



Factors associated with premature ovarian failure, early menopause and earlier onset of menopause in Japanese women

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ABSTRACT

Objective: The purpose of this study is to clarify the median age at natural menopause and the proportions of women with premature ovarian failure (POF) and early menopause (EM) by using Kaplan–Meier cumulative estimates and differences in reproductive and lifestyle factors associated with POF, EM and median age at menopause in a large population of Japanese women.

Subjects and methods: This study is a cross-sectional analysis of the Japan Nurses' Health Study (JNHS). We analyzed data for 24,152 pre- and postmenopausal women who were 40 years or older at the JNHS baseline survey.

Results: The overall estimated median age at natural menopause was 52.1 years, and the proportions of women with POF and EM were 0.28% and 1.67%, respectively. Older generation, cigarette smoking, low body mass index, regular menstruation cycles at 18–22 years of age, nulliparity and unilateral oophorectomy were associated with earlier onset of natural menopause.

Only unilateral oophorectomy was associated with increased risk of POF, and nulliparity and unilateral oophorectomy were associated with increased risk of EM.

Conclusion: Unilateral oophorectomy is a common factor associated with earlier onset of menopause, EM and POF, although other reproductive and lifestyle factors are not associated with POF or EM.

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1. Introduction

Premature ovarian failure (POF), which is defined as menopause before the age of 40 years, is estimated to affect approximately 1% of women under 40 years of age [1]. Results of studies on the prevalence of POF in Japanese women have been inconsistent, ranging from 0.1%, lower than that in other races [2], to 1.1% [3]. POF has been shown to influence various aspects of women's health including bone density, cardiovascular and neurological systems, well-being and sexual health due to long-term deprivation of estrogen [4]. On the other hand, early menopause (EM), which is characterized as the occurrence of menopause under 45 years of age, is also clinically important for women's health because of various diseases due to early deficiency of estrogen. Early age at menarche has been suggested as a risk factor for both POF and

EM [5]. However, the etiology of POF partly differs from that of EM since longer breastfeeding decreased the risk of POF and use of oral contraceptives decreased the risk of EM [5]. To the best of our knowledge, there has not been sufficient evidence regarding differences in factors associated with POF and EM.

Age at menopause varies considerably in the range of 44.6–52 years depending on the country [6]. The Study of Women's Health Across the Nation showed that natural menopause in Japanese women is later than that in Caucasian, African-American, Hispanic and Chinese women [7]. It has also been reported that Japanese American ethnicity was independently associated with relatively late natural menopause [8]. We found in the Japan Nurses' Health Study (JNHS), a nationwide prospective cohort study on the health of Japanese women, that the proportion of premenopausal women in women aged 40–54 years was 84.3% and that Japanese women were likely to be premenopausal at the ages of 40–54 years [9]. Differences in study designs and analytical methods as well as differences in life style and reproductive factors have been associated with differences in the timing of natural menopause.

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Kaczmarek estimated the median age at natural menopause in Poland by using the Kaplan–Meier estimate [10]. Recently, Dratva et al. also showed an increase over time in median age at natural menopause by using Kaplan–Meier estimations in two European cohort studies of women aged 30–60 years [11]. However, there has been no study on age at menopause using Kaplan–Meier estimations in a Japanese population.

The purpose of this study was to clarify the median age at natural menopause, the proportions of women with POF and EM by using the Kaplan–Meier cumulative premenopause estimate, and differences among reproductive and lifestyle factors associated with POF, EM and median age at menopause in a large population of Japanese women.

2. Methods

2.1. Study sample

The Japan Nurses' Health Study (JNHS) consists of a cross-sectional baseline survey and a 10-year follow-up study on the health of Japanese women [12]. A cross-sectional baseline survey was conducted from November 2001 to March 2007. The study population was designed for female registered nurses, licensed practical nurses, public health nurses, and/or midwives who were at least 25 years of age and resident in Japan at the baseline survey. This project proceeded in accordance with international guidelines of Good Epidemiology Practice and Japanese Ethical Guidelines for Epidemiological Research. Institutional review boards of Gunma University and the National Institute of Public Health reviewed and approved the study protocol. The Japanese Nursing Association would not permit detailed sampling based on a register of nurses because of protection for personal information of their members, as had been employed in the Nurses' Health Study (NHS). Given these conditions, we announced recruitment to the study at conferences of the Japanese Nursing Association and the Japan Menopause Society, by advertisements in newsletters sent to members of the Japanese Nursing Association, by invitation letters to nurses in the health/medical institutes in cooperation with the prefectural Nursing Associations, and by invitation from the JNHS Recruitment Committee. Interested medical institutes or individual nurses requested baseline questionnaire sets from the JNHS coordination center by application postcard, facsimile, e-mail, or telephone. At some nurses' conferences and hospitals, we distributed the baseline questionnaire sets directly to individual nurses. A total of 49,927 female nurses aged 25 years or older from all 47 prefectures in Japan replied and completed baseline health questionnaires. We could not determine the response rate in the general sense because the precise source population of the study is indefinable. These responses represented 8.6% of 579,665 members of the Japan Nursing Association (year 2005) or 0.104% of the 47.8 million Japanese females in the general population aged over 25 years.

2.2. Data collection

The baseline questionnaire based on the NHS was distributed with an invitation letter, photographs of female hormonal drugs, and a stamped self-addressed envelope. Participants who were informed of the purposes and procedures of the study in the invitation letter and agreed to be followed-up for 10 years each provided their name and address, signed the informed consent sheet, and returned the information. In addition, they completed the questionnaires, sealed the envelope, and mailed them back to the JNHS coordination center. The questionnaire addressed personal information and occupation, physical indicators, results of periodical medical examinations, habits and lifestyle, history of reproductive

health, use of female hormone agents, other drugs and supplements, medical history and family history of diseases, etc. Basic information on medical, anthropometric, reproductive and dietary factors, including body weight, body height, history of oral contraceptive use, cigarette smoking, parity and age at menarche, was collected through the questionnaires self-administered at the time of cohort enrollment. With respect to menopause, the women were asked in the baseline survey: "Has your menstrual period stopped permanently? (yes/yes but have periods now due to female hormones/no/not sure)". If the answer was yes, we asked the age at menopause. We included the women who answered "yes but have periods now due to female hormones" as postmenopausal women. Women who had not menstruated for 12 months or more without surgery were defined as naturally postmenopausal. With regard to regularity of the menstruation cycle, we asked cycle regularity at 18–22 years of age. Body mass index (BMI) was calculated as weight (kg)/height (m)² using self-reported information on current weight and height. POF and EM were defined as menopause characterized by the cessation of menstruation before the age of 40 years and before the age of 45 years, respectively.

2.3. Data analysis

Endpoints for this study were menopause, POF and EM. Data for 24,152 pre- and postmenopausal women who were 40 years or older at the JNHS baseline survey were used for analysis of menopause. We used Kaplan–Meier cumulative premenopause estimate for assessment of the timing of natural menopause, and we estimated cumulative proportions and 95% confidence intervals (95% CIs) of menopause at the ages of 40.0 and 45.0 years. Univariate and multivariate Cox proportional hazard models were used to assess the associations of age at menopause with reproductive and lifestyle factors. The observation was considered censored at the date of the survey for premenopausal women at the baseline survey. For women who had undergone hysterectomy and/or bilateral oophorectomy before menopause and women who had artificial menopause due to medication or radiation, the observation was censored at the age of surgery or artificial menopause.

For analysis of POF, data for 24,152 women who were 40 years or older at the survey were also used. Data for women who had undergone hysterectomy, bilateral oophorectomy, or artificial menopause due to medication and radiation before 40 years of age were excluded from the analyses. Similarly, data for 14,860 women whose ages were 45 years or older at the survey were used for analysis of EM, excluding data for women who had undergone hysterectomy, bilateral oophorectomy, or artificial menopause before 45 years of age. Univariate and multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% CIs for each risk factor. Age at menarche and BMI were treated categorically with ≤ 11 , 12 and ≥ 13 years and with < 18.5 , 18.5–25.0 and ≥ 25.0 in the logistic regression models. Trends of these variables were examined by testing the β -coefficient in separate models. After univariate analysis for candidate risk factors (age at menarche, number of deliveries, current BMI, cycle regularity, unilateral oophorectomy, use of oral contraceptive, ever smoker before menopause and birth year decade) that were related to reproductive health, multivariate regression analysis was performed to reveal adjusted risk factors for natural menopause. The model selection procedure was not applied to exclude factors causing collinearity.

$p < 0.05$ was considered statistically significant. All statistical data analyses were carried out using SAS ver 9.2 (SAS Institute Inc., Cary, NC).

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