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

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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

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Contributors and their role

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Competing interests

The authors declared that they have no conflicts of interests with respect of their authorship or the publication of this article.

findings provide support for the theory that natural menopause before age 40 may be a marker of accelerated somatic aging.

Keywords

Menopause; all-cause mortality; cardiovascular mortality; African-American

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].

2. Methods

2.1. Study Population

The Black Women Heath Study (BWHS), an ongoing prospective cohort study of approximately 59,000 U.S. black women, was established in 1995 [17]. Women aged 21 to 69 years from across the U.S. 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, 7,090 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 hours/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 menopause to mortality after the exclusion of 142 women who became naturally menopausal after enrollment and reported cardiovascular disease (stroke, myocardial infarction or angina) before their menopause (n=142); the results were unchanged. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC) [24].

3. Results

The median age at natural menopause was 50 years (interquartile range: 47-52), with15% of naturally menopausal women ceasing menstruation before age 45. As shown in Table 1, women with a menopause before age 40 were more likely to be younger at the start of the follow-up, be from a more recent birth cohort, be single or never married, smoke, exercise vigorously, have an unhealthy diet, have an early age at first birth, have used postmenopausal female hormones, and have less often reported a history of cardiovascular disease at baseline, compared with women who had a later age at natural menopause. The associations of younger age at menopause with younger age at entry and later birth year reflect the fact that the BWHS cohort was young (median age 38 at entry) and many women had not gone through the menopausal transition, even at the end of 13 years of follow-up.

During 91,829 person years of follow-up from 1995 through 2008, there were 692 deaths identified from all causes. The age-adjusted MRRs for age at natural menopause <40 and 40-44 years relative to natural menopausal at ages 50-54 years were 1.80 (95% CI 1.31-2.48) and 1.61 (95% CI 1.26-2.05), respectively. After control for all covariates, the corresponding multivariable MRRs were 1.34 (95% CI 0.96-1.84) and 1.33 (95% 1.04-1.70) (Table 2). Control for education, smoking status, and marital status had the greatest effect on the MRR estimates. The associations between age at natural menopause and mortality within strata of the women classified according to their year of birth (1925-1934, 1935-1944 and 1945-1973 were largely similar to those overall. In an analysis restricted to the 7,090 women

who experienced their natural menopause during follow-up, the MRR for age at natural menopause <40 years was 1.98 (95%CI 0.66-5.90), based on 5 deaths, and the MRR for age at menopause 40-44 was 1.20 (95% CI 1.59-2.45), based on 15 deaths, relative to natural menopause at age 50-54 years.

The association of age at natural menopause with specific causes of mortality is presented in Table 3. MRRs for natural menopause before age 40 relative to age 50-54 were 1.23 (95% CI 0.69-2.23) and 1.28 (95% CI 0.70-2.36) for cancer and cardiovascular mortality respectively, and there was no evidence of a dose-response relation for either outcome. For "other cause" of death, the MRR for natural menopause before age 40 relative to 50-54 was 1.46 (95% CI 0.85-2.50; P-trend=0.02).

Table 4 presents results within strata of postmenopausal female hormones use (never vs. ever). The MRR for overall mortality for menopause before age 40 was 1.97 (95%CI 1.30-2.99) among women who never used hormone supplements, whereas it was 1.00 (95% CI 0.56-1.79) among women who had used hormone supplements (P-interaction<0.001). For cause-specific mortality in never and ever users of postmenopausal female hormones (Table 4), we observed significant heterogeneity in MRRs for other-cause mortality (P-interaction <0.001), with a 3-fold increase of mortality among never users (P-trend<0.001), and a null association among ever users. Modest increases in cancer and cardiovascular mortality were observed among women with natural menopause before age 40 regardless of female hormone use, but there were no consistent trends in the MRRs and confidence intervals were wide.

In analyses among never and ever smokers (Table 5), there was evidence of increased overall mortality associated with earlier age at natural menopause in both groups, but numbers among the never smokers were small. The associations appeared stronger among ever smokers (P-interaction=0.07), which was also the case for cancer mortality. In an analysis among women who never used post-menopausal female hormones and never smoked, the MRR was 2.21 (95% CI 0.98-4.99) for menopause age <40, based on 11 deaths, and 0.96 (95% CI 0.46-2.01) for menopause at age 40-44, based on 11 deaths.

We also assessed age at natural menopause in relation to mortality within strata of BMI (data not shown). The estimates for natural menopause before age 40 were larger among women with BMI ≥30 kg/m^2, but the estimates were not statistically different from each other (P-interaction= 0.60 for BMI < 30 vs. ≥30 kg/m^2).

4. Discussion

In this prospective study of U.S. black women, natural menopause before age 40 was associated with increased all-cause mortality. The increase was in all three subcategories of death considered -- cancer, cardiovascular, and all other causes -- with a significant trend in other-cause mortality only. The association was stronger among women who had never used postmenopausal female hormones.. The associations were apparent among both smokers and nonsmokers but appeared stronger in smokers.

Previous studies provide some evidence of increased all-cause mortality in women with natural menopause age before 40 [4, 9-13]. In a 6-year follow-up study of California Seventh-Day Adventists, there was a 3-fold increase in all-cause mortality for women with a natural menopause at <40 years of age relative to 50-54 years, with a 2-fold increase in stroke mortality and a 4-fold increase in other causes of death after controlling for lifestyle factors, reproductive factors, and estrogen supplement use [4]. More recently, in an extended 12-year follow-up of the same population based on larger numbers of naturally postmenopausal women, natural menopause age 35-40 was associated with only a 30%

increase in all-cause mortality and 50% increase in ischemic heart mortality [9]. Similar results of all-cause mortality were observed in a large Dutch population of women who had never taken postmenopausal female hormones [11] and in a 37-years follow-up study of about 20,000 Norwegian women during the years that the use of postmenopausal hormones was very rare [13]. The American Cancer Society Cancer Prevention II mortality study (CPS-II), with follow-up from 1982 to 2002, found only a 4% increase in total mortality and a 9% increase in coronary heart disease mortality among women with natural menopause at 40-44 years relative to 50-54 years after the exclusion of women who had ever smoked or ever used postmenopausal female hormones [10]. The study assessed ages at menopause in the range of 40 to 55 years and thus it was not possible to test the association between extreme ages at natural menopause and mortality.

Our finding of associations of natural menopause age before 40 with increased mortality risk supports the hypothesis that an earlier natural menopause may serve as a marker of accelerated reproductive and somatic aging, resulting in earlier age at death. Premature or natural menopause before 40 is the result of an accelerated ovarian aging process determined by genetic and non-genetic causes, and this may be highly correlated to the aging of other tissues and organs [4, 28, 29]. In addition, several previous studies found that the association between age at natural menopause and mortality was stronger in women younger than 70 years of age [6, 9, 13]. This may explain the stronger association found in our study relative to other studies, given that more than 95% women were younger than 70 years at the end of the follow up.

In our data, there was evidence of an association of natural menopause age before 40 with increased risk of cardiovascular, cancer and other-cause mortality, although a significant trend was found only for other-cause mortality. Previous studies have found natural menopause before 40 to be associated with increased risk of cardiovascular disease [5, 30] and mortality from coronary heart disease [4, 9, 10, 12, 31]. The increase in cancer mortality among women with a natural menopause before age 45 in our study is contrary to findings from a previous study that found reduced cancer mortality among women with the earliest age at menopause considered, 40-44 [10]. That study was confined to never smokers and the reduction in cancer mortality was mainly due to a reduction in deaths from breast cancer [10]. Our study included smokers and there were an appreciable number of deaths from lung cancer. Thus, the different results for cancer mortality observed in the two studies may due to differences in the predominant causes of cancer death.

Interestingly, the association of natural menopause before age 40 and increased all-cause mortality was stronger among never users of postmenopausal female hormones. This interaction was primarily driven by a strong interaction for “other-cause” mortality. Use of postmenopausal hormone supplements is positively associated with education, more access to health care, and better health [32, 33], which may account, at least in part, for the weaker association of menopause before age 40 with mortality among users.

Our study has several strengths, including its large size, prospective design, high cohort retention, long length of follow–up, and focus on African American women. Also, it controlled for a wide range of potential confounders, including lifestyle factors, reproductive history, and postmenopausal female hormone use. The use of the NDI to ascertain deaths reduced the potential for differential loss to follow-up and enabled us to assess specific causes of death. Almost all BWHS participants (97%) had a high school degree at baseline [17] and national data indicate that 83% of black women of the same ages in 1995 had completed high school. Therefore, our results may apply to a large segment of U.S. black women [34].

The present analyses have some limitations. First, all information except for deaths was based on self-reported data and there will have been some misclassification. About 37% of naturally menopausal women experienced their menopause before baseline and may have not remembered exactly when menopause occurred. However, since the data were collected prior to death, misclassification was likely non-differential, which would have biased associations for extreme categories of exposure toward the null [35]. Second, it is impossible to completely adjust for lifestyle factors such as diet, smoking, alcohol use, and physical activity that influence age at menopause and mortality. Thus, the observed association may partially be due to residual confounding by unmeasured lifestyle and socio-economic related factors. Third, the 37% of the cohort that experienced natural menopause before baseline were subject to left-censoring; i.e., women with an early age at menopause may have also tended to die before the cohort was established, and this would have tended to bias the MRRs toward the null [36]. In an analysis that excluded those women, we found positive associations of menopause <40 and 40-44 with increased mortality, but they were based on small number of deaths and confidence intervals were wide.

Overall, our findings suggest that African-American women with natural menopause before age 40 have increased risk of mortality. This supports the idea that menopause before age 40 is an indicator not only of premature reproductive aging, but also of premature somatic aging. The observed interaction with postmenopausal female hormone use was unexpected and needs confirmation in other studies.

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REFERENCES

[1]. Greendale GA, Lee NP, Arriola ER. The menopause. Lancet. 1999; 353:571–80. [PubMed: 10028999]

[2]. Hill K, Hurtado A. The evolution of premature reproductive senescence and menopause in human females. Human Nature. 1991; 2:313–50.

[3]. Leidy LE. Biological Aspects of Menopause: Across the Lifespan. Annual Review of Anthropology. 1994; 23:231–53.

[4]. Snowdon DA, Kane RL, Beeson WL, Burke GL, Sprafka JM, Potter J, et al. Is early natural menopause a biologic marker of health and aging? Am J Public Health. 1989; 79:709–14. [PubMed: 2729468]

[5]. Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, Manson JE, et al. Age at Natural Menopause and Risk of Cardiovascular Disease. Arch Intern Med. 1999; 159:1061–6. [PubMed: 10335682]

[6]. Jacobsen BK, Nilssen S, Heuch I, Kvale G. Does age at natural menopause affect mortality from ischemic heart disease? J Clin Epidemiol. 1997; 50:475–9. [PubMed: 9179106]

[7]. Hsieh C, Trichopoulos D, Katsouyanni K, Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. Int J Cancer. 1990; 46(5):796–800. [PubMed: 2228308]

[8]. de Graaff J, Stolte LA. Age at menarche and menopause of uterine cancer patients. Eur J Obstet Gynecol Reprod Biol. 1978; 8:187–93. [PubMed: 264163]

[9]. Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. J Clin Epidemiol. 1999; 52:303–7. [PubMed: 10235170]

[10]. Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. Am J Epidemiol. 2005; 162:1089–97. [PubMed: 16221806]

[11]. Ossewaarde ME, Bots ML, Verbeek AL, Peeters PH, van der Graaf Y, Grobbee DE, et al. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology. 2005; 16:556–62. [PubMed: 15951675]

[12]. Hong JS, Yi S-W, Kang HC, Jee SH, Kang HG, Bayasgalan G, et al. Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study. Maturitas. 2007; 56:411–9. [PubMed: 17161927]

[13]. Jacobsen BK, Heuch I, Kvale G. Age at Natural Menopause and All-Cause Mortality: A 37-Year Follow-up of 19,731 Norwegian Women. American Journal of Epidemiology. 2003; 157:923–9. [PubMed: 12746245]

[14]. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol. 1997; 145:124–33. [PubMed: 9006309]

[15]. Cooper GS, Baird DD, Darden FR. Measures of menopausal status in relation to demographic, reproductive, and behavioral characteristics in a population-based study of women aged 35-49 years. Am J Epidemiol. 2001; 153:1159–65. [PubMed: 11415950]

[16]. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, et al. Factors Associated with Age at Natural Menopause in a Multiethnic Sample of Midlife Women. American Journal of Epidemiology. 2001; 153:865–74. [PubMed: 11323317]

[17]. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. J Am Med Womens Assoc. 1995; 50:56–8. [PubMed: 7722208]

[18]. Rosenberg L, Palmer JR, Rao RS, Adams-Campbell LL. Risk factors for coronary heart disease in African American women. Am J Epidemiol. 1999; 150:904–9. [PubMed: 10547135]

[19]. Carter-Nolan PL, Adams-Campbell LL, Makambi K, Lewis S, Palmer JR, Rosenberg L. Validation of physical activity instruments: Black Women's Health Study. Ethn Dis. 2006; 16:943–7. [PubMed: 17061751]

[20]. Wise LA, Palmer JR, Spiegelman D, Harlow BL, Stewart EA, Adams-Campbell LL, et al. Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. Epidemiology. 2005; 16:346–54. [PubMed: 15824551]

[21]. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology. 1990; 1:58–64. [PubMed: 2081241]

[22]. Boggs DA, Palmer JR, Spiegelman D, Stampfer MJ, Adams-Campbell LL, Rosenberg L. Dietary patterns and 14-y weight gain in African American women. Am J Clin Nutr. 2011; 94:86–94. [PubMed: 21593501]

[23]. National Death Index User's Manual: National Center for Health Statistics. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2000.

[24]. SAS Institute Inc. SAS/STAT User's Guide. SAS Institute; Cary, NC: 2004. Version 9

[25]. Andersen, PKaG, R. D. Cox's regression model for counting processes: a large sample study. Annals of Statistics. 1982; 10:1100–20.

[26]. Therneau, TM. Extending the Cox model. Lin, DY.; Fleming, TR., editors. Springer Verlag; Seattle, WA: 1997.

[27]. Report of a WHO Expert Committee. 1995. Physical status: the use and interpretation of anthropometry.

[28]. te Velde ER, Dorland M, Broekmans FJ. Age at menopause as a marker of reproductive ageing. Maturitas. 1998; 30:119–25. [PubMed: 9871906]

[29]. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010; 65:161–6. [PubMed: 19733988]

[30]. Lisabeth L, Bushnell C. Stroke risk in women: the role of menopause and hormone therapy. Lancet Neurol. 2012; 11:82–91. [PubMed: 22172623]

[31]. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al. Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in

Japanese postmenopausal women: the JACC study. J Epidemiol. 2006; 16:177–84. [PubMed: 16951536]

[32]. Rosenberg L, Palmer JR, Rao RS, Adams-Campbell LL. Correlates of postmenopausal female hormone use among black women in the United States. Obstet Gynecol. 1998; 91:454–8. [PubMed: 9491877]

[33]. Brett KM, Madans JH. Use of postmenopausal hormone replacement therapy: estimates from a nationally representative cohort study. Am J Epidemiol. 1997; 145:536–45. [PubMed: 9063344]

[34]. Day, JC.; Curry, AE. Educational attainment in the United States: March 1995. Commerce UDo; Washington, DC: 1996.

[35]. Greenland, S.; Rothman, KJ. Analysis of of polytomous exposures and outcomes. In: Rothman, KGS.; Lash, TL., editors. Modern Epidemiology. 3rd ed. Lippincott Raven; Philadelphia: 2008. p. 303-27.

[36]. Cain KC, Harlow SD, Little RJ, Nan B, Yosef M, Taffe JR, et al. Bias due to left truncation and left censoring in longitudinal studies of developmental and disease processes. Am J Epidemiol. 2011; 173:1078–84. [PubMed: 21422059]

Table 1

Characteristics according to age at natural menopause (N=11,212). The Black Women's Health Study, 1995-2008

Characteristics[a]	Age at natural menopause				
	< 40 (n=586)	40-44 (n=1,144)	45-49 (n=3,456)	50-54 (n=4,747)	> 55 (n=1,279)
Age at baseline, y (mean)	46.4	49.6	51.7	54.8	58.9
Birth year, y (mean)	1950	1948	1947	1945	1940
Body mass index, kg/m^2 (mean)	29.3	28.5	28.8	28.8	27.4
Education, y (mean)	14.1	14.4	14.5	14.6	13.3
Age at menarche, y (mean)	12.4	12.4	12.4	12.3	11.3
Single or never married (%)	18.7	18.3	18.1	14.0	12.1
Current smoking (%)	25.6	28.1	22.7	15.0	9.2
Cigarette smoking ≥10 packyears (%)	29.1	33.5	30.5	24.2	19.4
Current alcohol intake, ≥1 drinks/wk (%)	25.0	31.1	29.0	28.7	25.6
Vigorous physical activity, ≥5 h/wk (%)	10.4	9.1	7.5	6.3	7.3
High vegetables/fruit dietary pattern[b] (%)	16.8	19.6	20.2	19.2	21.6
High meats/fried food dietary pattern[b] (%)	22.4	23.8	21.1	18.2	15.8
Oral contraceptive use ≥5 y (%)	23.4	28.6	27.9	27.9	27.2
Parous (%)	77.4	80.5	81.5	84.3	79.6
Age at first birth <20 y[c] (%)	43.4	33.0	34.1	32.0	30.9
Ever female hormone use (%)	51.5	41.1	36.4	30.7	26.9
Cardiovascular disease at baseline[d, e] (%)	0.2	0.2	1.0	2.3	4.2

BMI=Body mass index;

[a]All characteristics are adjusted for age at enrollment in 1995 except for birth year and age at baseline;

[b]The 5th quintile of dietary pattern score for vegetables/fruit or meats/fried food;

[c]Among parous women.

[d]Self-reported stroke, myocardial infraction or angina.

[e]Among women who became menopausal during the follow-up

Table 2

Mortality rate ratios for age at natural menopause (N=11,212) Black Women's Health Study, 1995-2008

Age at natural menopause, years	Deaths	Person-years	Multivariate MRR[a] (95% CI)
All			
<40	50	5,832	1.34 (0.96, 1.84)
40-44	95	10,660	1.33 (1.04, 1.70)
45-49	197	29,320	1.04 (0.86, 1.26)
50-54	253	36,096	1.00 (ref)
≥55	97	9,921	1.02 (0.80, 1.31)
P-value, test for trend			0.04
1925-1934			
<40	13	539	1.49 (0.80, 2.79)
40-44	30	1361	1.41 (0.90, 2.21)
45-49	54	3017	0.93 (0.65, 1.34)
50-54	81	5319	1.00 (ref)
>55	67	3360	1.41 (1.01, 1.98)
P-value, test for trend			0.85
1935-1944			
<40	17	1118	1.32 (0.77, 2.27)
40-44	33	2784	1.22 (0.81, 1.82)
45-49	79	9644	0.98 (0.73, 1.31)
50-54	122	16384	1.00 (ref)
>55	27	4945	0.70 (0.46, 1.08)
P-value, test for trend			0.05
1945-1973[b]			
<40	20	4175	1.16 (0.59, 2.6)
40-44	32	6515	1.25 (0.75, 2.11)
45-49	64	16659	1.08 (0.72, 1.61)
50-54	50	14393	1.00 (ref)
≥55	3	1617	0.47 (0.14, 1.54)
P-value, test for trend			0.26

MRR= mortality rate ratio; CI = confidence interval.

[a]Model adjusts for age (1-year intervals) and time period (2-year intervals), education, marital status, BMI, smoking status, pack years of smoking, alcohol consumption, vigorous physical activity, vegetables/fruit dietary pattern, meats/fried food dietary pattern, and reproductive factors, age at menarche, parity, age at first birth, oral contraceptive use, lactation duration, and unilateral oophorectomy.

[b]Birth cohorts of 1955-1964 and 1965-1973 were collapsed with 1945-1954 due to small numbers.

Table 3

Cause-specific mortality rate ratios for age at natural menopause (N=11,212). Black Women's Health Study, 1995-2008

Age at natural menopause, years	Person-years	Cancer mortality		Cardiovascular mortality		Other-cause mortality	
		Deaths	Multivariable MRR[a] (95% CI)	Deaths	Multivariable MRR[a] (95% CI)	Deaths	Multivariable MRR[a] (95% CI)
< 40	5,832	13	1.23 (0.69, 2.23)	15	1.28 (0.70, 2.36)	22	1.46 (0.85, 2.50)
40-44	10,660	35	1.36 (0.91, 2.05)	24	1.18 (0.73, 1.90)	36	1.44 (0.95, 2.18)
45-49	29,320	69	1.02 (0.75, 1.40)	60	1.09 (0.76, 1.56)	68	1.02 (0.73, 1.43)
50-54	36,096	100	1.00 (ref)	70	1.00 (ref)	83	1.00 (ref)
≥55	9,921	44	1.20 (0.83, 1.74)	30	1.01 (0.64, 1.59)	23	0.81 (0.51, 1.30)
P-value, test for trend			0.56		0.37		0.02

MRR= mortality rate ratio; CI = confidence interval.

[a]Fully adjusted model, including age (1-year intervals), time period (2-year intervals), education years, marital status, BMI, smoking status, pack years of smoking, alcohol consumption, vigorous physical activity, vegetables/fruit dietary pattern, and meats/fried food dietary pattern, age at menarche, parity, age at first birth, oral contraceptive use, lactation, and unilateral oophorectomy

Table 4

All cause and cause-specific mortality rate ratios for age at natural menopause by female hormone use (N=11,052)[a]. Black Women's Health Study, 1995-2008

Age at natural menopause, years	All-cause mortality			Cancer mortality		Cardiovascular mortality		Other-cause mortality	
	Person-years	All Deaths	Mulbivariable MRR[b] (95% CI)	Deaths	Mulbivariable MRR[b] (95% CI)	Deaths	Mulbivariable MRR[b] (95% CI)	Deaths	Mulbivariable MRR[b] (95% CI)
Never used postmenopausal female hormones									
< 40	2,123	32	1.97 (1.30, 2.99)	6	1.36 (0.58, 3.18)	8	1.26 (0.56, 2.86)	18	3.04 (1.62, 5.72)
40-44	5,184	61	1.50 (1.08, 2.06)	22	1.82 (1.04, 3.19)	13	1.04 (0.54, 1.99)	26	1.66 (0.99, 2.81)
45-49	15,331	127	1.13 (0.88, 1.44)	43	1.32 (0.86, 2.03)	40	1.05 (0.67, 1.63)	44	1.05 (0.69, 1.62)
50-54	20,478	146	1.00 (ref.)	47	1.00 (ref.)	48	1.00 (ref.)	51	1.00 (ref.)
≥55	5,786	58	1.06 (0.77, 1.46)	26	1.56 (0.91, 2.52)	19	1.03 (0.59, 1.82)	13	0.68 (0.36, 1.29)
P-value, test for trend			0.002		0.41		0.72		<0.001
Ever used postmenopausal female hormones									
< 40	3,578	17	1.00 (0.56, 1.79)	7	1.38 (0.59, 3.23)	6	1.22 (0.40, 3.78)	4	0.71 (0.18, 2.72)
40-44	5,342	32	1.15 (0.75, 1.75)	12	1.05 (0.53, 2.06)	10	1.80 (0.78, 4.18)	10	1.08 (0.47, 2.52)
45-49	13,529	61	0.79 (0.57, 1.11)	24	0.67 (0.40, 1.12)	16	1.03 (0.51, 2.10)	21	0.92 (0.47, 1.80)
50-54	15,117	102	1.00 (ref.)	51	1.00 (ref.)	22	1.00 (ref.)	29	1.00 (ref.)
≥55	3,911	36	1.00 (0.67, 1.50)	17	1.01 (0.57, 1.83)	9	0.85 (0.35, 2.10)	10	1.09 (0.46, 2.59)
P-value, test for trend			0.95		0.94		0.29		0.68
P-value, test for interaction			<0.001		0.27		0.20		<0.001

MRR= mortality rate ratio; CI = confidence interval.

[a]Excluded women with missing female hormone use (n=160); total deaths= 672.

[b]Fully adjusted model, including age (1-year intervals), time period (2-year intervals), education years, marital status, BMI, smoking status, pack years of smoking, alcohol consumption, vigorous physical activity, vegetables/fruit dietary pattern, and meats/fried food dietary pattern, age at menarche, parity, age at first birth, oral contraceptive use, lactation, and unilateral oophorectomy.

Table 5

All cause and cause-specific mortality rate ratios for age at natural menopause by cigarette smoking (N=11,200)[a]. Black Women's Health Study, 1995-2008

Age at natural menopause, years	All-cause mortality			Cancer mortality		Cardiovascular mortality		Other-cause mortality	
	Person-years	All Deaths	Mulbivariable MRR[b] (95% CI)	Deaths	Mulbivariable MRR[b] (95% CI)	Deaths	Mulbivariable MRR[b] (95% CI)	Deaths	Multivariable MRR[b] (95% CI)
Never smoker									
< 40	2,972	16	1.38 (0.72, 2.63)	3	1.16 (0.30, 4.47)	6	1.20 (0.39, 3.75)	7	1.98 (0.71, 5.53)
40-44	4,889	18	0.91 (0.51, 1.50)	2	0.28 (0.06, 1.25)	8	1.39 (0.57, 3.40)	8	1.02 (0.43, 2.45)
45-49	13,881	71	1.32 (0.95, 1.82)	30	1.63 (0.98, 2.69)	22	1.60 (0.84, 3.06)	19	0.96 (0.53, 1.75)
50-54	18,816	90	1.00 (ref)	36	1.00 (ref)	21	1.00 (ref)	33	1.00 (ref)
≥55	5,471	47	1.02 (0.73, 1.56)	20	1.31 (0.72, 2.36)	17	1.08 (0.52, 2.78)	10	0.72 (0.34, 1.55)
P-value, test for trend			0.48		0.73		0.41		0.22
Ever smoker									
< 40	2,846	34	1.38 (0.93, 2.06)	10	1.25 (0.63, 2.47)	9	1.20 (0.56, 2.60)	15	1.69 (0.86, 3.29)
40-44	5,733	77	1.54 (1.14, 2.04)	33	1.83 (1.16, 2.89)	16	1.01 (0.56, 1.83)	28	1.61 (0.97, 2.67)
45-49	15,395	125	0.95 (0.75, 1.21)	38	0.81 (0.54, 1.23)	38	0.91 (0.58, 1.42)	49	1.15 (0.76, 1.75)
50-54	17,268	163	1.00 (ref.)	64	1.00 (ref)	49	1.00 (ref)	50	1.00 (ref)
≥55	4,450	50	0.94 (0.68, 1.31)	24	1.11 (0.69, 1.81)	13	0.75 (0.40, 1.42)	13	0.91 (0.48, 1.71)
P-value, test for trend			0.02		0.23		0.46		0.03
P-value, test for interaction			0.07		0.005		0.51		0.24

MRR= mortality rate ratio; CI = confidence interval.

[a]Excluded women with missing smoking history (n=12), total deaths=691.

[b]Fully adjusted model, including age (1-year intervals), time period (2-year intervals), education years, marital status, BMI, smoking status, pack years of smoking, alcohol consumption, vigorous physical activity, vegetables/fruit dietary pattern, and meats/fried food dietary pattern, age at menarche, parity, age at first birth, oral contraceptive use, lactation, and unilateral oophorectomy.