Age at Menopause and Later Life Survival and Healthy Longevity among Women in the Iowa EPESE Cohort

Tom SE, Cooper R, Wallace RB, Guralnik JM

I. Introduction

If age at menopause is a marker of the intrinsic rate of overall biological aging, then women with later menopause should have longer survival in later life. Most studies have found a relationship between early age at natural menopause and increased risk of all-cause mortality.[1-7] Studies have also demonstrated relationships between early age at natural menopause and increased risk of cardiovascular mortality[2;6;8-11] and death from other causes.[5] Conversely, the few relevant studies of cancer mortality[5;6;8] have tended to find a relationship between later age at natural menopause and increased mortality risk, which may be related to increased exposure to endogenous estrogen. Gynecological conditions leading to hysterectomy or oophorectomy may also be related to the rate of overall biological aging. However, there have been fewer studies of women with hysterectomy and oophorectomy. These studies have tended to show some relationship of early oophorectomy with increased cardiovascular disease risk, but only weak evidence of relationships between hysterectomy and overall mortality.[1-3;6;7;11;12] It is not clear if the relationships between menopause, oophorectomy, hysterectomy,and mortality are maintained at older ages. Only one dataset based on a population register has sufficiently considered mortality among women at oldest ages.[4;9]

The objective of this study is to examine the relationships between age at menopause or hysterectomy and survival over 25 years among a group of women who were aged 65 and over at baseline. We hypothesize that women with later menopause or later hysterectomy will have lower mortality from all causes, cardiovascular disease, and other causes, but higher cancer mortality and will be most likely to have survived in a non-disabled state at seven years of follow-up.

II. Data and Methods

Data

The Established Populations for the Epidemiologic Study of the Elderly (EPESE) is a longitudinal study of community-dwelling adults age 65 and over that began in 1981 in New

Haven Connecticut; East Boston, Massachusetts; and Iowa and Washington counties, Iowa.[13] There were 2253 women enrolled at baseline in Iowa.

Measures

At baseline, age, characteristics of menopause, educational attainment, number of pregnancies, age at menarche, smoking, height, weight, and ever use of estrogen therapy were assessed. Categorization into the hysterectomy or natural menopause group was based on the reason the respondent gave for her menstrual periods stopping. Women who reported their periods stopping for natural reasons were categorized as having a natural menopause, while women who reported surgery as the reason were categorized as having a hysterectomy. Women who reported other reasons were excluded from the analysis (n=39). A binary variable was created to indicate whether the respondent had completed at least high school. Number of pregnancies was categorized as none, 1, 2, 3, and 4 or more. Age at menarche was categorized as $\leq$ 12, 13, 14 and $\geq$ 15 years. Body mass index was calculated as (weight in kilograms/height in meters^2) categorized as $\leq$ 25, 25 – 30, and $\geq$ 30. Due to the small percentage of women who had used estrogen therapy for more than two years, estrogen therapy use was defined as never versus ever user.

Mortality follow-up occurred through 31 December 2005. Cause of death was grouped by underlying cause of death according to the *International Classification of Diseases, Ninth Revision (ICD-9).*[16] Deaths due to cardiovascular disease were defined by ICD9 codes 390 – 434 and 436 – 448. Deaths due to heart disease were defined by ICD9 codes 390 – 429 and 439 – 448 and cerebrovascular disease by ICD9 codes 430 – 434 and 436 - 438. Deaths due to cancer were defined by ICD9 codes 140 – 208. All remaining codes were grouped as other cause of death.

At seven years of follow-up, disability status was assessed. Women were asked whether they needed help with or were unable to perform the following activities: walking across a small room, bathing, grooming, dressing, eating, transferring from a bed to a chair, and using the toilet. Women were considered disabled if they needed help or could not perform at least one activity, and were considered not disabled otherwise.

Statistical Analysis

Cox proportional hazards model were utilized for mortality analysis. The models were first adjusted for age at baseline, and then for the following potential confounding variables: education, pregnancies, age at menarche, smoking, and body mass index. Women with hysterectomy were analyzed separately from women with menopause because of differences in the distributions of ages at natural menopause and hysterectomy. The analysis was carried out first for all-cause mortality, and second for deaths due to cardiovascular health, cancer, and other known cause of death. Cause-specific analyses included women with a known cause of death and women who were censored. For each cause of death, deaths due to that cause were considered deaths, while deaths due to all other known causes were censored. Women who survived through the end of follow-up were censored at that time.

To assess healthy survival at 7 years of follow-up, an ordinal logistic model was utilized for the outcome of not disabled, disabled, or dead.[14] The models were adjusted for age, education, pregnancies, age at menarche, smoking, and body mass index. Analyses were performed in Stata SE Version 10.

III. Results

The sample with complete data included 1684 women. Over 25 years of follow-up, 1102 women with natural menopause and 375 women with hysterectomy died. Women who had menopause were similar to women with hysterectomy for most characteristics (Table 1). Women with natural menopause had a slightly older mean age at this event than women with hysterectomy (49.3 years versus 45.0 years).

In the Cox proportional hazards models, for all-cause and cause-specific mortality there were no relationships between age at natural menopause or hysterectomy and survival (Table 2). At the 7 year follow-up, among 1140 women who had undergone natural menopause, 57.7% were not disabled, 19.7% were disabled, and 22.5% had died. Among 409 women with hysterectomy, 61.9% were not disabled, 23.5% were disabled, and 14.7% had died. The odds ratios for death

or disabled survival do not show a relationship between age at menopause or hysterectomy and this outcome at the 7 year follow-up (Table 3).

In summary, our examination of a group of community-dwelling women who were aged 65 and over at baseline and were followed for 25 years does not show a relationship between age at menopause/hysterectomy and survival or healthy survival. We do not find evidence that age at menopause or hysterectomy is a marker of the biological rate of aging. As women were at least age 65 at baseline, our analysis does not capture any mortality differentials that might occur earlier in the postmenopausal stage.

Table 1. Sample Characteristics by Type of Menopause

Characteristic	Natural Menopause (n = 1264) Percent or Average (SD)	Hysterectomy (n = 443) Percent or Average (SD)
Age at baseline	74.9 (6.7)	73.6 (5.8)
Age at menopause/hysterectomy	49.3 (5.1)	45.0 (7.3)
Number of pregnancies		
0	16.6	16.9
1	32.2	33.0
2	16.1	15.6
3	13.0	15.4
4 or more	22.1	19.2
Age at menarche	13.2 (1.5)	12.9 (1.5)
Education		
Less than high school	44.9	43.8
High school or more	55.1	56.2
Smoking		
Ever smoked	13.8	14.2
Never smoked	86.2	85.8
Body Mass Index		
Underweight/Normal	55.7	55.1
Overweight	30.2	30.5
Obese	14.1	14.5
Ever Used Estrogen Therapy		
Yes	17.2	33.6

No	82.8	66.4

Table 2. Hazard Ratios for Per Year Increase of Age at Menopause and Age at Hysterectomy, All-Cause and Cause-Specific Analyses

	Age-Adjusted All-Cause Mortality (95% CI)	Fully Adjusted All-Cause Mortality (95% CI)[1]	Fully-Adjusted Cardiovascular Deaths (95% CI)[1,2]	Fully-Adjusted Cancer Deaths (95% CI)[1,2]	Fully-Adjusted Other Deaths (95% CI)[1,2]
Age at menopause	n = 1247	n = 1247	n = 1172	n = 1172	n = 1172
per year increase	1.01 (0.99, 1.02)	1.01 (1.00, 1.02)	1.01 (0.99, 1.02)	1.02 (0.99, 1.05)	1.01 (0.98, 1.03)
Age at hysterectomy	n = 437	n = 437	n = 399	n = 399	n = 399
per year increase	1.00 (0.98, 1.01)	1.00 (0.98, 1.01)	0.99 (0.97, 1.01)	0.99 (0.95, 1.03)	1.00 (0.98, 1.02)

[1]Adjusted for age, education, pregnancies, age at menarche, smoking, and body mass index.
[2]Sample for cause-specific analyses includes only women with known cause of death or who were censored at the end of follow-up.

Table 3. Odds Ratios for Healthy Longevity 7 Year Follow-up

	Age-Adjusted Odds Ratio (95% CI)	Fully Adjusted Odds Ratio (95% CI)[1]
Age at menopause (n = 1140)		
per year increase	1.02 (0.99, 1.04)	1.02 (0.99, 1.04)
Age at hysterectomy (n = 409)		
per year increase	1.01 (0.99, 1.04)	1.02 (0.99, 1.04)

[1]Adjusted for age, education, pregnancies, age at menarche, smoking, and body mass index.

Reference List

1. Amagai Y, Ishikawa S, Gotoh T, Kayaba K, Nakamura Y, Kajii E. Age at menopause and mortality in Japan: the Jichi Medical School Cohort Study. J Epidemiol 2006;16:161-66.

2. Cooper GS, Sandler DP. Age at natural menopause and mortality. Ann Epidemiol 1998;8:229-35.

3. Cooper GS, Baird DD, Weinberg CR, Ephross SA, Sandler DP. Age at menopause and childbearing patterns in relation to mortality. Am J Epidemiol 2000;151:620-623.

4. Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and all-cause mortality: a 37-year follow-up of 19,731 Norwegian women. Am J Epidemiol 2003;157:923-29.

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

6. Ossewaarde ME, Bots ML, Verbeek AL et al. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology 2005;16:556-62.

7. Snowdon DA, Kane RL, Beeson WL et al. Is early natural menopause a biologic marker of health and aging? Am J Public Health 1989;79:709-14.

8. Hong JS, Yi SW, Kang HC et al. Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study. Maturitas 2007;56:411-19.

9. Jacobsen BK, Nilssen S, Heuch I, Kvale G. Does age at natural menopause affect mortality from ischemic heart disease? J Clin Epidemiol 1997;50:475-79.

10. 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.

11. van der Schouw YT, van der GY, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347:714-18.

12. Rivera CM, Grossardt BR, Rhodes DJ et al. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause 2009;16:15-23.

13. Cornoni-Huntley J, Ostfeld AM, Taylor JO et al. Established populations for epidemiologic studies of the elderly: study design and methodology. Aging (Milano) 1993;5:27-37.

14. Yi Z, Vaupel J. Association of late childbearing with healthy longevity among the oldest-old in China. Popul Stud (Camb) 2004;58:37-53.