Demographic Research a free, expedited, online journal
of peer-reviewed research and commentary
in the population sciences published by the
Max Planck Institute for Demographic Research
Konrad-Zuse Str. 1, D-18057 Rostock · GERMANY
www.demographic-research.org

DEMOGRAPHIC RESEARCH

VOLUME 18, ARTICLE 9, PAGES 263-284
PUBLISHED 15 APRIL 2008
http://www.demographic-research.org/Volumes/Vol18/9/

Research Article

Cohort fertility patterns and breast cancer mortality among U.S. women, 1948-2003

Patrick M. Krueger

Samuel H. Preston

Table of Contents

Demographic Research: Volume 18, Article 9
research article

Cohort fertility patterns and breast cancer mortality among U.S. women, 1948-2003

Patrick M. Krueger[1]
Samuel H. Preston[2]

Abstract

Epidemiological research has shown that women who have early and numerous births have reduced risks of being diagnosed with breast cancer. We use U.S. Vital Statistics and Census data and age-period-cohort models to examine whether cohort fertility patterns are associated with breast cancer mortality rates among women aged 40 and older in 1948-2003. Cohorts marked by higher proportions childless at ages 15-24 and lower cumulative second birth rates at ages 15-29 have higher rates of breast cancer mortality. This is the first demonstration that cohort fertility patterns have left a clear imprint on trends in U.S. breast cancer mortality rates.

[1] University of Texas-Houston School of Public Health, Division of Management, Policy, and Community Health; University of Texas-Austin Population Research Center; University of Pennsylvania, Leonard Davis Institute of Health Economics. E-mail: Patrick.M.Krueger@uth.tmc.edu
[2] University of Pennsylvania, Department of Sociology, University of Pennsylvania, Population Studies Center.

1. Introduction and background

Epidemiological studies using cohort and case-control designs have shown that reproductive factors – especially a woman's age at first birth and her total number of births – affect the risk of death from breast cancer. Kelsey, Gammon, and John (1993) provide an early review of the vast amount of literature on the topic. A great deal of subsequent research has been conducted and reviewed by Althius et al. (2004) and Merrill et al. (2005). Nearly all studies find that giving birth at younger ages and giving birth to numerous children are protective against breast cancer mortality. The accumulation of evidence led the National Cancer Institute's (2003) Workshop on Early Reproductive Events and Breast Cancer to conclude that the relationships between breast cancer and age at first birth and parity are "well established."

Ma et al. (2006) perform a meta-analysis and conclude that age at first birth and parity are significant factors in estrogen and progesterone receptor positive breast cancers but not in other breast cancers, suggesting that the hormonal changes associated with fertility play a strong role in breast cancer incidence (see also Althuis et al. 2004). Although the duration of breastfeeding is also inversely associated with all types of breast cancers (Collaborative Group on Hormonal Factors in Breast Cancer 2002), it does not account for the relationship between early or numerous births and breast cancer. Further, the relationship between breast cancer and reproductive factors is stronger among older (e.g., postmenopausal) women, because pregnancy is a short-term risk factor for breast cancer (Kelsey, Gammon, and John 1993; Ursin et al. 2004).

The relationships between breast cancer and reproductive factors, combined with dramatic changes in cohort fertility among American women, should have left an imprint on U.S. breast cancer mortality patterns. One example of such a population-level imprint has been demonstrated among a half-million women in Norway. A 25% excess mortality from breast cancer among well-educated women in Norway was statistically reduced to a non-significant 8% in regressions by adjusting for the earlier childbearing among more poorly educated women (Strand et al. 2005).

In the United States, the main efforts to relate fertility trends to breast cancer mortality at the national level have been mounted by Tarone and Chu (2000) and Tarone, Chu, and Gaudette (1997). Tarone and Chu (2000) fit an age-period-cohort model to data for 1950-1995. Because of the collinearity among age, period, and cohort (i.e., the value of any one of the variables can be uniquely identified by knowledge of the other two), they employ a model that can only detect non-linear cohort and period effects (see also Tarone and Chu 1996). Although they cite reproductive factors to interpret cohort trends in breast cancer mortality, they do not include measures of fertility directly in their models, and the cohort patterns they identify are weakly related to fertility patterns. Their estimates show decreasing breast cancer mortality rates

among baby boomers, whereas the lower fertility among baby boomers would predict increasing rates.

Given the persistent finding that the timing of early births and total parity are predictive of breast cancer incidence and mortality, it is reasonable to hypothesize that those factors shape U.S. breast cancer mortality rates and to test that influence directly. We extend research in this area by modeling the impact of cohort fertility patterns on breast cancer mortality rates in an age-period-cohort framework, for calendar periods ranging from 1948-2003. Our fertility measures include the age-specific proportion of women who are childless and age-specific cumulative second birth rates when women in cohorts were aged 15-19, 20-24, and 25-29, and their cumulative birth rate at ages 35-39. We focus on breast cancer mortality among women aged 40 and older because the effects of reproductive factors on morality among older women may differ from those among younger women, and so that we can include a measure of fertility that is close to women's completed family size.

2. Data and methods

We examine breast cancer mortality rates for women aged 40-44 to 85 and older, for every fifth calendar year from 1948 to 2003. By using five-year age groups during every fifth calendar year, we can uniquely identify five-year birth cohorts as they pass through life. The numerators (numbers of deaths) of the age-specific breast cancer mortality rates come from vital statistics data (National Center for Health Statistics various years-a; b), and the denominators (numbers of women at risk) come from U.S. Census data (U.S. Census Bureau various years).

We use the age-specific proportion childless and the age-specific cumulative second birth rate when cohorts of women were aged 15-19, 20-24, and 25-29 to capture the timing of first and second births in women's early reproductive years. The age-specific proportion childless is the inverse of the age-specific cumulative first birth rate and is measured as the number of women who have never had a live birth and who are aged x to x+4 in a given calendar year, divided by the number of women aged x to x+4 in the same year. The age-specific cumulative second birth rate is the number of women who have ever had two or more live births and who are aged x to x+4 in a given calendar year, divided by the number of women aged x to x+4 in the same year. We use the proportion childless and the cumulative second birth rate because age-specific first and second birth rates are confounded by the exclusion of women who had first or second births at prior ages and women who have had no births from the numerators. The cumulative fertility rate is an indicator of the volume of childbearing and is measured as the total number of live births to women who are aged 35-39 in a given

calendar year, divided by the total number of women aged 35-39 in that year. Most women have completed most of their childbearing by age 39. Limiting our measures to completed fertility at ages 35-39 allows us to predict breast-cancer mortality rates among women aged 40 and older.

The cohort fertility measures for women aged 15 and older in 1917 and later are derived from U.S. vital statistics data (Heuser 1976; National Center for Health Statistics various years-b). We use U.S. Census tables and linear interpolation to identify additional data points for women in cohorts that were aged 15-39 between the 1900 and 1910 Censuses (Truesdell 1945; Carter et al. 2006). The Census data present the age-specific proportion childless and the number of children ever born to ever married women. We recalculate these measures for all women by using counts of never married women and assuming that they had no children, a reasonable assumption given that women who had children out of wedlock likely would have reported being divorced or separated (Carter et al. 2006). The fertility rates derived from the Census data show excellent continuity with the rates collected from vital statistics. The Census tables do not provide cumulative second birth rates.

2.1 Missing data

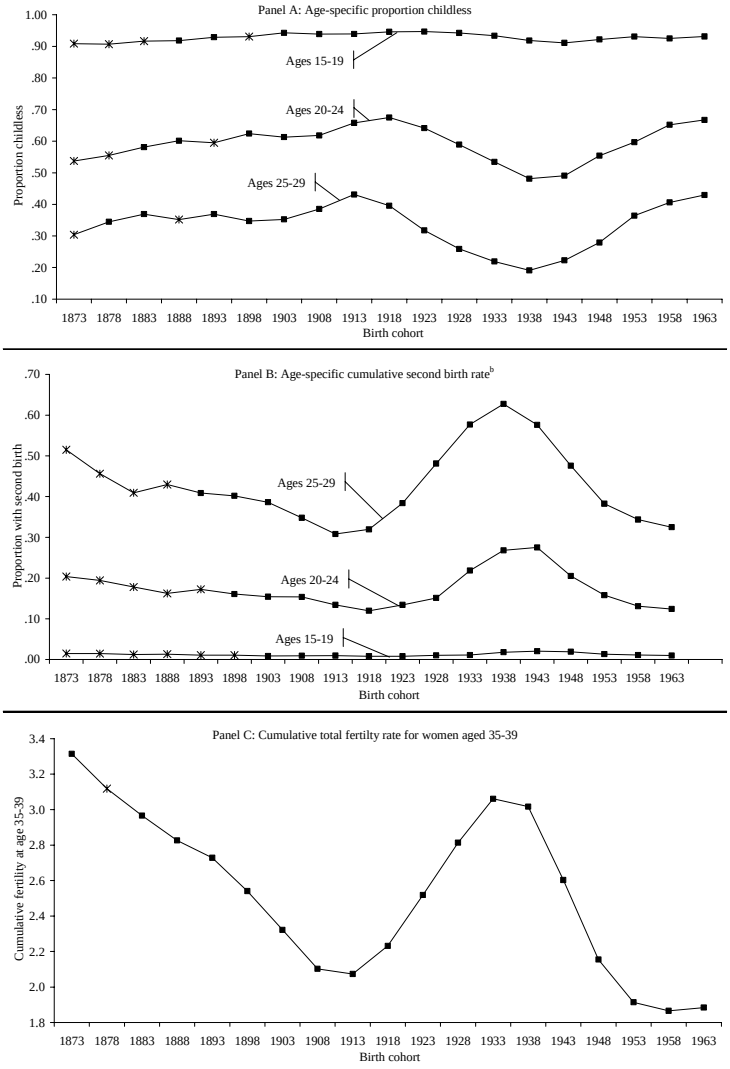
Up to 28% of the values on some of the cohort fertility measures are missing because of lapses in the collection of historical data, with the highest percentages for fertility rates at the youngest ages. For example, U.S. vital statistics data provide annual age-specific fertility rates starting in 1917 (Heuser 1976). Because birth cohort is identified as calendar year minus age, we can use those data to identify fertility at ages 15-19 for women born in 1902, ages 20-24 for women born in 1897, and so on.

Fortunately, the cohort measures are missing at random – conditional on factors that predict lapses in historical data, including age and period – rather than due to unobserved mechanisms, thereby meeting a key assumption of multiple imputation (Rubin 1987). Multiple imputation relies on weaker (i.e., more plausible) assumptions than other commonly used methods for dealing with missing data, including hot-deck imputation or dropping observations that have missing values on covariates of interest (Schafer 1997). Multiple imputation entails creating multiple (we create 90) imputed data sets, each with a different set of likely values that are drawn from the posterior predictive distribution that is estimated with variables that are correlated with the missing values and the propensity to be missing (Schafer 1997; Allison 2002; Royston 2005). We use information about cohorts' fertility at older ages to predict their fertility at younger ages. But we know too little about fertility in the 1863 and 1868 birth cohorts (women aged 80 or older in 1948 and women aged 85 or older in 1953) to

reasonably infer their fertility at younger ages; therefore, we drop these cohorts from our analyses. We estimate our models separately in each data set and combine the coefficients and standard errors as shown elsewhere (Rubin 1987). Variation across the data sets reflects our uncertainty about the imputed values and inflates our standard errors accordingly. Our results are quite similar when using imputed values, dropping all cases with missing data, or excluding different age groups to test the robustness of our findings (see Appendix).

Figure 1 shows the fertility measures by birth cohort. Asterisks indicate average values from multiply imputed data, and the boxes denote values from vital statistics or census data. Panel A shows the age-specific proportion childless. The proportion of women who are childless at ages 15-19 varies little, but the proportion childless at ages 20-24 and 25-29 increases across the 1873-1913 cohorts, declines among the 1918-1938 cohorts that give birth to the baby boom generation, and then increases across the 1943-1963 cohorts. Panel B presents age-specific cumulative second birth rates. Across all cohorts, less than 2% of women aged 15-19 have had a second birth. But fertility varies more substantially at ages 20-24 and 25-29, reflecting higher fertility in early cohorts and cohorts who gave birth to the baby boomers. There are more imputed data points for the cumulative second birth rates than for the proportion childless at each age because the 1900-1910 Census tables do not report cumulative second birth rates. Panel C shows that cumulative fertility at age 35-39 fell from 3.31 births per woman born in 1873 to 2.07 births per woman born in 1913, rose to 3.06 births per woman born in 1933, then fell to 1.8 births per woman born in 1963.

Figure 1: Age-specific fertility measures for the 1873-1963 birth cohorts in the United States



a. Asterisks indicated mean values of multiple imputed data and boxes denote values from Vital Statistics or Census data.

b. The cumulative second birth rates are missing more often than the proportion childless because they were not tabulated in the 1900 and 1910 Census Data.

2.2 Analyses

Statistically identifying the distinct impacts of age, period, and cohort is problematic because each variable is a linear combination of the other two variables. Many scholars resolve this issue by introducing constraints that are arbitrary or that can only identify non-linear trends (e.g., Tarone and Chu 2000; Arbeev et al. 2005). Instead of relying on those methods, we include direct measures of cohort fertility. Preston and Wang (2006) used a similar method to examine cohort smoking patterns and mortality trends. We use negative binomial regression to model the expected number of deaths as:

$$C_{ijk} = \exp\{\ln(E_{ijk}) + \beta_i x_i + \pi_j x_j + \lambda f_k + v_{ijk}\}$$

where C_{ijk} equals the number of breast cancer deaths to women in age group *i*, period *j*, and cohort *k*; E_{ijk} indicates the population exposed to the risk of breast cancer mortality in each age, period, and cohort; x_i is a dummy variable indicating membership in age group *i*; x_j is a dummy variable indicating that the observation pertained to period *j*; f_k indicates the age-specific fertility measure for members of cohort *k*; and β_i, π_j, and λ are estimated coefficients for the relationship between each variable and breast cancer mortality. We test for over-dispersion (i.e., the variance of breast cancer mortality rates is greater than the mean) by allowing for an omitted variable v_{ijk} whose exponential is gamma distributed with a mean 1 and variance α. Increasing values of α indicate greater over-dispersion; if $\alpha = 0$ then there is no evidence of over-dispersion and the model could be fit more parsimoniously with Poisson regression. Stata (StataCorp 2005) parameterizes α as $\ln(\alpha)$, which we report in our tables.

Our models sequentially add and remove each fertility measure to assess their impact on breast-cancer mortality rates; collinearity precludes including multiple fertility measures simultaneously. We use *F*-tests to compare model fit when using multiply imputed data, as described elsewhere (Allison 2002).We report our results in the form of exponentiated coefficients, or incidence rate ratios.

3. Results

Table 1 presents descriptive statistics for the cohort fertility measures. The proportion childless declines with age. In the cohorts studied here, an average of 93.2% of women aged 15-19 were childless compared to 33.4% of women aged 25-29. The cumulative second birth rate increases with age: 1.1% of women aged 15-19 have had a second live birth compared to 42.2% of women aged 25-29. The cumulative birth rate at ages 35-39

shows that women average 2.5 births in our data. Table 1 also shows that the proportion of values that are imputed declines with age and is highest for the cumulative second birth rates, for the reasons noted above.

Table 2 presents incidence rate ratios for the relationship between breast cancer mortality rates and the age, period, and cohort fertility measures. Model 1 includes only the variables for age and period and shows that breast cancer mortality increases with age: compared to women aged 40-44, women aged 45-49 have 1.6 times, women aged 65-69 have 3.9 times, and women aged 85 and older have 8.1 times the rate of breast cancer mortality. Compared to breast cancer mortality rates in 1948, mortality was persistently but not significantly lower from 1953-1993, and then fell by 16% in 1998 and 24% in 2003.

Table 1: Means and standard deviations for age-specific cohort fertility measures

	Mean	Standard Deviation	Proportion Imputed
Proportion Childless			
15-19	0.932	0.019	0.171
20-24	0.599	0.057	0.120
25-29	0.334	0.069	0.077
Cumulative Second Birth Rate			
15-19	0.011	0.006	0.282
20-24	0.169	0.047	0.214
25-29	0.422	0.093	0.154
Cumulative Fertility Rate			
35-39	2.53	0.387	0.034

N=117

Models 2 through 4 examine the impact of the age-specific proportion childless on the breast cancer death rates. Model 2 predicts that cohorts that had no first births at ages 15-19 would have 26.6 times the rate of breast cancer mortality as cohorts where all women had first births at ages 15-19. Although this result may apply to individual women who transition from childlessness to having a first birth, there is little variability in the proportion childless at ages 15-19 at the population level. An alternate way to express this relationship is that a two standard deviation (from Table 1) increase in the rate of childless at ages 15-19 is associated with a 13% increase in the breast cancer mortality rate.

Table 2: Negative binomial regression incidence rate ratios for the relationship between breast cancer mortality rates and the age-specific cohort fertility measures

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Proportion Childless								
15-19		26.64**						
20-24			1.68***					
25-29				1.05				
Cumulative Second Birth Rate								
15-19					0.0001**			
20-24						0.51***		
25-29							0.82**	
Cumulative Fertility Rate								
35-39								0.99
Age Groups								
40-44	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
45-49	1.65***	1.64***	1.65***	1.65***	1.65***	1.65***	1.65***	1.65***
50-54	2.34***	2.33***	2.35***	2.34***	2.33***	2.35***	2.34***	2.34***
55-59	2.95***	2.94***	2.96***	2.95***	2.94***	2.96***	2.95***	2.95***
60-64	3.42***	3.41***	3.43***	3.42***	3.39***	3.43***	3.43***	3.43***
65-69	3.91***	3.89***	3.91***	3.91***	3.85***	3.90***	3.91***	3.92***
70-74	4.64***	4.61***	4.61***	4.63***	4.55***	4.61***	4.62***	4.64***
75-79	5.42***	5.38***	5.38***	5.41***	5.29***	5.37***	5.39***	5.42***
80-84	6.34***	6.31***	6.29***	6.32***	6.19***	6.28***	6.28***	6.34***
85+	8.10***	8.11***	8.03***	8.08***	7.89***	8.01***	8.03***	8.11***
Calendar Periods								
1948	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
1953	0.96	0.96	0.96	0.96	0.96	0.96	0.96	0.96
1958	0.94	0.93	0.93*	0.94	0.94	0.93*	0.94	0.94
1963	0.94	0.93	0.93*	0.94	0.94	0.93*	0.94	0.94
1968	0.98	0.95	0.97	0.98	0.98	0.97	0.97	0.98
1973	0.98	0.95	0.96	0.98	0.97	0.96	0.97	0.97
1978	0.97	0.94	0.96	0.97	0.97	0.96	0.97	0.97
1983	0.96	0.94	0.96	0.96	0.97	0.96	0.97	0.96
1988	1.00	0.98	1.00	1.00	1.02	1.00	1.00	0.99
1993	0.95	0.94	0.96	0.96	0.98	0.96	0.96	0.95
1998	0.84***	0.83***	0.84***	0.84***	0.86**	0.84***	0.84***	0.84***
2003	0.76***	0.75***	0.76***	0.76***	0.78***	0.76***	0.77***	0.76***
Ln(α)	-4.91***	-5.22***	-5.02***	-4.91***	-5.11***	-5.03***	-4.96***	-4.91***
F-test vs. Model 1		*p*=.004	*p*=.001	*p*=.690	*p*=.022	*p*=.002	*p*=.034	*p*=.83

* p≤.10; ** p≤.05; ***p≤.01 (two tailed tests)
N=117

Model 3 estimates that a cohort that had no first births at age 20-24 would have a 68% higher breast cancer mortality rate than a cohort in which all women had children by age 20-24. Although the incidence ratio for the proportion childless at ages 20-24 is smaller than for ages 15-19, the standard deviation is larger (see Table 1); thus, a two standard deviation increase in the proportion childless at ages 20-24 is associated with a 6.1% increase in the breast cancer mortality rate. The proportion of women who are childless at ages 25-29 is not significantly associated with breast cancer mortality in our data (Model 4).

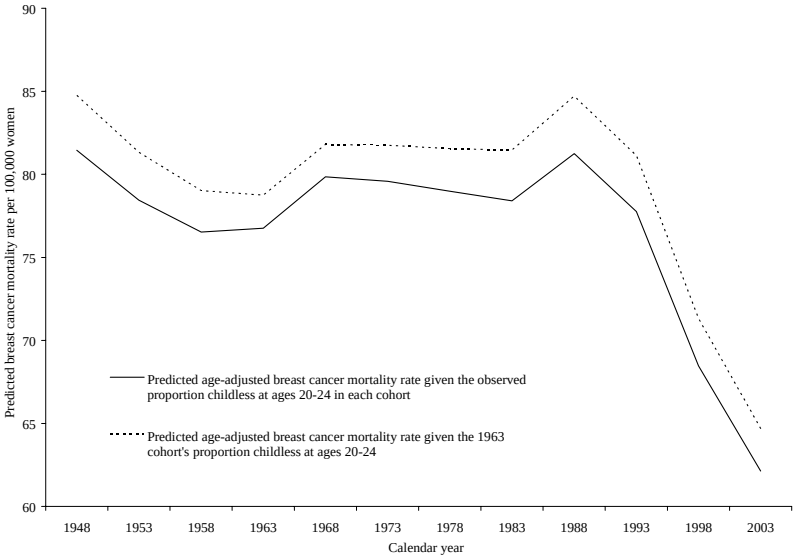
Models 5 through 7 examine the relationship between the cumulative second fertility rate and breast cancer mortality. Model 5 shows that a cohort in which all women aged 15-19 had second births would have a 99.99% lower rate of breast cancer mortality rate than if no women had second births. As with the proportion childless at age 15-19, this result may hold for individual women, but there is very little variability in the cumulative second birth rate at ages 15-19. Thus, a two standard deviation increase in the rate of childless at ages 15-19 is associated with a 10.1% decrease in the breast cancer mortality rate.

Model 6 predicts that cohorts in which all women had second births by ages 20-24 would have 49% lower breast cancer mortality rates than cohorts in which no women had second births. A two standard deviation increase in the cumulative second birth rate at ages 20-24 is associated with a 6.1% decrease in the breast cancer mortality rate. Model 7 estimates that cohorts where all women aged 25-29 have a second birth would have 18% lower breast cancer mortality rates than cohorts where no women had second births. In the context of observed U.S. fertility patterns, a two standard deviation increase in the cumulative second birth rate at ages 25-29 is associated with a 3.7% decrease in the breast cancer mortality rate.

Model 8 examines whether total parity is associated with breast cancer mortality and shows that cumulative fertility among women aged 35-39 is not significantly associated with breast cancer mortality among women aged 40 and older in these data. Separate models included the cumulative fertility rate at ages 35-39 as well as the age-specific proportion childless or the age-specific second birth rates. An unexpected result emerged: cumulative fertility rates were associated with *increased* breast cancer mortality in models that also adjusted for the proportion childless at ages 20-24, or the cumulative second birth rate at ages 20-24 or 25-29 (results not shown). The estimated relationships were modest in magnitude, and likely resulted from the high level of collinearity between the cumulative fertility rate and the proportion childless at ages 20-24 (r=-.62), the cumulative second birth rate at ages 20-24 (r=.50), and the cumulative second birth rate at ages 25-29 (r=.71), even before adjusting for age and calendar period variables.

Introducing counterfactual fertility assumptions allows us to shed light on the role of reproductive factors in period trends in breast cancer mortality. We focus on the proportion childless at ages 20-24 because it is significantly related to breast cancer mortality in our models and in prior studies, and because it varies substantially over time and might leave a large imprint on period trends in mortality. Figure 2 graphs age-adjusted breast cancer mortality rates across calendar periods, as predicted by Model 3, Table 2. The solid line shows the predicted breast cancer mortality rate per 100,000 women, given the observed proportion childless at ages 20-24 among the birth cohorts that are present in each period. The mortality rates are fairly inconsistent from the early 1950s until the early 1980s, whereupon the rates increase until the late 1980s, and then decline substantially until 2003.

Figure 2: Predicted breast cancer mortality by calendar year, given different proportions childless at ages 20-24



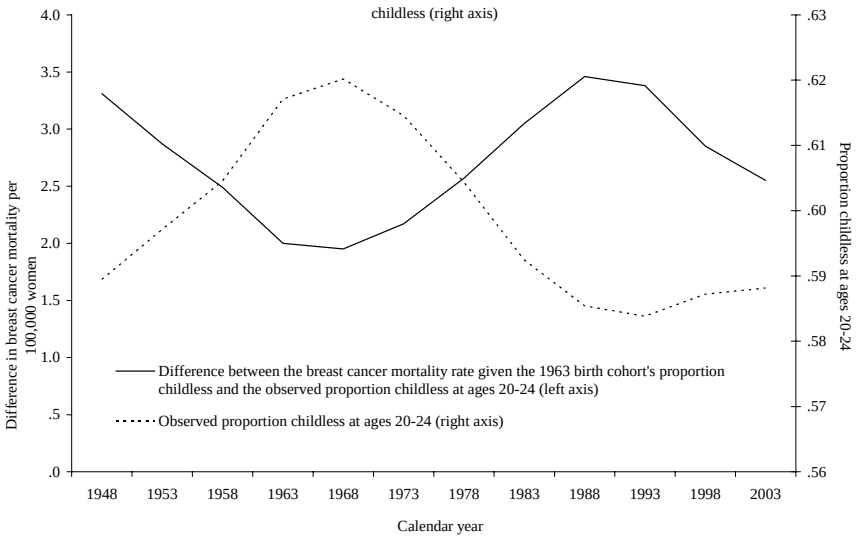
Estimates derived from Table 2, Model 3

The dotted line shows the predicted breast cancer mortality rate that we would expect if all cohorts had the proportion childless at ages 20-24 of women in the 1963 birth cohort, which is marked by nearly the highest proportions childless in our data (see Figure 1, Panel A). Across all calendar periods, the breast cancer mortality rate would have been higher if all cohorts had the same proportion childless at ages 20-24 that was exhibited by the 1963 birth cohort. Breast cancer mortality would likely have been much higher in the past if not for the higher fertility of earlier cohorts. Conversely, the recent declines in breast cancer mortality would likely have been even greater if women had the higher levels of early fertility exhibited by earlier cohorts.

An additional counterfactual comparison estimates the share of breast cancer mortality that could be attributed to the observed variation in fertility. We compared the predicted breast cancer mortality rates from Model 3, Table 2 when holding the proportion childless at ages 20-24 at the lowest observed level (.48 in the 1938 cohort) and then at the highest observed level (.68 in the 1918 cohort), and holding age and period at their means (analyses not tabled). If cohorts had the 1918 proportion childless we would expect a breast cancer mortality rate of 79.57 per 100,000 women, or 10.5% higher than the expected mortality rate of 71.98 deaths per 100,000 if given the 1938 cohort's proportion childless. Thus, cohort fertility patterns leave a substantial impact on national breast cancer mortality rates, although other factors that change on an age, period or cohort basis – including changes in nutrition, improved breast cancer detection, and more effective adjuvant therapies – are also important (Breen and Kessler 1994; Tarone and Chu 2000; Jatoi and Miller 2003).

Although Figure 2 shows that breast cancer mortality would likely have been higher at all points in the past if cohorts were marked by the high proportion childless of the 1963 cohort, it is not immediately apparent that the difference between the predictions vary across the calendar years. The solid line on Figure 3 shows the difference in the numbers of deaths per 100,000 women that would be expected given the observed proportions childless at ages 20-24 (i.e., the solid line on Figure 2) and numbers of deaths that would be expected given the 1963 cohort's proportion childless (i.e., the dotted line on Figure 2). The difference between the two sets of predictions is greater than 2.5 deaths per 100,000 women in 1953 or earlier and in 1978 or later. The dotted line illustrates that the magnitude of the difference is driven by variation in the proportion childless at ages 20-24 among cohorts that pass through each calendar period.

Figure 3: Comparison of period trends in the difference between the age adjusted breast cancer mortality rates given the 1963 birth cohort's and the observed proportions childless (left axis), and the observed proportion childless (right axis)



4. Discussion

Our incidence rate ratio of 1.68 for the proportion of women who are childless at ages 20-24 (from Model 3, Table 2) is consistent with epidemiologic literature. Ma et al. (2006: Table 3) conduct a meta-analysis of three studies of estrogen and progesterone receptor positive breast cancer among post-menopausal women. Across studies, older women who had first births at older ages had 1.65 times (95% confidence interval: 1.15-2.38) the risk of contracting breast cancer as women who had first births at younger ages. The categories for age at first birth used in the three studies were a dichotomous break at 25, as in our study; a dichotomous break at 30; and a comparison of those aged 28 and older to those aged 24 and younger. For the smaller numbers contracting estrogen- and progesterone-receptor negative breast cancers, the three studies had a combined relative risk in the older/younger comparisons of 1.28 among

older women. Rusiecki and colleagues (2005) find that between 13% and 34% of tumors are both estrogen and progesterone receptor negative across 7 studies, depending on the sample and how receptor status was define.

Our results for the proportion childless are also consistent with studies showing that age 25 is the significant break-point in the relation between age at first birth and breast cancer mortality among older women (see Ursin et al. 2004: Table 2). We are aware of no epidemiologic studies of cumulative second birth rates with which we can compare our results. Prior studies have found that total parity is associated with breast cancer mortality (Althuis et al. 2004; Ursin et al. 2004; Ma et al. 2006). Total parity at ages 35-39 was unassociated with breast cancer mortality rates among women aged 40 and older, but separate analyses (not shown) tested for interactions between parity and age and found that total parity at ages 35-39 was inversely associated with breast cancer mortality rates among women aged 80 and older ($F_{(9, 766553)}$=1.68; p=.088). None of the other fertility measures demonstrated significant interactions with age.

Given the highly correlated trends in the age-specific birth rates (see Figure 1), one might expect that the fertility variables would be largely interchangeable in the multivariate models. But this is not the case. Cumulative fertility at ages 35-39 did not demonstrate a significant association with breast cancer mortality in our data, and further analyses (not shown) found that the proportion childless and the cumulative second birth rate at ages 30-34 were unassociated with breast cancer mortality rates. Thus, even national level data show that giving birth to first and second children at earlier ages is significantly protective against breast cancer mortality.

The period trend in breast cancer mortality rates that we find in Table 2 and show in Figure 2, has been documented previously (Chu et al. 1996; Tarone, Chu, and Gaudette 1997; Wingo et al. 1998). The upward trend in the early 1980s has been attributed to the increased use of mammography, the earlier detection of palpable tumors, and the addition of progestin to hormone replacement therapy during the decade, and the sharp declines starting in the late 1980s likely reflect the benefits of both early detection and adjuvant therapy (Breen and Kessler 1994; Tarone and Chu 2000; Jatoi and Miller 2003). Although the incidence of breast cancer declined in 2003, possibly due to the declining usage of hormone replacement therapies (Ravdin et al. 2007) or reductions in mammography (Breen et al. 2007), it may take several years to ascertain whether there will be a concomitant decline in breast cancer mortality rates.

Tarone and Chu (2000) visually compared their estimated trends of breast cancer mortality with graphs of cohort fertility, and noted that breast cancer mortality trends increasingly diverged from fertility patterns for cohorts born after 1930. In separate analyses (not shown), we tested for this relationship directly by including a variable that indicated cohorts born in 1930 or earlier and interactions between the indicator variable and the proportion childless at ages 15-19, 20-24, and 25-29 to Models 2, 3, and 4

(Table 2), respectively. Consistent with Tarone and Chu (2000), the age-specific proportions childless were stronger predictors of breast cancer mortality for cohorts born before 1930, and they were relatively weaker predictors of breast cancer mortality rates among women born after 1930.

Fertility has many important demographic consequences, and the hormonal fluctuations during pregnancy and after giving birth have strong and well recognized biological connections to breast cancer mortality. But we do not have long-term population level data on other factors that might leave strong imprints on breast cancer incidence and mortality, such as the use of hormone replacement therapy or adjuvant therapy (Jatoi and Miller 2003; Ravdin et al. 2007), the population level utilization of preventive breast exams (Breen and Kessler 1994; Breen et al. 2007), or the duration between menarche and the age of first birth (Li et al. 2007). Further, despite the increased risks of breast cancer incidence and mortality, women may live longer if they delay childbearing or have fewer children, because reproduction requires resources that could otherwise be used for somatic maintenance (Westendorp and Kirkwood 1998; Westendorp et al. 2001). Future research could examine whether education or race shape the impact of fertility on breast cancer mortality trends.

5. Conclusion

Cancer is among the top three (and often among the top two) causes of death for women aged 40 and older in the U.S., and breast cancer is the second leading cause of cancer mortality after lung cancer (Hoyert et al. 2006; Heron and Smith 2007). Declines in fertility among some population subgroups in the U.S. presage a possible slowing of the declines in breast cancer mortality that are achieved by improved screening and therapies. Based on research that focuses on hormone receptor tumors, it also seems likely that declining fertility may lead to an increased prevalence of estrogen and progesterone receptor positive tumors (Althuis et al. 2004; Ma et al. 2006), which might shape the kinds of therapies that will be required most frequently. Jatoi and colleagues (2007) found that mortality from estrogen receptor positive breast cancers has declined more than mortality from estrogen receptor negative tumors between 1990 and 2003, suggesting that current adjuvant therapies and mammography may be more successful at identifying and treating hormone receptor positive tumors.

Demographers seldom have access to national data on risk factors with strong biological connections to specific causes of death, over long spans of time. But long-term data on cohort fertility patterns and breast cancer mortality rates have allowed us to use demographic methods to extend findings from prior epidemiological studies. Over the past half century, cohorts marked by high levels of fertility at young ages have

exhibited lower breast cancer mortality rates than cohorts with low fertility levels. Specifically, low proportions of childless women at ages 15-24, or high cumulative second birth rates at ages 15-29, are associated with significantly and substantially lower rates of breast cancer mortality in later life. In sum, this is the first demonstration that cohort fertility patterns have left a clear imprint on trends in U.S. breast cancer mortality rates.

6. Acknowledgements

This paper benefited from presentation at the 2007 meetings of the Population Association of America in New York, NY, and the comments of Phil Morgan. The authors would like to acknowledge the Robert Wood Johnson-Health & Society Scholars Program at the University of Pennsylvania and the University of Texas Population Research Center (NICHD R24 HD42849) for administrative and research support, Emily Buzzell and Haidong Wang for assistance in creating the data set, and Xainglin Du for helpful comments on an earlier draft of this paper.

References

Allison P. D. (2002). *Missing data*. Thousand Oaks, CA: Sage.

Althuis M. D., Fergenbaum J. H., Garcia-Closas M., Brinton L. A., Madigan M. P., and Sherman M. E. (2004). "Etiology of hormone receptor-defined breast cancer: a systematic review of the literature." *Cancer Epidemiology, Biomarkers, and Prevention* 13:1558-1568.

Arbeev K. G., Ukraintseva S. V., Arbeeva L. S., and Yashin A. I. (2005). "Decline in human cancer incidence rates at old ages: age-period-cohort considerations." *Demographic Research* 12:273-300.

Breen N., Cronin K. A., Meissner H. I., Taplin S. H., Tangka F. K., Tiro J. A., and McNeel T. S. (2007). "Reported drop in mamography: is this cause for concern?" *Cancer* 109:2405-2409.

Breen N. and Kessler L. (1994). "Changes in the use of screening mamography: evidence from the 1987 and 1990 National Health Interview Surveys." *American Journal of Public Health* 84:62-7.

Carter S. B., Gartner S. S., Haines M. R., Olmstead A. L., Sutch R., and Wright G. (2006). "Historical Statistics of the United States: Millennial Edition." Cambridge, UK: Cambridge University Press.

Chu K. C., Tarone R. E., Kessler L. G., Ries L. A. G., Hankey B. F., Miller B. A., and Edwards B. K. (1996). "Recent trends in U.S. breast cancer incidence, survival, and mortality rates." *Journal of the National Cancer Institute* 88:1571-1579.

Collaborative Group on Hormonal Factors in Breast Cancer. (2002). "Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease." *The Lancet* 360:187-195.

Heron M. P. and Smith B. L. (2007). *Deaths: leading causes for 2003. National vital statistics reports.* Hyattsville, MD: National Center for Health Statistics.

Heuser R. L. (1976). *Fertility tables for birth cohorts by color: United States, 1917-73*. Rockville, MD: National Center for Health Statistics.

Hoyert D. L., Heron M. P., Murphy S. L., and Kung H.-C. (2006). *Deaths: final data for 2003. national vital statistics report.* Hyattsville, MD: National Center for Health Statistics.

Jatoi I., Chen B. E., Anderson W. F., and Rosenberg P. S. (2007). "Breast cancer mortality trends in the United States according to estrogen receptor status." *Journal of Clinical Oncology* 25:1683-1690.

Jatoi I. and Miller A. B. (2003). "Why is breast-cancer mortality declining?" *The Lancet Oncology* 4:251-254.

Kelsey J. L., Gammon M. D., and John E. M. (1993). "Reproductive factors and breast cancer." *Epidemiological Reviews* 15:36-47.

Li C. I., Maline K. E., Daling J. R., Potter J. D., Bernstein L., Marchbanks P. A., Strom B. L., Simon M. S., Press M. F., Ursin G., Burkman R. T., Folger S. G., Norman S. A., McDonald J. A., and Spirtas R. (2007). "Timing of menarche and first full-term birth in relatin to breast cancer risk." *American Journal of Epidemiology* 167:230-239.

Ma H., Bernstein L., Pike M. C., and Ursin G. (2006). "Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies." *Breast Cancer Research* 8:1-11.

Merrill R. M., Fugal S., Novilla L. B., and Raphael M. C. (2005). "Cancer risk associated with early and late maternal age at first birth." *Gynecologic Oncology* 96:583-593.

National Cancer Institute. (2003). *Summary report: early reproductive events and breast cancer workshop*: Online access at www.cancer.gov.

National Center for Health Statistics. (various years-a). *National vital statistics reports*. Hyattsville, MD.

—. (various years-b). *Vital Statistics of the United States*. Hyattsville, MD: U.S. Department of Health, Education, and Welfare.

Preston S. H. and Wang H. (2006). "Sex mortality differences in the United States: the role of cohort smoking patterns." *Demography* 43:631-646.

Ravdin P. M., Cronin K. A., Howlader N., Berg C. D., Chlebowski R. T., Feuer E. J., Edwards B. K., and Berry D. A. (2007). "The decrease in breast-cancer incidence in 2003 in the United States." *New England Journal of Medicine* 356:1670-1674.

Royston P. M. (2005). "Multiple imputation of missing values: update of ICE." *The Stata Journal* 5:527-536.

Rubin D. B. (1987). *Multiple imputation for nonresponse in surveys*. New York: Wiley.

Rusiecki J. A., Holford T. R., Zahm S. H., and Zheng T. (2005). "Breast cancer risk factors according to joint estrogent receptor and progesterone receptor status." *Cancer Detection and Prevention* 29:419-429.

Schafer J. L. (1997). *Analysis of incomplete multivariate data*. London: Chapman and Hall.

StataCorp. (2005). "Stata statistical software: release 9." College Station, TX: Stata Press.

Strand B. H., Tverdal A., Claussen B., and Zahl P. H. (2005). "Is birth history the key to highly educated women's higher breast cancer mortality? A follow-up study of 500,000 women aged 35-54." *International Journal of Cancer* 117:1002-1006.

Tarone R. E. and Chu K. C. (1996). "Evaluation of birth cohort patterns in population disease rates." *American Journal of Epidemiology* 143:85-91.

—. (2000). "Age-period-cohort analyses of breast-, ovarian-, endometrial-, and cervical-cancer mortality rates for Caucasian women in the USA." *Journal of Epidemiology and Biostatistics* 5:221-231.

Tarone R. E., Chu K. C., and Gaudette L. A. (1997). "Birth cohort and calendar period trends in breast cancer mortality in the United States and Canada." *Journal of the National Cancer Institute* 89:251-256.

Truesdell L. E. (1945). *Differential fertility 1940 and 1910, women by number of children ever born: sixteenth Census of the United States*. Washington, DC: United States Government Printing Office.

U.S. Census Bureau. (various years). *Current population reports, series P25-311, P25-314, P25-519, P25-870, P20-441*. Washington, DC.

Ursin G., Bernstein L., Wang Y., Lord S. J., Deapen D., Liff J. M., Norman S. A., Weiss l. K., Daling J. R., Marchbanks P. A., Malone K. E., Folger S. G., McDonald J. A., Burkman R. T., Simon M. S., Strom B. L., and Spirtas R. (2004). "Reproductive factors and risk of breast carcinoma in a study of White and African-American women." *Cancer* 101:353-362.

Westendorp R. G. J. and Kirkwood T. B. (1998). "Human longevity at the cost of reproductive success." *Nature* 396:743-746.

Westendorp R. G. J., van Dunne F. M., Kirkwood T. B., Halmerhorst F. M., and Huizinga T. W. J. (2001). "Optimizing human fertility and survival." *Nature Medicine* 7:873.

Wingo P. A., Ries L. A. G., Rosenberg H. M., Miller D. S., and Edwards B. K. (1998). "Cancer incidence and mortality, 1973-1995." *Cancer* 82:1197-1207.

Appendix

Table 3 compares coefficients from models that exclude or include the multiply imputed data. Each coefficient comes from a separate model that further controls for age and calendar period. The first column presents coefficients (the natural logarithm of the incidence rate ratios) from models that include multiply imputed data on the fertility measures – these results correspond to those shown in Table 2. The second column excludes women aged 40-44 who might still bear children. The third column excludes women aged 85 and older who may be marked by selective mortality and who are not members of a uniquely-defined five-year cohort. The results from models that exclude specific age groups are similar in magnitude and significance to those that include all age groups, with the exception that the coefficient for the cumulative second fertility rate at ages 25-29 falls from significance when excluding women aged 85 and older. The fourth through sixth columns replicate the first three columns but come from models that exclude any cases with missing data on the fertility measures. In all cases, the coefficients are similar in magnitude and significance to those that include missing data, although the coefficients estimated with the imputed data often have smaller absolute values.

Table 3: Negative binomial regression coefficients for the relationship between cohort fertility measures and breast cancer mortality rates: comparisons of results with imputed and non-imputed data.[a, b]

	Multiply Imputed Data			Non-Imputed Data		
	All Ages[c]	Ages 45+	Ages 40-84	All Ages	Ages 45+	Ages 40-84
Proportion Childless						
15-19	3.28**	3.08**	3.21**	6.14***	6.28***	5.67***
20-24	0.52***	0.61***	0.43***	0.63***	0.79***	0.52***
25-29	0.05	0.18	-0.05	0.04	0.18	-0.06
Cumulative Second Birth Rate						
15-19	-9.07**	-10.20*	-8.65**	-14.13***	-16.42***	-12.89***
20-24	-0.67***	-0.79***	-0.58***	-0.82***	-1.02***	-0.70***
25-29	-0.20**	-0.26**	-0.13	-0.20**	-0.29***	-0.13
Cumulative Fertility Rate						
35-39	-0.01	-0.01	0.01	-0.01	-0.02	0.01

* $p \leq .10$; ** $p \leq .05$; *** $p \leq .01$ (two tailed tests)

a. Coefficients are calculated as the natural logarithm of incidence rate ratios.

b. Each coefficient comes from a separate model that further adjusts for the age groups and calendar periods.

c. Coefficients in this column correspond to the incidence rate ratios presented in Table 2.

Comparing models that use multiply imputed data and that drop all cases with missing data is informative, but that may not be the most effective test of whether our imputations are improving our analyses, or at least introducing little bias. We take several additional steps to assure that our imputations are reasonable. First, we examine cohort trends in the fertility rates (see Figure 1), to assure that our imputations show reasonable continuity with the observed data. Second, we follow Royston's (2005) advice to assure that our imputed values oscillate randomly within a range of values that is consistent with the non-missing data (results not shown). Third, we examine bivariate relationships to ensure that the imputed fertility rates retain their correlations with the mortality rates and other variables as expected (results not shown). Finally, we test various imputation models. Imputations from some models provide cohort fertility rates that exhibit greater continuity with observed fertility measures than other models, but in all cases our final estimated results were virtually identical in terms of direction, magnitude, and statistical significance. Each of our tests suggest, in combination with the results shown in Table 3, that our imputations do not introduce systematic bias into our estimates and allow us to use more data points for breast cancer mortality than would otherwise be possible with the available fertility data.