25.0
30+	11.3	12.8	11.2	12.4	13.9	16.0	12.4	17.4
5-year Survival rate	89.7		89.3		90.1		91.8	
Breast cancer-specific	92.8		92.3		94.3		94.4	

[a] Among postmenopausal women only.

[b] Mammography screening within the five years prior to diagnosis.

[c] Among parous women only.

Table 2

Breast cancer-specific and all-cause mortality by parity status and stratified by histologic subtype[a]

	All histologies			Ductal subtype			Lobular subtype			Mixed Ductal-lobular subtype		
	Cases	**Events**	**HR (95%CI)**	**Cases**	**Events**	**HR (95%CI)**	**Cases**	**Events**	**HR (95%CI)**	**Cases**	**Events**	**HR (95%CI)**
Parity						**Breast cancer-specific mortality**						
Nulliparous	3046	445	1	2463	366	1	235	42	1	108	10	1
1	2502	401	1.06 (0.93 – 1.22)	2007	341	1.08 (0.93 – 1.25)	192	24	0.82 (0.48 – 1.40)	100	14	2.77 (1.02 – 7.50)
2	6469	820	0.91 (0.81 – 1.02)	5135	679	0.89 (0.78 – 1.01)	550	76	0.98 (0.65 – 1.48)	267	25	1.31 (0.54 – 3.18)
3	4815	628	0.92 (0.81 – 1.04)	3787	515	0.92 (0.80 – 1.05)	462	65	0.81 (0.54 – 1.24)	199	19	1.70 (0.65 – 4.40)
4	2790	371	0.86 (0.74 – 0.98)	2198	298	0.83 (0.71 – 0.97)	265	41	0.89 (0.56 – 1.41)	85	11	1.01 (0.33 – 3.09)
5+	2660	385	0.86 (0.74 – 0.99)	2088	311	0.85 (0.73 – 1.00)	249	37	0.70 (0.43 – 1.14)	90	9	1.93 (0.64 – 5.87)
P_{Trend}			0.002			0.002			0.18			0.85
Parity						**All-cause mortality**						
Nulliparous	3046	910	1	2463	737	1	235	80	1	108	22	1
1	2502	798	1.01 (0.92 – 1.11)	2007	659	1.03 (0.92 – 1.14)	192	58	0.95 (0.66 – 1.35)	100	27	1.31 (0.67 – 2.55)
2	6469	1634	0.91 (0.84 – 0.99)	5135	1325	0.90 (0.83 – 0.99)	550	141	0.91 (0.68 – 1.22)	267	43	0.76 (0.42 – 1.37)
3	4815	1281	0.90 (0.82 – 0.98)	3787	1031	0.90 (0.82 – 0.99)	462	129	0.77 (0.57 – 1.03)	199	35	0.84 (0.45 – 1.57)
4	2790	838	0.86 (0.78 – 0.95)	2198	670	0.86 (0.77 – 0.96)	265	87	0.80 (0.58 – 1.09)	85	18	0.52 (0.25 – 1.09)
5+	2660	941	0.92 (0.84 – 1.01)	2088	753	0.92 (0.83 – 1. 02)	249	85	0.83 (0.60 – 1.14)	90	21	0.84 (0.42 – 1.68)
P_{Trend}			0.002			0.004			0.09			0.12

HR indicates hazard rate ratio; CI confidence interval

[a]Proportional hazards models were stratified by state of residence, year of interview and age at diagnosis and adjusted for menopausal status, BMI, hormone replacement therapy use, smoking status, mammography, time from date of diagnosis to interview and stage of disease at diagnosis.

Table 3

All-cause and breast cancer-specific mortality by age at first birth and stratified by histologic subtype[a]

	All histologies			Ductal subtype			Lobular subtype			Mixed ductal-lobular subtype		
	Cases	Events	HR (95% CI)	Cases	Events	HR (95% CI)	Cases	Events	HR (95% CI)	Cases	Events	HR (95% CI)
Age at first birth						**Breast cancer-specific mortality**						
Nulliparous		445	1.09 (0.95 – 1.25)	2463	366	1.10 (0.95 – 1.28)	235	42	0.89 (0.55 – 1.44)	108	10	1.03 (0.32 – 3.30)
<20	3041	405	1	2439	342	1	226	35	1	110	8	1
20-24	8891	1219	1.00 (0.90 – 1.12)	7068	1008	1.01 (0.89 – 1.14)	769	104	0.71 (0.47 – 1.07)	312	36	1.74 (0.68 – 4.45)
25-29	5064	652	0.93 (0.82 – 1.05)	3970	532	0.94 (0.82 – 1.08)	475	63	0.63 (0.40 – 0.98)	220	19	1.24 (0.43 – 3.58)
30+	2260	335	1.11 (0.96 – 1.29)	1756	268	1.11 (0.94 – 1.30)	249	41	1.05 (0.65 – 1.70)	99	15	2.39 (0.80 – 7.12)
P_{Trend}			0.66			0.65			0.87			0.41
Age at first birth						**All-cause mortality**						
Nulliparous	3046	910	1.02 (0.92 – 1.12)	2463	737	1.05 (0.94 – 1.17)	235	80	0.98 (0.69 – 1.38)	108	22	1.31 (0.65 – 2.66)
<20	3041	848	1	2439	681	1	226	66	1	110	20	1
20-24	8891	2503	0.93 (0.86 – 1.00)	7068	2053	0.97 (0.89 – 1.06)	769	214	0.78 (0.58 – 1.04)	312	63	1.00 (0.56 – 1.78)
25-29	5064	1455	0.87 (0.80 – 0.95)	3970	1170	0.91 (0.82 – 1.00)	475	141	0.76 (0.56 – 1.04)	220	36	0.94 (0.50 – 1.77)
30+	2260	702	1.01 (0.91 – 1.12)	1756	548	1.02 (0.91 – 1.14)	249	80	0.97 (0.69 – 1.37)	99	25	1.51 (0.76 – 3.03)
P_{Trend}			0.44			0.51			0.96			0.37

HR indicates hazard rate ratio; CI confidence interval

[a]Proportional hazards models were stratified by state of residence, year of interview and age at diagnosis and adjusted for menopausal status, BMI, hormone replacement therapy use, smoking status, mammography, time from date of diagnosis to interview and stage of disease at diagnosis.