Age at Menarche and Natural Menopause and Number of Reproductive Years in Association with Mortality: Results from a Median Follow-Up of 11.2 Years among 31,955 Naturally Menopausal Chinese Women

Xiaoyan Wu¹, Hui Cai¹, Asha Kallianpur¹, Yu-Tang Gao², Gong Yang¹, Wong-Ho Chow³, Hong-Lan Li², Wei Zheng¹, Xiao-Ou Shu¹*

1 Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America, 2 Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China, 3 Occupational Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, United States of America

Abstract

Background: Studies conducted in Western countries suggest that early age at menarche and early age at menopause are both associated with increased total mortality, but limited data are available for Asian populations. We examined associations of age at menarche and natural menopause and duration of the reproductive span with mortality in a population-based cohort study of Chinese women.

Methods: We evaluated the effects of age at menarche, age at natural menopause, and number of reproductive years on total and cause-specific mortality among 31,955 naturally menopausal Chinese women who participated in the Shanghai Women’s Health Study, a population-based, prospective cohort study.

Results: A total of 3,158 deaths occurred during a median follow-up of 11.2 years. Results from Cox proportional hazards models showed that younger age at menopause (<46.64 years) was associated with higher risk of total mortality (Ptrend = 0.02). Younger age at menarche (<14 years) was associated with higher risk of mortality from stroke (Ptrend = 0.03) and diabetes (Ptrend = 0.02) but lower risk of mortality from respiratory system cancer (Ptrend = 0.01). Women with a shorter reproductive span had lower risk of mortality from gynecological cancers (Ptrend = 0.03).

Conclusions: Our study found that menstrual characteristics are important predictors of mortality, suggesting an important role of sex hormones in biological aging.

Introduction

The interval between menarche and menopause defines a woman’s natural reproductive span [1]. Due to exposure to different hormonal environments, early or late onset of these events may be associated with an increased risk of many chronic health problems. Early menopause has been associated with increased risk of mortality from all causes [2–4], cardiovascular disease (CVD), and coronary heart disease (CHD) [4–7], but has not been associated with mortality from stroke or ischemic heart disease (IHD) [4,8]. Early menarche has been associated with increased risk of mortality from all causes and CVD [9–11]. Other than CVD, few studies have examined the association of age at menarche and menopause with cause-specific mortality, and the results have been inconsistent [3,4].

These findings are primarily based on studies conducted in Western populations. The few studies conducted among Asian women [12–15] were limited by one or more of the following factors: small sample size, focused only on cardiovascular cause-specific mortality, included only one component of reproductive factors: small sample size, focused only on cardiovascular cause-specific mortality, included only one component of reproductive information (e.g., age at menarche or age at menopause), no adjustment for other menstrual variables, or inadequate information on the cause of menopause. For example, Cui et al. found no statistically significant association of age at menarche, age at menopause, or number of reproductive years with mortality from CVD in a prospective study of 37,965 Japanese women [16]. Among 2,685 Korean women, Hong et al. observed that early...
Menstrual variables

At baseline, each participant was asked her age at the time of her first period, which was recorded as age at menarche. Menopausal status was defined based on the World Health Organization’s definition of menopause as the absence of menstruation for ≥12 months. The age at which menopause occurred and the reasons for its occurrence (natural menopause, hysterectomy or ovariectomy, or another cause) were recorded at baseline. The number of reproductive years (i.e., the “reproductive span”) was then calculated as the interval between age at menarche and age at menopause.

Outcome definition

The outcome for this study was death from any cause that occurred after the baseline survey but before December 31, 2009. For surviving participants, follow up time was censored at December 31, 2009. The International Classification of Diseases, 9th Revision (ICD-9) [19], was used to define the cause of death, which was classified into CVD (ICD codes: 390–459), IHD (ICD codes: 410–414), stroke (ICD codes: 430–438), diabetes (ICD code: 250), any cancer (ICD codes: 140–200), gynecological cancers (ICD codes: 174, 179–183), digestive system cancers (ICD codes: 150–159), and respiratory system cancers (ICD codes: 160–163).

Measurement of selected potential confounders

Socio-demographic information collected at baseline using the structured questionnaire included age at study enrollment (years), level of education (none, elementary school, middle school, high school, college or above), occupation (professional, clerical, manual laborer, housewife/retired), family income in yuan/year (<10,000; 10,000–19,999; 20,000–29,999; ≥30,000), marital status (yes: married; no: single, widow, divorced, separated), current smoking (yes, no), current drinking (yes, no), age at menarche (years), age at menopause (years), and number of live births. BMI (kg/m²) was calculated from weight (kg) and height squared (m²). WHR was calculated from waist circumference (cm) and hip circumference (cm). Physical activity was measured in metabolic equivalents (MET-h/day/year) based on a validated physical activity questionnaire [20].

Statistical analyses

Person-years of follow-up for each participant were calculated from the date of the baseline interview through the date of death or December 31, 2009. Women were divided into quintiles of menstrual variables based on their distributions in the study population. The following menstrual variable categories were used as the reference groups in the analyses: aged 15 years for age at menarche, aged 48.80–50.15 years for age at natural menopause, and 30.16–32.45 years for number of reproductive years. These reference groups were chosen because they cover the medians of each menstrual variable (i.e., age at menarche, 15 years; age at natural menopause, 49.58 years; and number of reproductive years, 31.33 years).

Selected demographic and other factors were compared across categories of age at menopause, using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Cox proportional hazards models stratified by birth calendar year were employed to estimate hazard ratios (HR) and their 95% confidence intervals (95% CIs) for each group of menstrual variables adjusting for age at study enrollment (years), education (4 categories), occupation (4 categories), income (4 categories), marital status (yes/no), BMI (kg/m²), WHR (continuous), regular exercise (met/hour/year), current smoking (yes/no), current alcohol consumption (yes/no), number of live births, age at menarche (years, included in the Cox models for age at menopause and reproductive years), and age at menopause (years, included in the Cox models for age at menarche). Linear trends were tested across categories of menstrual variables by modeling the median values in each category.

SAS (version 9.2, SAS Institute, Inc., Cary, NC) was used in all analyses and two-sided P-values <0.05 were considered statistically significant.
Table 1. Population characteristics by age at menopause (years), Shanghai Women’s Health Study.

| Characteristics                          | Quintiles of age at menopause (years) | All (N=31,955) | P value<sup>a</sup> |
|------------------------------------------|---------------------------------------|----------------|---------------------|
|                                          | <46.64 (N=6,389)                      |                |                     |
|                                          | 46.64–48.79 (N=6,375)                |                |                     |
|                                          | 48.80–50.15 (N=6,363)                |                |                     |
|                                          | 50.16–52.03 (N=6,425)                |                |                     |
|                                          | ≥52.04 (N=6,403)                     |                |                     |
| Age at recruitment (years), mean (SD)    | 59.65(7.43)                          |                | <0.001              |
| Body mass index, mean (SD)               | 24.49(3.77)                          |                | <0.001              |
| Waist-to-hip ratio, mean (SD)            | 0.826(0.057)                         |                | 0.07                |
| Education, high school (%)               | 16.67                                |                | 0.001               |
| Occupation, professional (%)             | 16.95                                |                | 0.001               |
| Family income, < 10,000 yuan/year (%)    | 23.08                                |                | <0.001              |
| Regular exercise (%)                     | 46.58                                |                | 0.001               |
| Current smoking (%)                      | 7.12                                 |                | 0.001               |
| Current alcohol consumption (%)          | 3.70                                 |                | 0.001               |
| Married (%)                              | 79.34                                |                | 0.002               |
| Age at menarche (years), mean (SD)       | 15.21(1.88)                          |                | 0.02                |
| Number of reproductive years, mean (SD)  | 25.53(4.62)                          |                | <0.001              |
| Number of live births, mean (SD)         | 2.48(1.46)                           |                | <0.001              |

<sup>a</sup>ANOVA for continuous variables and Chi-square test for categorical variables.

doi:10.1371/journal.pone.0103673.t001
Table 2. HRs (95% CIs) of age at menopause (years) with total and cause-specific mortality, Shanghai Women’s Health Study.

| Cause of death          | Quintiles of age at menopause (years) |  |  |  |  |  |  |
|-------------------------|--------------------------------------|---|---|---|---|---|---|
|                         | <46.64 (N=6,389)                     | 46.64–48.79 (N=6,375) | 48.80–50.15 (N=6,363) | 50.16–52.03 (N=6,425) | ≥ 52.04 (N=6,403) |  |
| All causes              | Number of deaths                     | 675 | 629 | 606 | 652 | 596 |  |
|                         | Age-adjusted hazard ratio            | 1.17 (1.05, 1.31) | 1.04 (0.93, 1.17) | 1.00 | 1.08 (0.97, 1.21) | 0.93 (0.83, 1.04) | <0.001 |
|                         | Multivariate hazard ratio            | 1.16 (1.04, 1.29) | 1.03 (0.92, 1.15) | 1.00 | 1.11 (0.99, 1.24) | 0.99 (0.88, 1.11) | 0.02 |
| All CVD                 | Number of deaths                     | 215 | 201 | 219 | 172 | 194 |  |
|                         | Age-adjusted hazard ratio            | 1.03 (0.85, 1.24) | 0.92 (0.76, 1.11) | 1.00 | 0.80 (0.65, 0.98) | 0.84 (0.69, 1.02) | 0.02 |
|                         | Multivariate hazard ratio            | 1.01 (0.83, 1.22) | 0.90 (0.74, 1.09) | 1.00 | 0.82 (0.67, 1.00) | 0.89 (0.73, 1.08) | 0.15 |
| Ischemic heart disease  | Number of deaths                     | 52  | 47  | 43  | 42  | 52  |  |
|                         | Age-adjusted hazard ratio            | 1.27 (0.85, 1.90) | 1.10 (0.72, 1.66) | 1.00 | 1.00 (0.65, 1.52) | 1.15 (0.76, 1.72) | 0.50 |
|                         | Multivariate hazard ratio            | 1.24 (0.83, 1.86) | 1.07 (0.71, 1.62) | 1.00 | 1.02 (0.66, 1.56) | 1.23 (0.82, 1.84) | 0.84 |
| Stroke                  | Number of deaths                     | 110 | 104 | 133 | 98  | 108 |  |
|                         | Age-adjusted hazard ratio            | 0.88 (0.68, 1.13) | 0.79 (0.61, 1.02) | 1.00 | 0.75 (0.58, 0.97) | 0.77 (0.60, 1.00) | 0.37 |
|                         | Multivariate hazard ratio            | 0.86 (0.66, 1.11) | 0.77 (0.60, 1.00) | 1.00 | 0.76 (0.59, 0.99) | 0.81 (0.63, 1.04) | 0.71 |
| Diabetes                | Number of deaths                     | 53  | 54  | 51  | 43  | 45  |  |
|                         | Age-adjusted hazard ratio            | 1.08 (0.74, 1.59) | 1.06 (0.72, 1.55) | 1.00 | 0.86 (0.57, 1.29) | 0.84 (0.56, 1.25) | 0.13 |
|                         | Multivariate hazard ratio            | 1.06 (0.72, 1.56) | 1.02 (0.70, 1.50) | 1.00 | 0.90 (0.60, 1.36) | 0.95 (0.63, 1.42) | 0.47 |
| All cancers             | Number of deaths                     | 273 | 247 | 227 | 300 | 274 |  |
|                         | Age-adjusted hazard ratio            | 1.27 (1.07, 1.52) | 1.10 (0.92, 1.32) | 1.00 | 1.31 (1.11, 1.56) | 1.14 (0.95, 1.36) | 0.52 |
|                         | Multivariate hazard ratio            | 1.27 (1.06, 1.51) | 1.09 (0.91, 1.31) | 1.00 | 1.34 (1.13, 1.60) | 1.18 (0.99, 1.41) | 0.88 |
| Gynecological cancers   | Number of deaths                     | 25  | 30  | 39  | 39  | 41  |  |
|                         | Age-adjusted hazard ratio            | 0.67 (0.41, 1.11) | 0.77 (0.48, 1.24) | 1.00 | 0.99 (0.64, 1.55) | 1.02 (0.66, 1.58) | 0.07 |
|                         | Multivariate hazard ratio            | 0.69 (0.42, 1.15) | 0.78 (0.48, 1.25) | 1.00 | 1.03 (0.66, 1.61) | 1.07 (0.68, 1.67) | 0.05 |
| Digestive system cancers| Number of deaths                     | 145 | 126 | 107 | 144 | 133 |  |
|                         | Age-adjusted hazard ratio            | 1.43 (1.12, 1.84) | 1.19 (0.92, 1.54) | 1.00 | 1.34 (1.05, 1.73) | 1.17 (0.91, 1.52) | 0.18 |
|                         | Multivariate hazard ratio            | 1.43 (1.11, 1.84) | 1.18 (0.91, 1.53) | 1.00 | 1.38 (1.07, 1.77) | 1.21 (0.94, 1.57) | 0.31 |
Results

Women in the lowest quintile for age at menopause were more likely to be current smokers, current alcohol drinkers, and not married and to have lower household income; they were less likely to have a professional job; and they had fewer live births compared with other groups. Women in the highest quintile for age at menopause were older, were more likely to exercise regularly, were younger at menarche, had higher BMI, had more reproductive years, and were less likely to have attained a high school education compared with other groups. Differences in WHR across quintiles of age at menopause approached a statistically significant level (Table 1).

During a median follow-up of 11.2 years, 3,158 women died. These deaths included 1,001 from all CVD (IHD: 236, stroke: 553), 246 from diabetes, 1,321 from all cancers (gynecological cancer: 174, digestive system cancer: 655, respiratory system cancer: 271), and 590 from other causes.

Table 2 presents age-and multivariable-adjusted HRs of total and cause-specific mortality according to age at menopause. After adjustment for potential confounding factors, younger age at menopause (<46.64 years) was associated with higher risk of total mortality (HR (95% CIs): 1.16 (1.04, 1.29), P trend = 0.02). Compared with the reference group (aged 48.80–50.15 years at menopause), being younger (<46.64 years) or older (50.16–52.03 years) at menopause was associated with higher risk of mortality from all cancers (HR (95% CIs): 1.27 (1.06, 1.51) for women aged <46.64 years and 1.34 (1.13, 1.60) for women aged 50.16–52.03 years). Additionally, being younger (<46.64 years) or older (50.16–52.03 years) at menopause than the reference group was also associated with higher risk of mortality from digestive system cancers (HR (95% CIs): 1.43 (1.11, 1.84) for women aged <46.64 years and 1.38 (1.07, 1.77) for women aged 50.16–52.03 years). All of these associations were statistically significant. However, the trend for increasing mortality with increasing or decreasing age at menopause was not significant for all cancers combined or for digestive system cancers.

In the multivariable models, younger age at menarche was associated with a trend of increased risk of mortality from all causes (Table 3). Compared with women aged 15 years at menarche, HRs and 95% CIs were 1.09 (0.97, 1.23) for women aged 14 years at menarche, 0.97 (0.86, 1.09) for women aged 14 years, 0.93 (0.83, 1.03) for women aged 16 years, and 0.94 (0.85, 1.03) for women aged ≥17 years (P trend = 0.01). Younger age at menarche was also associated with mortality from stroke. Compared with women aged 15 years at menarche, HRs and 95% CIs were 1.23 (0.93, 1.62) for women aged <14 years at menarche, 1.00 (0.75, 1.33) for women aged 14 years, 0.99 (0.76, 1.30) for women aged 16 years, and 0.87 (0.68, 1.12) for women aged ≥17 years (P trend = 0.03). Younger age at menarche was also associated with mortality from diabetes. Compared with women aged 15 years at menarche, HRs and 95% CIs were 1.27 (0.81, 1.99) for women aged <14 years at menarche, 1.33 (0.88, 2.01) for women aged 14 years, 1.06 (0.72, 1.58) for women aged 16 years, and 0.84 (0.58, 1.23) for women aged ≥17 years (P trend = 0.02). On the other hand, younger age at menarche was associated with a trend of lower risk of mortality from respiratory system cancers. Compared with women aged 15 years at menarche, HRs and 95% CIs were 0.74 (0.48, 1.14) for women aged <14 years at menarche, 0.71 (0.47, 1.09) for women aged 14 years, 0.96 (0.67, 1.39) for women aged 16 years, and 1.15 (0.82, 1.61) for women aged ≥17 years (P trend = 0.01).
| Cause of death       | Quintiles of age at menarche (years) |       |       |       |       |
|---------------------|--------------------------------------|-------|-------|-------|-------|
|                     | <14 (N=5,934)                        | 14 (N=5,784) | 15 (N=6,590) | 16 (N=6,178) | 17 (N=7,469) |
| All causes          | Number of deaths                     | 503   | 492   | 646   | 629   | 888   |
|                     | Age-adjusted hazard ratio            | 0.99 (0.88, 1.12) | 0.92 (0.82, 1.03) | 1.00   | 0.96 (0.86, 1.07) | 1.03 (0.93, 1.14) |
|                     | Multivariate hazard ratio            | 1.09 (0.97, 1.23) | 0.97 (0.86, 1.09) | 1.00   | 0.93 (0.83, 1.03) | 0.93 (0.84, 1.03) |
| All CVD             | Number of deaths                     | 150   | 150   | 198   | 216   | 287   |
|                     | Age-adjusted hazard ratio            | 1.01 (0.81, 1.25) | 0.93 (0.75, 1.15) | 1.00   | 1.05 (0.87, 1.28) | 1.04 (0.86, 1.24) |
|                     | Multivariate hazard ratio            | 1.14 (0.92, 1.41) | 1.00 (0.81, 1.23) | 1.00   | 1.02 (0.84, 1.24) | 0.93 (0.78, 1.12) |
| Ischemic heart disease | Number of deaths                     | 28    | 36    | 47    | 54    | 71    |
|                     | Age-adjusted hazard ratio            | 0.80 (0.50, 1.27) | 0.95 (0.61, 1.46) | 1.00   | 1.11 (0.75, 1.64) | 1.07 (0.74, 1.56) |
|                     | Multivariate hazard ratio            | 0.91 (0.56, 1.45) | 1.01 (0.65, 1.56) | 1.00   | 1.05 (0.71, 1.55) | 0.93 (0.64, 1.35) |
| Stroke              | Number of deaths                     | 91    | 84    | 11    | 11    | 150   |
|                     | Age-adjusted hazard ratio            | 1.09 (0.83, 1.44) | 0.93 (0.70, 1.24) | 1.00   | 1.02 (0.78, 1.32) | 0.96 (0.75, 1.23) |
|                     | Multivariate hazard ratio            | 1.23 (0.93, 1.62) | 1.00 (0.75, 1.33) | 1.00   | 0.99 (0.76, 1.28) | 0.87 (0.68, 1.12) |
| Diabetes            | Number of deaths                     | 33    | 45    | 46    | 55    | 67    |
|                     | Age-adjusted hazard ratio            | 0.98 (0.62, 1.53) | 1.21 (0.80, 1.81) | 1.00   | 1.15 (0.77, 1.69) | 1.02 (0.70, 1.49) |
|                     | Multivariate hazard ratio            | 1.27 (0.81, 1.99) | 1.33 (0.88, 2.01) | 1.00   | 1.06 (0.72, 1.58) | 0.84 (0.58, 1.23) |
| All cancers         | Number of deaths                     | 215   | 210   | 293   | 254   | 349   |
|                     | Age-adjusted hazard ratio            | 0.90 (0.75, 1.07) | 0.85 (0.71, 1.01) | 1.00   | 0.87 (0.74, 1.03) | 0.93 (0.81, 0.99) |
|                     | Multivariate hazard ratio            | 0.94 (0.78, 1.12) | 0.87 (0.73, 1.04) | 1.00   | 0.85 (0.72, 1.01) | 0.89 (0.76, 1.04) |
| Gynecological cancers | Number of deaths                     | 30    | 29    | 37    | 33    | 45    |
|                     | Age-adjusted hazard ratio            | 0.94 (0.58, 1.52) | 0.91 (0.56, 1.48) | 1.00   | 0.92 (0.58, 1.48) | 1.01 (0.65, 1.57) |
|                     | Multivariate hazard ratio            | 0.90 (0.55, 1.46) | 0.89 (0.55, 1.46) | 1.00   | 0.91 (0.57, 1.46) | 1.01 (0.65, 1.58) |
| Digestive system cancers | Number of deaths                     | 109   | 112   | 150   | 123   | 161   |
|                     | Age-adjusted hazard ratio            | 0.90 (0.70, 1.15) | 0.89 (0.69, 1.13) | 1.00   | 0.82 (0.65, 1.04) | 0.83 (0.67, 1.04) |
|                     | Multivariate hazard ratio            | 0.95 (0.74, 1.23) | 0.92 (0.72, 1.17) | 1.00   | 0.80 (0.63, 1.02) | 0.79 (0.63, 0.98) |
| Respiratory system cancers | Number of deaths                     |       |       |       |       |       |
|                     | Age-adjusted hazard ratio            |       |       |       |       |       |
|                     | Multivariate hazard ratio            |       |       |       |       |       |
Women with a longer reproductive span had a significant trend of increased risk of mortality from gynecological cancers after adjustment for potential confounding factors ($P_{\text{trend}} = 0.03$, Table 4). Compared with women with a reproductive span of 30.16–32.45 years, HRs and 95% CIs were 0.66 (0.40, 1.11) for women with a reproductive span of $<27.11$ years, 0.84 (0.52, 1.35) for a span of 27.11–30.15 years; 1.24 (0.80, 1.94) for a span of 32.46–34.86 years, and 1.11 (0.68, 1.80) for a span of $\geq 34.87$ years.

Older age at menarche was associated with higher risk of mortality from lung cancer ($P_{\text{trend}} = 0.02$), and a similar association was observed among non-smokers ($P_{\text{trend}} = 0.02$). However, no other statistically significant associations were found in the current study between the three menstrual history variables and mortality from breast, endometrial, colorectal, or gastric cancers (data not shown).

**Discussion**

Results from this large, prospective cohort study of Chinese women aged 40–70 years suggest that younger age at menopause was associated with higher total mortality. Early menarche was associated with higher risk of mortality from all causes, stroke, and diabetes, but with lower risk of mortality from respiratory system cancers. A longer reproductive span was associated with higher mortality from gynecological cancers.

Our result that early menopause increases total mortality is consistent with results from most previous studies on this topic [2,4,5,17,21], which supports the hypothesis that early natural menopause is a general indicator of premature aging [22]. In line with results from studies in Western populations [9,11,23], an inverse association between age at menarche and total mortality was also found in our study. Our findings that both late menarche and late natural menopause were associated with lower risk of total mortality adds further support to previous findings that women who are biologically younger than their chronologic age (have late menarche or late natural menopause) have lower mortality than women with an average age at menarche or natural menopause [23].

In the Seventh-Day Adventist study in California, postmenopausal women were categorized into groups according to age at menarche (12, 12, 13, 14, 15). Each increase in category of age at menarche was observed to decrease risk of stroke mortality by 9.6% (95% CI:0.4–18.6) after adjustment for BMI, physical activity, age at first birth, type of menopause, and use of HRT [11]. Similar to this finding, late menarche was associated with lower risk of stroke and diabetes mortality in our study. Many studies have shown that early menarche is associated with increased cardiovascular disease, possibly due to the increased body fatness in childhood [24]. Early menarche has also been associated with increased risk of diabetes in adults [25], one of the main risk factors for stroke [26]. Consequently, the inverse association between age at menarche and stroke mortality could also partly be explained by the inverse association between age at menarche and diabetes risk.

Late menarche was related to high risk of mortality from respiratory system cancers in our study. Our results also indicated that lung cancer mortality contributed to this association. Studies examining late menarche and lung cancer risk have been inconsistent, indicating either no significant effect or decreased risk [27–30]. To our knowledge, the association of late menarche with higher lung cancer mortality is a novel finding and needs to be confirmed in further studies.

**Table 3.**

| Quintiles of age at menarche (years) | $P_{\text{trend}}$ | Number of deaths | Age-adjusted hazard ratio | Multivariate hazard ratio |
|-------------------------------------|---------------------|-----------------|--------------------------|--------------------------|
| 14 (W=5.59)                         | 0.01                | 34              | 0.75 (0.49, 1.14)         | 0.74 (0.49, 1.14)         |
| 15 (W=5.99)                         | 0.01                | 34              | 0.71 (0.46, 1.08)         | 0.71 (0.46, 1.08)         |
| 16 (W=6.39)                         | 0.01                | 58              | 1.00 (0.65, 1.53)         | 1.00 (0.65, 1.53)         |
| 17+ (W=7.46)                        | 0.01                | 88              | 1.15 (0.82, 1.61)         | 1.15 (0.82, 1.61)         |

Abbreviation: HR: hazard ratio; CI: confidence interval.

Reference category.

Adjusted for age at study enrollment, BMI, WHR, education, occupation, regular exercise (met/hour/year), current smoking (yes/no), current alcohol consumption (yes/no), marital status, age at menopause, and number of live births.

$P_{\text{trend}}$ for age at menarche (categorical).

doi:10.1371/journal.pone.0103673.t003

Menstrual and Reproductive History and Mortality

PLOS ONE | www.plosone.org 7 August 2014 | Volume 9 | Issue 8 | e103673
Table 4. HRs (95%CIs) of reproductive years with total and cause-specific mortality, Shanghai Women’s Health Study.

| Cause of death   | Quintiles of reproductive years (years) | $P_{trend}$ |
|------------------|-----------------------------------------|------------|
|                  | <27.11 (N= 6,373)                      | 27.11–30.15 (N= 6,404) | 30.16–32.45 (N= 6,386) | 32.46–34.86 (N= 6,394) | $\geq$ 34.87 (N= 6,398) |
| All causes       | Number of deaths                        | 730        | 703        | 625        | 582        | 518        |
|                  | Age-adjusted hazard ratio               | 1.11(0.99,1.25) | 1.03(0.92,1.16) | 1.00      | 1.01(0.90,1.14) | 0.88(0.78,1.00) | 0.001      |
|                  | Multivariate hazard ratio               | 1.10(0.98,1.22) | 1.03(0.92,1.15) | 1.00      | 1.06(0.94,1.19) | 0.99(0.88,1.12) | 0.16       |
| All CVD          | Number of deaths                        | 242        | 228        | 198        | 176        | 157        |
|                  | Age-adjusted hazard ratio               | 1.19(0.97,1.46) | 1.04(0.85,1.28) | 1.00      | 1.01(0.82,1.26) | 0.86(0.69,1.09) | 0.004      |
|                  | Multivariate hazard ratio               | 1.11(0.92,1.35) | 1.03(0.85,1.24) | 1.00      | 1.06(0.87,1.30) | 1.03(0.83,1.28) | 0.43       |
| Ischemic heart disease | Number of deaths                      | 50         | 58         | 51         | 45         | 32         |
|                  | Age-adjusted hazard ratio               | 0.91(0.60,1.39) | 0.94(0.62,1.43) | 1.00      | 1.03(0.67,1.59) | 0.63(0.38,1.04) | 0.41       |
|                  | Multivariate hazard ratio               | 0.87(0.58,1.30) | 0.99(0.68,1.45) | 1.00      | 1.09(0.73,1.64) | 0.87(0.55,1.38) | 0.64       |
| Stroke           | Number of deaths                        | 126        | 121        | 109        | 98         | 98         |
|                  | Age-adjusted hazard ratio               | 1.14(0.86,1.49) | 1.04(0.79,1.37) | 1.00      | 1.02(0.76,1.37) | 0.99(0.73,1.33) | 0.30       |
|                  | Multivariate hazard ratio               | 1.05(0.81,1.37) | 0.99(0.76,1.28) | 1.00      | 1.07(0.81,1.41) | 1.16(0.87,1.54) | 0.61       |
| Diabetes         | Number of deaths                        | 54         | 64         | 53         | 45         | 30         |
|                  | Age-adjusted hazard ratio               | 1.01(0.67,1.50) | 1.05(0.71,1.56) | 1.00      | 0.99(0.65,1.52) | 0.62(0.38,1.01) | 0.12       |
|                  | Multivariate hazard ratio               | 0.89(0.60,1.32) | 1.05(0.73,1.52) | 1.00      | 1.07(0.72,1.60) | 0.85(0.54,1.35) | 0.80       |
| All cancers      | Number of deaths                        | 294        | 272        | 231        | 263        | 241        |
|                  | Age-adjusted hazard ratio               | 1.12(0.93,1.33) | 0.99(0.83,1.19) | 1.00      | 1.07(0.89,1.28) | 0.99(0.82,1.19) | 0.27       |
|                  | Multivariate hazard ratio               | 1.13(0.95,1.34) | 1.02(0.86,1.22) | 1.00      | 1.13(0.95,1.35) | 1.04(0.87,1.26) | 0.52       |
| Gynecological cancers | Number of deaths                      | 25         | 32         | 37         | 43         | 37         |
|                  | Age-adjusted hazard ratio               | 0.60(0.36,1.00) | 0.79(0.49,1.27) | 1.00      | 1.08(0.69,1.68) | 0.93(0.59,1.48) | 0.04       |
|                  | Multivariate hazard ratio               | 0.66(0.40,1.11) | 0.84(0.52,1.35) | 1.00      | 1.24(0.80,1.94) | 1.11(0.68,1.80) | 0.03       |
| Digestive system cancers | Number of deaths                      | 153        | 131        | 126        | 134        | 111        |
|                  | Age-adjusted hazard ratio               | 1.18(0.92,1.53) | 1.02(0.78,1.32) | 1.00      | 1.12(0.86,1.46) | 0.94(0.71,1.24) | 0.16       |
|                  | Multivariate hazard ratio               | 1.21(0.95,1.53) | 1.00(0.78,1.28) | 1.00      | 1.13(0.89,1.45) | 0.93(0.71,1.21) | 0.11       |
Among 68,154 US women who experienced natural menopause and had not used tobacco or HRT, Mondul et al. observed that mortality from breast or ovarian cancer was lower among women whose age at menopause was 40–44 years (rate ratio [95% CIs]: 0.68 [0.56, 0.82] or 45–49 years [0.93 [0.83, 1.03]], compared with women whose age at menopause was 50–54 years [3]. Although no significant association between age at menopause and gynecological cancer mortality was found in our study, we observed that having a shorter reproductive span was associated with lower risk mortality from gynecological cancers. It has been suggested that the inverse association between age at menopause and gynecological cancer risk is due to the cessation of cyclical ovarian hormone production at menopause [31–33]. The shorter the reproductive span, the lower the cumulative lifetime exposure to endogenous hormones would be in these women. Consequently, the reduction in circulating hormone concentrations might lead to a reduction in relative risk for gynecological cancers. The ‘U-shaped’ relationship between age at menopause and mortality from all cancers observed in the current study appears to be related to death due to an excess of digestive and respiratory system cancers among women with early age at menopause and an excess of gynecological cancers for women with late age at menopause. More studies are warranted to investigate the role of sex hormone in the etiology and prognosis of these cancers.

Strengths of this study include: the prospective design, the large population-based sample size, and the high response rates. In addition, the current study was restricted to women who had natural menopause and had never used HRT. The main limitation of this study is that ages at menarche and menopause were self-reported and may, therefore, be subject to recall bias. However, previous studies have reported that the recall of age at menarche and menopause is relatively accurate [34,35]. In addition, although P-values for the trend tests were significant, many point estimates were not statistically significant and confidence intervals included 1.00. It should also be noted that our study involved multiple comparisons which may have led an increase of false positive findings (inflated type 1 error). Moreover, event numbers for some of the sub-group analyses were low, and thus, some results could have been due to chance findings. Furthermore, due to the differences in dietary and environmental exposures, the findings of our study may not be directly generalizable to other populations.

In summary, this study of Chinese women found inverse associations for age at menarche and natural menopause with total mortality and for age at menarche with mortality from stroke and diabetes. However, we found positive associations for age at menarche with mortality from respiratory system cancers, as well as for duration of the reproductive span with mortality from gynecological cancers. Our results demonstrate that women who experience early menarche or early natural menopause tend to have increased total mortality.

Acknowledgments

We thank the participants and study staff of the Shanghai Women’s Health Study, and Ms. Bethanie Rammer and Mrs. Jacqueline Stern for editing and preparing the manuscript.

Author Contributions

Conceived and designed the experiments: YTG WZ XOS. Performed the experiments: HLL GY. Analyzed the data: XW HC. Contributed reagents/materials/analysis tools: WHC WZ XOS. Wrote the paper: XW AK XOS. Approved the manuscript: XW HC AK YTG GY WHC HLL WZ XOS.

Table 4. Cont.

| Quintiles of reproductive years (years) | Number of deaths | Age-adjusted hazard ratio | Multivariate hazard ratio |
|---------------------------------------|------------------|--------------------------|---------------------------|
| < 27.11                               | 65               | 1.31 (0.90, 1.91)        | 1.25 (0.85, 1.83)         |
| 27.11–30.15                           | 72               | 1.42 (0.98, 2.05)        | 1.36 (0.94, 1.98)         |
| 30.16–32.45                           | 47               | 1.00                     | 1.00                      |
| 32.46–34.86                           | 40               | 0.93 (0.61, 1.42)        | 0.97 (0.63, 1.51)         |
| ≥ 34.87                               | 47               | 1.00 (0.61, 1.60)        | 1.15 (0.75, 1.79)         |

Abbreviations: HR: hazard ratio; CI: confidence interval.

Ptrend for number of reproductive years (categorical).

P-values for number of reproductive years (categorical).

Menstrual and Reproductive History and Mortality

PLOS ONE | www.plosone.org 9 August 2014 | Volume 9 | Issue 8 | e103673
References

1. Thomas F, Renaud F, Benicke E, de Meurs T, Guenae JF (2001) International variability of ages at menarche and menopause: patterns and main determinants. Hum Biol 73: 271–290.

2. Jacobsen BK, Heuch I, Kvale G (2003) Age at natural menopause and all-cause mortality: a 37-year follow-up of 19,731 Norwegian women. Am J Epidemiol 157: 923–929.

3. Mounih AM, Rodriguez C, Jacobs EJ, Calle EE (2005) Age at natural menopause and cause-specific mortality and total life expectancy. Epidemiology 16: 556–562.

4. Jacobsen BK, Knutsen SF, Fraser GE (1999) Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. J Clin Epidemiol 52: 303–307.

5. Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, et al. (1999) Age at natural menopause and risk of cardiovascular disease. Arch Intern Med 159: 1061–1066.

6. Schouw TY vd, Graaf Y vd, Steyerberg EW, Eijkemans MJ C, Banga JD (1996) Association of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. Stroke 40: 3428–3435.

7. Jacobsen BK, Heuch I, Kvale G (2007) Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. Am J Epidemiol 166: 1431–1437.

8. Jacobsen BK, Heuch I, Kvale G (2003) Age at natural menopause and all-cause mortality in South Korean women: Kangwha Cohort Study. Int J Epidemiol 32: 714–718.

9. Jacobsen BK, Heuch I, Kvale G (2004) Age at natural menopause and stroke mortality: cohort study with 3561 stroke deaths during 37-year follow-up. Stroke 35: 1548–1551.

10. Jacobsen BK, Heuch I, Kvale G (2007) Association of low age at menarche with increased all-cause mortality: the Kangwha Cohort Study, 1985–2005. Menopause 18: 1205–1212.

11. Jacobsen BK, Heuch I, Kvale G (2004) Age at natural menopause and stroke mortality: cohort study with 3561 stroke deaths during 37-year follow-up. Stroke 35: 1548–1551.

12. Jacobsen BK, Heuch I, Kvale G (2003) Age at natural menopause and all-cause mortality in South Korean women: Kangwha Cohort Study. Int J Epidemiol 32: 714–718.

13. Chang HS, Odongo N, Olhur H, Sull JW, Nam CM (2011) Reproductive risk factors for cardiovascular disease mortality among postmenopausal women in Korea: the Kangwha Cohort Study, 1985–2005. Menopause 18: 1205–1212.

14. Mueller NT, Odegaard AO, Gross MD, Koh WP, Yuan JM, et al. (2012) Age at menarche and cardiovascular disease mortality in Singaporean Chinese women: the Singapore Chinese Health Study. Ann Epidemiol 22: 717–722.

15. Tamakoshi K, Yatsuha Y, Tamakoshi A (2011) Early age at menarche associated with increased all-cause mortality. Eur J Epidemiol 26: 771–778.

16. Cui R, Ito H, Toyoshima H, Date C, Yamamoto A, et al. (2006) Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. J Epidemiol 16: 177–184.

17. Hong JS, Yi SW, Kang HC, Jee SH, Kang HG, et al. (2007) Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study. Maturitas 56: 411–419.

18. Zheng W, Chow WH, Yang G, Jin F, Rothman N, et al. (2005) The Shanghai Women’s Health Study: rationale, study design, and baseline characteristics. Am J Epidemiol 162: 1125–1131.

19. SIEVE VN (1978) The International Classification of Diseases: Ninth Revision (ICD-9). Annals of International Medicine 88: 424–426.

20. Matthews CE, Shu XO, Yang G, Jin F, Ainsworth BE, et al. (2003) Reproducibility and validity of the Shanghai Women’s Health Study physical activity questionnaire. Am J Epidemiol 158: 1114–1122.

21. Cooper GS, Sandler DP (1996) Age at natural menopause and mortality. Ann Epidemiol 8: 229–235.

22. Snowdon DA, Kane RL, Besson WL, Burke GL, Sprafka JM, et al. (1989) Is early natural menopause a biologic marker of health and aging? Am J Public Health 79: 709–714.

23. Jacobsen BK, Heuch I, Kvale G (2007) Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. Am J Epidemiol 166: 1431–1437.

24. Liu Y, Inoue M, Sobue T, Tsugane S (2005) Reproductive factors, hormone use and the risk of lung cancer among middle-aged never-smoking Japanese women: a large-scale population-based cohort study. Int J Cancer 117: 662–666.

25. Kreuzer M, Gerken M, Heinrich J, Kreienbrock L, Wichmann HE (2003) Hormonal factors and risk of lung cancer among women? Int J Epidemiol 32: 263–271.

26. Brenner AV, Wang Z, Kleinerman RA, Lei S, Metayer C, et al. (2003) Menstrual and reproductive factors and risk of lung cancer among Chinese women, Eastern Gansu Province, 1994–1998. J Epidemiol 13: 22–28.

27. Yang L, Kuper H, Sandin S, Margolis KL, Chen Z, et al. (2009) Reproductive history, oral contraceptive use, and the risk of ischemic and hemorrhagic stroke in a cohort study of middle-aged Swedish women. Stroke 40: 1050–1058.

28. de Graaff J, Stek TA (1978) Age at menarche and menopause of uterine cancer patients. Eur J Obstet Gynecol Reprod Biol 8: 187–193.

29. Maccall F, Real PG, Flana E, Sunyer J, Anto J, et al. (2011) Early age at menarche, lung function, and adult asthma. Am J Respir Crit Care Med 183: 8–14.

30. Gaudineau A, Ehlinger V, Yassier C, Jouret B, Arnaud C, et al. (2010) Factors associated with early menarche: results from the French Health Behaviour in School-aged Children (HBSC) study. BMC Public Health 10: 175.

31. Belsky J, Steinberg L, Houts RM, Halpern-Felsher BL (2010) The development of reproductive strategy in females: early maternal harshness —-> earlier menarche —-> increased sexual risk taking. Dev Psychol 46: 128–128.