Associations of parity and age at first pregnancy with overall and cause-specific mortality in the Cancer Prevention Study II

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Objective: To evaluate the association of parity, number of live births, and age at first birth with mortality using multivariable-adjusted Cox proportional hazards regression models.
Design: Observational cohort.
Setting: Not applicable.
Patient(s): A total of 424,797 women.
Intervention(s): None.
Main Outcome Measure(s): All-cause and cause-specific mortality.
Result(s): During median follow-up of 24.93 years, 238,324 deaths occurred. Parous, compared with nulliparous, women had lower rates of all-cause (hazards ratio [HR] = 0.94, 95% confidence interval [CI] 0.93–0.96) mortality, driven by heart disease and overall cancer mortality. A linear trend was found for more births and diabetes mortality ($P<.001$) with having ≥6 births, compared with 2, associated with an HR of 1.28 (95% CI 1.15–1.43). Compared with age at first birth from 20–22 years, age at first birth <20 years was associated with higher mortality rates overall (HR = 1.04, 95% CI 1.02–1.06), driven by heart disease and chronic obstructive pulmonary disease mortality; whereas, ≥35 years was associated with higher overall cancer mortality (HR = 1.13, 95% CI 1.06–1.20).
Conclusion(s): Although parity was associated with a slight reduction in rates of all-cause mortality resulting in a minimal impact on average lifespan, the higher diabetes mortality in grand multiparous women might warrant continuous monitoring, particularly for abnormal glucose metabolism, among these women. (Fertil Steril® 2017;107:179–88. ©2016 by American Society for Reproductive Medicine.)
Key Words: Parity, diabetes, mortality

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In the past 45 years, women in the United States have experienced significant declines in parity. In the 1950s, at the height of the Baby Boom, US women had on average more than three births, whereas the most recent statistics from the National Bureau of Health Statistics suggest that the average number of births per woman is just under two. A larger proportion of women also now delay childbearing until their late 30s and early 40s. Parity and age at first birth are associated with significant social, biological, and health effects for women (1, 2). The associations of these reproductive factors with risk of breast and ovarian cancers have been well-studied (3, 4), although less is known about associations with all-cause and cause-specific mortality.

More than 20 years ago, experimental studies in *Drosophila melanogaster* (5, 6) led to the disposable soma theory on the evolution of ageing that stipulates there is a trade-off between reproductive success and longevity (7, 8), suggesting that parity is associated with higher rates of mortality in humans. In contrast, contemporary studies in humans find a mortality advantage for parous compared with nulliparous women (9, 10). However, the magnitude and

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dose-response of the associations of number of births and age at first birth with mortality are not completely understood (9, 10). Inconsistencies across studies might be due to the large number of registry-based studies with limited control for possible confounders, limited sample size of some prospective cohort studies, and/or short follow-up time (9, 10). In an early analysis from the American Cancer Society's Cancer Prevention Study II (CPS-II), a US nationwide prospective cohort study of men and women, no association was found between parity and coronary heart disease mortality; however, the study did not explore other mortality outcomes and was based on only 8 years of follow-up (11). More recently, findings from the European Prospective Investigation of Nutrition and Cancer (EPIC), a large prospective cohort study of 322,972 women, showed that parous women had a 20% lower all-cause mortality rate than in nulliparous women, but that no linear dose-response was observed for number of births or for early or later ages at first birth (12).

We examined the associations of parity, number of births, and age at first birth with all-cause and cause-specific mortality and estimated the number of years of life lost/gained due to parity in CPS-II. In this cohort, nearly 1.2 million men and women, who were on average 61.3 years old at baseline in 1982, have been followed for a median of nearly 25 years. This analysis is the largest, most comprehensive prospective study to date to examine parity, number of births, and age at first birth with mortality.

MATERIALS AND METHODS

Study Population

A total of 676,141 women in all 50 US states, the District of Columbia, and Puerto Rico were enrolled in CPS-II by 75,000 American Cancer Society volunteers. Volunteers were instructed to enroll families in which at least one person was $\geq$45 years, ask each family member aged <30 years to complete the questionnaire, and try to enroll older people, if possible. Study participants completed a confidential four-page questionnaire in the fall of 1982 (13). For this analysis, we excluded women who were premenopausal or perimenopausal at baseline (n = 169,939) and/or missing information on menopausal status (n = 17,148) because reproductive information might have changed after the baseline survey; women who self-reported a "difficulty becoming pregnant" (n = 70,600) because the reason for possible infertility might have been associated with mortality; and women who were aged $\geq$95 years at baseline (n = 270) because the small percentage of deaths missed by the National Death Index (14) could result in significant misclassification of vital status at older ages. A total of 418,184 women were available for analysis. The Emory University School of Medicine Institutional Review Board approves all aspects of Cancer Prevention Study II Nutrition Cohort.

Exposure Assessment

The 1982 CPS-II baseline, self-administered questionnaire queried participants for information on demographic, medical, occupational and behavioral factors, dietary intake of major food groups, height and weight, among others. For reproductive factors, women were asked, "How many times have you been pregnant?" and were subsequently asked about age at first pregnancy, age at first live birth, and number of live births. After ruling out statistical interaction between parity ($\geq$1/0 live births) and age at first birth, in relation to each mortality endpoint, we defined three independent exposures with categories selected a priori based on prior studies: parity, number of live births among parous women (1, 2 [referent], 3, 4, 5, or $\geq$ 6 live births), and age at first birth among parous women (<20, 20–22 [referent], 23–24, 25–26, 27–29, 30–34, or $\geq$35 years).

Ascertainment of Mortality

Vital status was determined using two approaches (14). First, in September 1984, 1986, and 1988, American Cancer Society volunteers made personal inquiries to determine whether the participants they enrolled were alive or dead, and then they recorded the dates and places of deaths. Reported deaths were verified by obtaining death certificates from state health departments. At completion of the 1988 follow-up, vital status was known for 98.2% of the cohort. Subsequently, linkage to the National Death Index was used to identify deaths that occurred from September 1988 through December 2012 and to identify deaths among the 21,704 participants lost to follow-up between 1982 and 1988. In a validation study conducted among the CPS-II participants who reportedly died in 1985, the National Death Index was found to have 92.9% sensitivity and 99.9% specificity of vital status compared with volunteer report and death certificates (14). Death certificates or codes for cause of death were obtained for >99% of all known deaths. In CPS-II, the underlying cause of death was coded consistent with the International Classification of Disease (ICD) (ICD-9 and ICD-10) (15, 16). For this analysis, the specific outcomes of interest were all-cause mortality, as well as with top common causes of death in the United States including disease of the heart (ICD-9: 390.0–429.9, ICD-10: 100.0–151.9), malignant neoplasms (ICD-9: 140.0–239.9, ICD-10: C00–D49.9), chronic lower respiratory diseases (chronic obstructive pulmonary disease [COPD]; ICD-9: 490.0–496.0, ICD-10: J47.0–47.9), cerebrovascular diseases (ICD-9: 430.0–438.9, ICD-10: 160.0–169.9), kidney disease (ICD-9: 580.0–589.9, ICD-10: N00–N07.9, N17.0–N19.9, N2.05–N27.9), and diabetes mellitus (ICD-9: 250.0–250.9, ICD-10: E10.0–E14.9). We conducted secondary analyses also examined the 10 most common causes of cancer death in this cohort, including lung (C33–C34), breast (C50), colorectal (C18–C21), pancreatic (C25), ovarian (C56–C57), uterine (C54), leukemia (C91–C95), liver (C22), non-Hodgkin's lymphoma (C82–C85, C96), and brain cancer (C71).

Statistical Analysis

Participants contributed person-time to the analysis from the return of the baseline questionnaire until they were censored at the date of death for those who died before the end of follow-up or the date of the day before their 95th birthday.