Age at natural menopause in relation to all-cause and cause-specific mortality in a follow-up study of US black women

Se Li [a,b,*], Lynn Rosenberg [a,b], Lauren A. Wise [a,b], Deborah A. Boggs [a], Michael LaValley [c], Julie R. Palmer [a,b]

[a] Slone Epidemiology Center at Boston University, Boston, MA 02215, United States
[b] Department of Epidemiology, Boston University School of Public Health, Boston, MA 02118, United States
[c] Department of Biostatistics, Boston University School of Public Health, Boston, MA 02118, United States

ARTICLE INFO

ABSTRACT

Objectives: Early age at natural menopause has been associated with increased all-cause mortality in several studies, although the literature is not consistent. This relation has not been examined among African American women.

Study design: Data were from the Black Women's Health Study, a follow-up study of African-American women enrolled in 1995. Among 11,212 women who were naturally menopausal at entry to the study or during follow-up through 2008, we assessed the relation of age at natural menopause to all-cause and cause-specific mortality. At baseline and biennially, participants reported on reproductive and medical history, including gynecologic surgeries and exogenous hormone use. Mortality data were obtained from the National Death Index. Multivariable Cox proportional hazard models were used to estimate mortality rate ratios (MRR) and 95% confidence intervals (CI) for categories of age at menopause.

Results: Of 692 deaths identified during 91,829 person years of follow-up, 261 were due to cancer, 199 to cardiovascular diseases and 232 to other causes. Natural menopause before age 40 was associated with increased all-cause mortality (MRR = 1.34, 95% CI 0.96–1.84, relative to menopause at 50–54 years; P-trend = 0.04) and with the subcategories of death considered – cancer, cardiovascular disease, and all other causes. The associations were present among never and ever users of postmenopausal female hormones and among never and ever smokers.

Conclusions: In this large prospective cohort of African-American women, natural menopause before age 40 was associated with a higher rate of all-cause and cause-specific mortality. These findings provide support for the theory that natural menopause before age 40 may be a marker of accelerated somatic aging.

Published by Elsevier Ireland Ltd.

1. Introduction

Natural menopause is defined as the permanent cessation of menstruation due to natural loss of ovarian follicular function [1]. In the United States, natural menopause occurs on average at age 50, before the senescence of other somatic systems [2], and is accompanied by altered serum lipid profiles and other neuroendocrine and immune system changes [3]. Age at natural menopause may be a marker not only of reproductive aging but also of general health and somatic aging [4]. There is some evidence that an early menopause (<44 years) increases risk of cardiovascular disease [5,6]. In contrast, menopause before age 40 is associated with a reduced risk of breast and endometrial cancer [7,8] due to a reduction in levels of endogenous estrogens. It is unclear whether age at natural menopause influences mortality independent of specific effects on cardiovascular disease and hormone-related cancers. Although some studies have observed a higher mortality rate among women with natural menopause before age 40 [4,9–13], the increase in mortality has been small [10,13], and was statistically significant in only one study after adjustment for all covariates [11].

We used prospective data from a large cohort of African American women to assess age at natural menopause in relation to all-cause and cause-specific mortality. To our knowledge, no study has assessed this relation in African American women. Two studies suggest that black women may experience natural menopause earlier than white women [14,15], but another study found no difference [16].

* Corresponding author at: Slone Epidemiology Center, 1010 Commonwealth Avenue, Boston, MA 02215, United States. Tel.: +1 617 734 6006; fax: +1 617 738 5519.
E-mail address: lise@bu.edu (S. Li).

2. Methods

2.1. Study population

The Black Women Heath Study (BWHS), an ongoing prospective cohort study of approximately 59,000 US black women, was established in 1995 [17]. Women aged 21–69 years from across the US enrolled by completing self-administered questionnaires; the median age at baseline was 38. The baseline questionnaire collected information on demographic characteristics, anthropometric factors, lifestyle factors, reproductive history, and medical history variables [18]. Health related information was updated biennially through follow-up questionnaires. Follow-up of the baseline cohort was 80% of the original cohort in 2009.

The present analyses are based on data collected from 1995 through 2008, with death information obtained from National Death Index (NDI) searches. We restricted the analyses to women who reported a natural menopause either at enrollment in 1995 or during the follow-up (n = 11,471). After exclusion of 214 participants with missing age at menopause and 425 who were diagnosed with cancer before their menopause, the analytic cohort comprised 11,212 women. Among them, 7090 became post-menopausal during the 13 years of follow-up and the others were already post-menopausal at the time of enrollment. The human subjects protocol for BWHS was approved by the Boston University Medical Center Institutional Review Board.

2.2. Age at menopause

Questions on menopausal status were included on the baseline and all follow-up questionnaires. Women were asked if they had stopped menstruating at least 12 months earlier. If yes, they were asked for the reason their periods had stopped (natural, surgical (e.g., hysterectomy), medical (e.g., chemotherapy), unknown), and the age at which they had stopped. They were also asked whether a hysterectomy had been performed, the number of ovaries removed, and their age at each surgery. We considered a participant to have had a natural menopause if she reported cessation of her periods due to natural causes and had not had a hysterectomy or bilateral oophorectomy before that time. Age at natural menopause was considered to be the age at which the periods had stopped.

2.3. Covariates

Information on marital status, years of education, adult height and diet quality was obtained at baseline in 1995. Data on current weight, vigorous exercise, alcohol intake, smoking history, number of births, age at each birth, total duration of breastfeeding, use of oral contraceptives, and use of postmenopausal female hormones were obtained at baseline and on biennial follow-up questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. In a validation study among 115 participants, Spearman correlation coefficients for self-reported versus technician-measured weight and height were 0.97 and 0.93 respectively [19,20]. Diet quality was estimated based on responses in 1995 to a 68-item Block NCI food frequency questionnaire [21]. Factor analysis was used to calculate scores on two diet patterns, (1) "meats/fried foods" also known as the "Western" pattern (high in meat and fats) and (2) "vegetables/fruit" also known as the "prudent" pattern (high in vegetables and fruit). A high score on the meats/fried food score indicates a relatively unhealthy diet, and a high score on the vegetables/fruit score indicates a relatively healthy diet [22].

2.4. End points

The primary endpoint was death from all causes from March 1995 through December 2008. Deaths were identified by notification from next of kin and postal authorities and through searches of the NDI database [23] for non-respondents. A total of 692 deaths occurred in the analytic cohort of naturally menopausal women. Immediate and underlying causes of death were obtained for each participant from either a state-issued death certificate or from the NDI-Plus. We used the International Classification of Diseases, Ninth Revision (ICD-9), to classify underlying cause of death as death from cancer (ICD-9, 140–239) (n = 261), death from cardiovascular diseases (ICD-9, 390–459) (n = 199), or death from other causes (n = 232). The most common cancer deaths were from lung, breast, colon, and pancreatic cancer. The most common "other" causes of death were respiratory disease, renal disease, diabetes mellitus, and liver disease.

2.5. Statistical analysis

Follow-up began at the age at enrollment March 1995 for women who were already naturally post-menopausal at enrollment, or the age at menopause for women who became naturally post-menopausal after enrollment. Each woman contributed person-time from the beginning of follow-up until the date of death, loss to follow-up, or end of follow up (December 2008), whichever came first. Age at natural menopause was categorized as <40, 40–44, 45–49, 50–54, ≥55 years. Mortality rates were computed as the number of deaths divided by person-time in the same category of age at menopause. Mortality rate ratios (MRRs) were estimated using Cox proportional hazards regression analysis (SAS PROC PHREG) [24] for all deaths and, separately, for cancer deaths, cardiovascular deaths, and deaths from all other causes, using age as the time scale. The Anderson–Gill data structure was used to update time-varying covariates [25,26], which were controlled in the analyses. Multivariable models conditioned on questionnaire cycle and age included indicator terms for marital status (single, married or living as married, divorced or separated, widowed), years of education (≤12, 13–15, 16, ≥17 years), age at menarche (≤10, 11, 12, 13, 14, ≥15 years), scores of "meats/fried food" dietary pattern and "vegetables/fruit" dietary pattern (categorized into quintiles), BMI (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, ≥35.0) [27], smoking status (never, former, current), pack years of smoking (<5, 5–9, 10–14, 15–19, 20–24, ≥25), alcohol intake (never, former, current: <1, 1–6, 7–13, ≥ 14 drinks/week), vigorous physical activity (0, <5, ≥5 h/week), parity (0, 1, 2, 3, ≥4), age at first birth (<18, 18–24, 25–29, ≥30 years old), lactation (ever, never), oral contraceptive use (never, <1, 1–4, ≥5 years), and unilateral oophorectomy (yes, no). Data on marital status, years of education, age at menarche, and dietary intake were from the baseline 1995 questionnaire for all women. Other covariates were from the questionnaire at baseline for women who were already naturally post-menopausal at enrollment or from the questionnaire on which natural menopause was reported for women who became naturally post-menopausal during follow-up. Missing covariate data were modeled using indicator variables. Tests for linear trend were performed using a single ordinal variable for the independent variable in the model.

Statistical interaction was assessed using likelihood ratio tests, comparing models with and without cross-product terms between each potential effect modifier, such as smoking status (never vs. ever) and BMI (<30 vs. ≥30 kg/m^2). Because female hormone supplements were used after menopause and could be a potential causal intermediate, we also conducted separate analyses among women who had never used postmenopausal female hormones and among users. Finally, to reduce potential downstream effects from previous illness, we analyzed the relation of age at natural