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Association between duration of reproductive lifespan and Framingham risk score in postmenopausal women

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ABSTRACT

Context: The benefit of estrogen therapy in postmenopausal women is still uncertain. Based upon extensive observational data, it was believed that estrogen was cardioprotective. The relationship between the period of exposure to endogenous estrogens and the risk of cardiovascular disease (CVD) has not been studied in Korean women.
Objective: To assess associations between reproductive lifespan and CVD by using the Framingham risk score (FRS) in postmenopausal Korean women.
Design and setting: This cross-sectional, population-based study used data from the Korea National Health and Nutrition Examination Survey (KNHANES) for the five years 2008–2012,after adjustment for relevant variables using complex sample analysis and data weighting.
Participants: Among 25,534 women, 1973 women were enrolled, after excluding those <20 or >80 years of age ($n = 6194$), those with diabetes, CVD or cancer ($n = 491$), those with unrecorded physical measurements ($n = 7335$), those with menarche age ≤8 years or ≥20 years ($n = 6194$), and premenopausal women ($n = 3347$).
Results: The FRS tended to show a significant negative correlation with the reproductive lifespan ($p < 0.001$). In multiple linear regression analysis, a negative correlation was observed between the reproductive lifespan and FRS (adjusted relative risk [RR] for <28 reproductive years [shortest lifespan group] compared with 28–33 reproductive years [moderate lifespan group], 1.2, $p < 0.001$ and adjusted RR for >33 reproductive years [longest lifespan group] compared with 28–33 reproductive years [moderate lifespan group], −0.42, $p = 0.011$).
Conclusion: A longer reproductive lifespan is associated with a lower estimated risk of CVD in the next 10 years in postmenopausal women. This result suggests that estrogen has a long-term protective effect against CVD.

1. Introduction

The incidence of cardiovascular disease (CVD) has declined, it but remains the leading cause of death for women [1]. To reduce the incidence of CVD, much effort has focused on the implementation of appropriate lifestyle changes and the pharmacological management of hypertension and blood lipid levels, and on improved therapy for acute myocardial infarction. As part of the initiative, much research on hormone therapy (HT) has been done. But randomized trials of exogenous estrogen for the primary or secondary prevention of CVD have not shown benefit [2,3]. Whether HT benefits vascular health is therefore still intensely debated. However, several prospective studies have indicated that early menopause increases the risk of CVD [4–7]. The incidence of CVD is lower in premenopausal than in postmenopausal women [8]. After menopause, estrogen levels decrease dramatically in women, and this is associated with an increased risk of CVD, due to endothelial dysfunction and increased platelet aggregation [9]. The collective data suggest that endogenous estrogen has an atheroprotective effect and reduces the risk of CVD.

Our a priori hypothesis was that a shorter reproductive lifespan would be associated with an increased CVD risk because the woman would have had a shorter duration of exposure to estrogen. Indeed, a number of cohort studies have identified an association between reproductive lifespan and cardiovascular risk. Therefore, the aim of this study was to evaluate the Framingham risk score (FRS) using a cross-sectional design to estimate CVD risk in the next 10 years using data from the Korea National Health and Nutrition Examination Survey (KNHANES) covering the period 2008–2012 in healthy postmenopausal Korean women.

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2. Methods

2.1. Study subjects

The KNHANES has been conducted periodically by the Korea Centers for Disease Control and Prevention since 1998. The survey provides comprehensive information on health status, health behavior, nutritional status, and socio-demographics in each of the national provinces in Korea. Data from the fourth (IV-2 and IV-3, 2008, 2009) and fifth (V-1 to V-3, 2010–2012) KNHANES were used in this cross-sectional analysis. From an initial total of 25,534 postmenopausal women, 6194 subjects were excluded due to age (<20 and >80 years of age); 491 subjects were excluded due to chronic diseases, including diabetes, CVD, and cancer; and 7335 subjects were excluded due to missing data. An additional 6194 subjects were excluded due to reported menarche at age <8 years or >20 years because this was likely to be due to a recall error or non-physiological conditions. 3347 subjects were excluded due to premenopausal women. Therefore, in the end, 1973 women were enrolled (Fig. 1).

2.2. Data collection

At the time of the health checkup, a standard questionnaire was used to obtain information on age, educational level (less than high school, high school, or more), smoking status (never, current or former), alcohol intake (never, current or former), use of oral contraceptives, and use of hormone replacement therapy. Physical activity was assessed by a questionnaire and categorized as yes (>30 min of moderate physical activity three or more times in the last week, after which the subject was tired compared to ordinary levels) or no. Laboratory tests included total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) cholesterol. LDL cholesterol was calculated as TC-HDL-TG/5. The reproductive lifespan was calculated by age at menopause minus age at menarche. The FRS was calculated on the basis of age, gender, TC, smoking status, HDL cholesterol, and systolic blood pressure (SBP), following the National Cholesterol Education Program – Adults Treatment Panel (NCEP ATPIII).

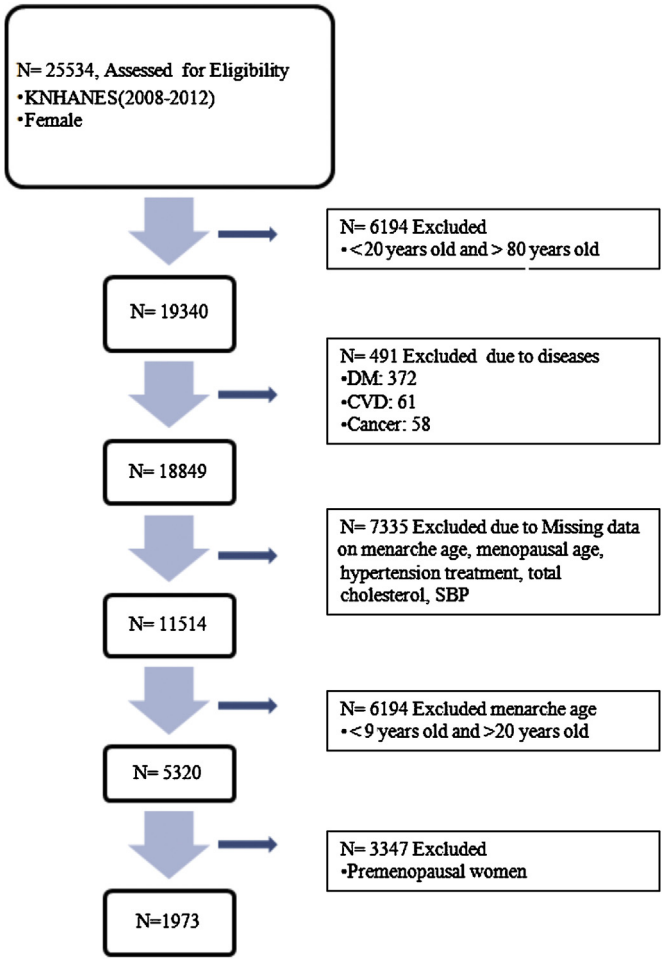

Fig. 1. Flowchart for study data selection. DM, diabetes mellitus; CVD, cardiovascular disease; KNHANES, Korea National Health and Nutrition Examination Survey; SBP, systolic blood pressure.

2.3. Statistical analyses

Complex sample analysis was used for the KNHANES data to weight all values following the guidance on statistics from the Korea Centers for Disease Control and Prevention. We stratified the subjects into three groups by reproductive lifespan: G1 (first tertile), G2 (second tertile), and G3 (third tertile). General characteristics including age, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, HDL, and TG were evaluated by a descriptive method after data weighting. In addition, smoking, drinking, and moderate physical activity were assessed by frequency without data weighting. The Framingham risk equations were used to predict the risk of experiencing coronary disease events (death from myocardial infarction or coronary heart disease) over the next 10 years for adults ≥20years of age without heart disease or diabetes. To assess the relationship between reproductive lifespan and individual components of the FRS, Pearson correlation coefficients relating individual risk factor scores and the total FRS to the log-transformed reproductive lifespan were analyzed. Because the distribution of reproductive lifespan values was skewed, a natural log transformation was applied. Finally, the 10-year CVD risk was compared using G2 as the reference by linear regression analysis after adjustment for education, moderate physical activity, drinking, depression, oral contraceptive use, hormone replacement therapy, WC, BMI, LDL, and DBP, which were not used in the NECP ATP III. The results of group data are expressed as mean ± standard deviation (SD). All p-values were the p for trend that was used to assess the significance of all analyses, and $p < 0.05$ was considered statistically significant. Data were analyzed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA).

3. Results

Characteristics of the 1973 postmenopausal women stratified by tertile according to length of reproductive lifespan are shown in Table 1. Having a shorter reproductive lifespan was associated with higher age at menarche, SBP, TG, and 10-year CVD risk, and lower age at menopause. HDL, WC, and BMI did not differ between the groups. The correlation coefficient between the log-transformed reproductive lifespan and 10-year CVD risk was $r = -0.124$ ($p < 0.001$) in the study subjects (Table 2). The log-transformed reproductive lifespan also correlated well with individual risk factors. Linear regression analysis (Table 3) showed that women with a shorter reproductive lifespan had significantly greater mean values for 10-year CVD risk after additional adjustments for education, moderate physical activity, drinking, depression, use of oral contraceptives, hormone replacement therapy, WC, and the conventional cardiovascular risk factors of LDL, BMI, and DBP. The corresponding regression coefficients were 1.2