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Several prospective studies have indicated that women who experience natural menopause at an early age have a higher risk of coronary heart disease; however, the relation between exogenous estrogen use for post-menopausal women and risk of coronary heart disease are controversial. Exogenous estrogen use for post-menopausal women has been associated with reduced risk of coronary heart disease. On the other hand, clinical trials demonstrated no benefit of hormone replacement therapy on risk of coronary heart disease. A recent prospective study has indicated that age at natural menopause was unrelated to stroke mortality. These findings are based on studies in Caucasian women, and no study has examined the potential effect of menstrual variables on the risk of coronary heart disease among Asian women.

Previous prospective studies indicated that serum total cholesterol levels were higher in post-menopausal women and in women on hormone replacement therapy than in premenopausal women. Endothelial dysfunction is pronounced after menopause possibly due to the reduction of endogenous estrogen. Using urinary cGMP excretion, a second messenger of nitric oxide, to estimate endothelial function, we have reported that nitric oxide bioactivity declined with higher serum total cholesterol levels in a general population; this relationship was more evident among post-menopausal women. Our a priori hypothesis was that early menopause and shorter duration of reproductive year are associated with an increased risk of mortality from coronary heart disease, and that these associations are more pronounced in younger age groups at baseline.

A large prospective cohort study with 10 years of follow-up was used to examine the relationship between a broad range of age at menarche, age at menopause, and duration of reproductive period with mortality from stroke, coronary heart disease, and total cardiovascular disease among Japanese post-menopausal women.

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study) began in 1988-1990, when 110,792 individuals (46,465 men and 64,327 women) aged 40-79 years living in 45 communities across Japan participated in municipal health screening examinations and completed self-administered questionnaires about their lifestyles and medical histories, and women were also asked for age at menarche, age at menopause, and type of menopause. Late menarche was defined as the age at menarche ≥17 years and early menopause was defined as the age at menopause ≥44 years. Duration of reproductive year was defined as the number of years between age at menarche and menopause. Informed consent was obtained from these individuals when they completed the questionnaire. Follow-up surveys were conducted annually to verify the vital status of the participants. We excluded 23,785 premenopausal women, and 2,577 women who had a history of stroke, coronary heart disease or cancer at baseline. Therefore, 37,965 women were enrolled in the present study.

Baseline Surveillance of Mortality from Cardiovascular Disease

Follow-up surveys were conducted annually to determine the vital status of the participants, and the investigators conducted systematic review of death certificates, all of which were forwarded to the public health center in the area of residency. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying cause of deaths was coded according to the International Classification of Diseases (ICD), 9th Revision from 1988 through 1994, and 10th Revision from 1995 through 1999 for the National Vital Statistics. Registration of death is required by the Family Registration Law in Japan and is believed to be followed across Japan. Therefore, all deaths that occurred in the cohort were ascertained by death certificates from public health centers, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case. The follow-up was conducted until the end of 1999, and the average follow-up period of time for the participants was 10.0 years. The Ethics Committee of the University of Tsukuba approved the present study in advance.

Cause-specific mortality of cardiovascular disease was determined based on the ICD-9th revision and ICD-10th revision as follows: total cardiovascular disease (ICD-9th revision, codes 390 to 459, ICD-10th revision, codes I01 to I99), coronary heart disease (410 to 414, I20 to I25), total stroke (430 to 438, I60 to I69), and stroke subtypes such as subarachnoid hemorrhage (430 and I60), intraparenchymal hemorrhage (431 and I61), and ischemic stroke (433 and I63).

Statistical Analyses

Statistical analyses were based on mortality rates of stroke, coronary heart disease and total cardiovascular disease during the follow-up from 1988-90 through 1999. For each participant, follow-up was calculated from the date of filling out the baseline questionnaire through time of death, moving out of the community, or the end of 1999, whichever was first. The hazard ratio of mortality from cardiovascular disease was defined as the death rate among participants in categories of age at menarche (≤13, 14, 15, 16, and ≥17 years), age at menopause (≤44, 45-46, 47-48, 49-50, and ≥51 years), and duration of reproductive year (≤27, 28-30, 31-33, 34-36, and ≥37 years). We used categories of age at menarche ≤13 years, age at menopause ≥51 years, and duration of reproductive period ≥37 years as the reference. The category of early age at menarche and menopause or shorter duration of reproductive period was defined as the approximately lowest deciles.

Age-adjusted means and proportions of selected cardiovascular risk factors and psychological factors were presented among the categories of age at menarche, age at menopause, and duration of reproductive period, using analysis of covariance or chi-square tests. Testing for a linear trend across the age at menarche, age at menopause, and duration of reproductive period categories was
During the 10-year follow-up of 37,965 post-menopausal women aged 40-79 years, 1,010 women died of total cardiovascular disease. These deaths included 487 from stroke including 111 subarachnoid hemorrhages, 99 intraparenchymal hemorrhages, 167 ischemic stroke, and 178 from coronary heart disease.

Table 1 shows mean age and age-adjusted mean values and prevalence of selected cardiovascular risk factors by five categories of age at menarche and menopause, and duration of reproductive period. Women with age at menarche ≥17 years were older, smoked more, were less hypertensive and diabetic, had

| No. at risk | Age (average, year) | Body mass index (average, kg/m²) | Smoker (%) | History of hypertension (%) | History of diabetes (%) | Ethanol intake (average, g/day) | College or higher education (%) | Married (%) |
|-------------|---------------------|----------------------------------|------------|-----------------------------|------------------------|--------------------------------|---------------------------------|------------|
| ≤13         | 5,595               | 59.1                             | 23.3       | 4.7                         | 29.7                   | 10                             | 11                              | 77.8       |
| 14          | 7,336               | 60.1                             | 22.9       | 4.1                         | 27.7                   | 9.3                            | 9.6                             | 79.6       |
| 15          | 8,578               | 61.1                             | 22.9       | 4.4                         | 27.7                   | 4.3                            | 7.9                             | 81.1       |
| 16          | 7,387               | 62.8                             | 23.1       | 5.1                         | 25.9                   | 4.1                            | 8.8                             | 80.8       |
| ≥17         | 9,069               | 63                               | 22.8       | 5.5                         | 29.0                   | 4                             | 10.1                            | 81.5       |
| P for trend |                     | 0.05                             | 0.06       | <0.001                      | 0.001                  | 0.63                           | 0.001                           | 0.001      |

The study began in 1988 to 1990 at baseline, followed until the end of 1999.
### Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality from cardiovascular disease according to age at menarche, menopause, and duration of reproductive period.

| Age at menarche (year) | Person-years | Total stroke deaths | Age-adjusted HR (95% CI) | Multivariable HR (95% CI) | Coronary heart disease deaths | Age-adjusted HR (95% CI) | Multivariable HR (95% CI) | Total cardiovascular disease deaths | Age-adjusted HR (95% CI) | Multivariable HR (95% CI) |
|------------------------|--------------|---------------------|--------------------------|--------------------------|-----------------------------|--------------------------|--------------------------|----------------------------------|--------------------------|--------------------------|
| ≤13                    | 55,608       |                     | 42                       | 1.00 (0.89-1.86)          | 1.00                         | 18                       | 1.00 (0.89-1.88)          | 1.00                             | 18                       | 1.00 (0.89-1.88)          |
| 14                     | 73,075       |                     | 83                       | 1.28 (0.89-1.86)          | 1.29 (0.89-1.88)             | 21                       | 0.74 (0.39-1.38)          | 1.22 (0.70-2.11)               | 0.98 (0.55-1.73)          | 1.28 (0.75-2.20)          |
| 15                     | 96           |                     | 90                       | 21                       | 0.77 (0.41-1.45)             | 36                       | 1.36 (0.96-1.92)          | 1.32                             | 1.19 (0.70-2.03)          | 1.23 (0.97-1.54)          |
| 16                     | 18           |                     | 18                       | 96                       | 1.00                         | 58                       | 1.00 (0.72-1.50)          | 1.03                             | 0.97 (0.51-1.60)          | 1.12 (0.75-1.82)          |
| 17                     | 23           |                     | 21                       | 1.00 (0.72-1.50)          | 1.03 (0.71-1.49)             | 45                       | 1.04 (0.72-1.50)          | 1.03                             | 0.97 (0.51-1.60)          | 1.12 (0.75-1.82)          |
| 18                     | 18           |                     | 90                       | 1.46 (1.03-2.07)          | 1.42 (1.00-2.02)             | 36                       | 1.19 (0.70-2.03)          | 1.22                             | 1.19 (0.70-2.03)          | 1.23 (0.97-1.54)          |
| 19                     | 23           |                     | 21                       | 1.36 (0.96-1.92)          | 1.32 (0.93-1.87)             | 45                       | 1.19 (0.70-2.03)          | 1.23                             | 1.19 (0.70-2.03)          | 1.23 (0.97-1.54)          |
| 20                     | 18           |                     | 90                       | 1.28 (0.89-1.88)          | 1.29 (0.89-1.88)             | 36                       | 1.19 (0.70-2.03)          | 1.22                             | 1.19 (0.70-2.03)          | 1.23 (0.97-1.54)          |
| 21                     | 23           |                     | 21                       | 1.22 (0.70-2.11)          | 0.98 (0.55-1.73)             | 58                       | 1.19 (0.70-2.03)          | 1.22                             | 1.19 (0.70-2.03)          | 1.23 (0.97-1.54)          |
| 22                     | 18           |                     | 90                       | 1.19 (0.70-2.03)          | 1.20 (0.86-1.62)             | 36                       | 1.19 (0.70-2.03)          | 1.20                             | 1.19 (0.70-2.03)          | 1.23 (0.97-1.54)          |
| 23                     | 23           |                     | 21                       | 1.19 (0.70-2.03)          | 1.20 (0.86-1.62)             | 45                       | 1.19 (0.70-2.03)          | 1.20                             | 1.19 (0.70-2.03)          | 1.23 (0.97-1.54)          |
| 24                     | 18           |                     | 90                       | 1.19 (0.70-2.03)          | 1.20 (0.86-1.62)             | 36                       | 1.19 (0.70-2.03)          | 1.20                             | 1.19 (0.70-2.03)          | 1.23 (0.97-1.54)          |

Multivariable adjustment: age, body mass index (kg/m²), histories of hypertension and diabetes, current smoking, ethanol intake, marital status, college or higher school, and type of menopause.

Categories of age at menarche ≤13 years, age at menopause ≥51 years, and duration of reproductive period ≥37 years as the reference groups.

The study began in 1988-1990 at baseline, followed until the end of 1999.
The associations between age at menopause and coronary heart disease were further examined when stratified by age at baseline survey (Table 3). We found no excess risk of mortality associated with later age at menarche. Women with a longer duration of reproductive period were older and more hypertensive, had higher mean body mass index, and were less educated in the present study. These characteristics have been associated with risk of mortality from stroke among total subjects aged 40 to 79 years, and early menopause tended to be associated with increased risk of mortality from coronary heart disease among younger ages of 40 to 64 years.

Table 2 shows age- and multivariable-adjusted hazard ratios of mortality from stroke, coronary heart disease, and total cardiovascular disease according to age at menarche and menopause, and duration of menstruation. Women with age at menarche ≥17 years had tended to increase risk of mortality from stroke; the respective multivariable hazard ratio was 1.85 (95% CI: 0.92-3.73, p = 0.08) and 0.84 (95% CI: 0.60-1.19, p = 0.32), respectively.

Table 3. Multivariable hazard ratios (HRs) and 95% confidence intervals of mortality from coronary heart disease according to age at menopause stratified by age at the baseline survey.

| Age at menopause (year) | Age at baseline survey = 40-64 years | Age at baseline survey = 65-79 years |
|-------------------------|-------------------------------------|-------------------------------------|
| No                      | 6 4 8 6 11                            | 17 12 25 34 55                      |
| Multivariable HR        | 1.82 (0.61-5.41) 1.49 (0.47-4.75) 1.61 (0.64-4.07) 0.72 (0.27-1.97) 1.00 | 0.65 (0.37-1.15) 0.51 (0.27-0.96) 0.74 (0.46-1.19) 0.59 (0.39-0.91) 1.00 |

Multivariable adjustment: age, body mass index (kg/m²), history of hypertension and diabetes, current smoking, ethanol intake, marital status, college or higher school, and type of menopause.

The study began in 1988-1990 at baseline, followed until the end of 1999.

In this large prospective study of Japanese menopausal women, late age at menarche tended to be associated with increased risk of mortality from stroke among total subjects aged 40 to 79 years, and early menopause tended to be associated with increased risk of mortality from coronary heart disease among younger ages of 40 to 64 years.

Mechanisms for the possible association between late menarche and stroke are not clear at present. Women with late age at menarche were older, smoked more, and were less educated in the present study. These characteristics have been associated with risk of stroke among Japanese. One-year case-fatality of ischemic stroke was 2-fold higher for Finnish women with lower income and 3-fold higher in those with lower education than those with higher socioeconomic status. A follow-up study showed that women with late age at menarche were likely to have lower body mass index and to be less obese among women aged 45 to 52 years. Further, our recent prospective study indicated that women with body mass index <18.5 kg/m² had 2-fold higher risk of mortality from total stroke. Other potential confounding socioeconomic conditions such as income levels, which were not examined in the present study, may explain the association. Alternatively, the association could be due to chance.

Previous case-control studies reported that age at menarche (<13 vs. ≥13 years, or <15 vs. ≥15 years old) was associated with the 2-to 3-fold higher prevalence of subarachnoid hemorrhage, and the 5-fold higher prevalence of intraparenchymal hemorrhage. However, the present study showed that earlier age at menarche was not significantly associated with the risk of mortality from subarachnoid hemorrhage or intraparenchymal hemorrhage.

Early menopause tended to increase the risk of mortality from coronary heart disease among post-menopausal women aged 40 to
64 years, but not among those aged 65 to 79 years in the present study. This result is consistent with the finding that early menopause was associated with higher risk of mortality from coronary heart disease among American and European women.2-8 In studies of Norwegian and Dutch women, this association was more evident in women of younger ages than those of older ages.2-8 One of the reasons for the larger impact of early menopause at younger ages may be a longer duration of elevated serum total or LDL-cholesterol levels along with endogenous estrogen depletion.9 Depletion of estrogen itself may have an adverse effect on the development of atherosclerosis due to endothelial dysfunction10,11 and increased platelet aggregability.12

Observational studies have reported that the use of hormone replacement therapy was associated with reduced risk of coronary heart disease.13 Clinical trials, however, demonstrated no benefit of hormone replacement therapy on the risk of coronary heart disease.14 However, a potential benefit of estrogen therapy was found for young postmenopausal women aged 50-59 years.9 In the Nurses Health Study, early menopause was associated with a higher risk of coronary heart disease among current smokers, but not among never-smokers.4 This interaction was not found in the present study, where a very low prevalence (5%) of current smoking in our cohort made it difficult to evaluate the interaction reliably.

The strengths of the present study include its prospective design and large sample size. The limitations are that first we used the self-report of age at menarche and menopause. We did not test the reliability of these variables. However, previous studies using two-year repeated questionnaires showed that 81 to 88% of post-menopausal women reported concordant responses for age at menarche20 and for age at menopause.21,22 Second, we excluded 23,785 premenopausal women at baseline: 94.3% of these women were aged 40-64 years. Thus, for the younger age group, women with an early menopause would be over represented in the data set analyzed. This, however, is unlikely to introduce a serious bias in the evaluation of association between age at menopause and cardiovascular disease because the actual distribution of exposure variables may be irrelevant for the evaluation.

Mechanisms for the association between late menarche and mortality from stroke are uncertain, and could be due to chance. The possible association between early menopause and coronary heart disease among young women in the present study was consistent with the results in Caucasian women, which can be explained by a protective effect of endogenous estrogen on the development of atherosclerosis.

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