

## 論文の内容の要旨

### 論文題目

Female reproductive factors and risk of all-cause and cause-specific mortality among women: The Japan Public Health Center-based prospective Study (JPHC Study)

(日本人女性の生殖関連要因と全死亡および主要死因別死亡の関連に関する研究 (多目的コホート研究))

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### INTRODUCTION

Reproductive events and their accompanying fluctuations in sex hormones in women lead to a series of physiological and psychological changes throughout life. Although numerous long-term studies have investigated the impact of reproductive events on women's health, the potential link between reproductive factors and mortality is not necessarily fully understood. As reproductive factors are intricately linked with several diseases, analysis of reproductive parameters on mortality risk could provide further insights to clarify women's long-term health. Since most studies have been conducted in Western countries, further analysis is needed from other populations. The fact that Japan has the highest life expectancy is another motivating reason to focus on Japanese women.

Previous epidemiological studies on the association between reproductive factors and all-cause and cause-specific mortality have shown inconsistent results. To date, no study has comprehensively investigated reproductive factors as potential markers for mortality risk of external causes. Post-menopausal women have a potentially higher risk of mortality independent of age, but few studies have analysed this idea with stratification by menopausal status.

### *Objective*

The originality of this study lies in its suggestion of how reproductive factors modulate the risk of mortality, including external causes of death among women. Therefore, this study aims to:

- Evaluate the effect of female reproductive factors associated with risk of all-cause and leading causes of death including cancer, heart disease, stroke, and respiratory disease;
- Assess the risk of all-cause and major causes of external death according to female reproductive factors.

## **METHODS**

### *Study design and study population*

The data from the Japan Public Health Center-based Prospective Study (JPHC Study) was used. The JPHC Study enrolled 140,420 registered residents aged 40-69 years within 11 public health center areas nationwide from 1990 to 1994. Comprehensive information regarding sociodemographic characteristics, lifestyle, family and personal medical history, lifestyle and reproductive events was collected using a self-administrated questionnaire at entry.

Of the 71,698 women, non-eligible subjects were excluded. Of these, 59,983 women (89.6%) returned the completed questionnaire. Participants were followed from the baseline survey (1990, 1994) until death, last confirmation of survival, or end of follow-up (December 31, 2014), whichever occurred first. Survival or relocation of participants in the study was identified using municipal registries. Of eligible subjects, 8,477 (14.1%) died, 35 (0.06%) emigrated outside of Japan, and 469 (0.8%) were lost to follow-up during the study period.

### *Identification of cause of mortality*

Death certificates were collected through the local public health centers and used to confirm the cause of death with permission from the Ministry of Health, Labor and Welfare. The major causes of death in Japanese women were used based on the International Classification of Diseases, 10<sup>th</sup> edition (ICD-10), namely cancer (C00–C97); heart disease (I20–I52); cerebrovascular disease (I60–I69); respiratory disease (J10–J18 and J40–J47); all external causes (V01–Y89); suicide (X60–X84, Y87.0); and accidents (V01–X59, Y85–Y86). Cancer was further divided into the most common subgroups among the cohort, including cancer of the lung (C34), stomach (C16), pancreatic (C25), breast (C50), and ovary (C56).

### *Exclusion criteria*

Women with a history of diseases including cancer, heart disease, stroke, and surgical menopause at baseline survey (n=7,089) were excluded when assessing the risk of all-cause and internal causes of death. Subjects with at least one missing value of exposure variables and relevant covariates were also excluded. These exclusions left 40,149 subjects in the complete-case analyses for assessment of all-cause and internal causes of death, and 49,279 subjects for that of external causes of death.

### *Main variables*

Reproductive events captured at the baseline survey were selected as follows: parity, as the number of live birth or stillbirth, age at first birth, experience of breastfeeding, age at menarche, exogenous hormone use, length of menstrual cycle, menopausal status, age at menopause, and total fertility span. Potential confounders associated with mortality were selected based on prior research: body mass index (kg/m<sup>2</sup>);

smoking status; alcohol consumption; living arrangement; and history of disease (cancer, heart disease, stroke, hypertension, and diabetes). Additional variables were selected as follows: leisure-time sports or physical activity exercise; job status; total energy intake (kcal/d); and consumption of coffee and green tea for all-cause and internal causes of death, and perceived stress level for external causes of death.

### *Statistical analysis*

Cox proportional hazards regression models were employed to estimate hazard ratios (HR) and 95% confidence intervals (CI) to assess the risk of death by all-cause and cause-specific mortality according to reproductive factors. Analyses were performed based on complete-case analysis. Because age at recruitment was found to violate the proportional hazards assumption, age group was stratified in the models or attained age was used as the time scale. Study areas were stratified in all models to allow for different baseline hazard due to the varying distribution of death rate across Japan. A multivariate-adjusted model was constructed with additional adjustment for the possible confounders.

Additional sub analyses were conducted for different study populations based on complete-case analysis; analysis restricted to post-menopausal women, analysis restricted to non-smoking women, subjects stratified by BMI, and including surgically menopausal women for analysis of all-cause and internal cause of death. Stratified analysis by menopausal status at baseline was conducted for analysis of external cause end points. Further sensitivity analyses were performed to address selection bias due to missing values using the multiple imputations by chained equation with 20 iterations.

## **RESULTS**

### *All-cause and internal cause of death*

After a mean follow-up of 20.9 years of 40,149 women (840,375 person-years), 4,788 total deaths were identified. Inverse associations with all-cause mortality were found in parous women [HR=0.74, 95% CI (0.67–0.82)], women with two or three births compared with a single birth [2 births: 0.88 (0.78–0.99); 3 births: 0.83 (0.74–0.94)], parous women who breastfed [0.81 (0.75–0.87)], women who were older at menopause [0.88 (0.80–0.97);  $P_{\text{trend}} < 0.01$ ] and women who had a longer fertility span [0.85 (0.76–0.95);  $P_{\text{trend}} < 0.01$ ]. A positive association was seen between all-cause mortality and later age at first birth ( $\geq 30$  years) than early childbearing ( $\leq 22$  years). The longer menstrual cycle [ $P_{\text{trend}}: 0.04$ ] was associated with an increased risk of mortality from cerebrovascular disease, while an inverse trend of mortality risk from respiratory disease was found [ $P_{\text{trend}} < 0.01$ ].

### *External cause of death*

Among parous women, ever versus never breastfeeding was associated with a decreased risk of all injuries and death by accidents. Risk of suicide was inversely associated with ever versus never parity and

three births.

## **CONCLUSION**

Based on a large-scale population-based cohort study, results of this study support the vital role played by reproductive factors in the risk of all-cause and major causes of deaths in Japanese women. To my knowledge, this is the first large-scale prospective study to examine the impact of reproductive factors and risk from all-cause and cause-specific mortality including external cause among the Japanese population.

In summary, protective factors for mortality included parous, two or three births, breastfeeding, late age at menopause and long fertility span. In contrast, late age at menarche or first birth were positively associated with mortality risk. The results from the length of menstrual cycle provided different directions in cause-specific mortality. The data also revealed null associations between several reproductive factors and each cause of death: these findings are also meaningful in understanding the underlying mechanism. Study strengths include a large population-based sample with long follow-up period, its prospective design, high response rate, low loss to follow-up and its availability of a variety of reproductive factors. Major limitations were raised as follows; the exclusion of subjects due to missing data, single assessment of variables at baseline survey, the lack of causal framework between reproductive factors and the possibility of residual confounders.

Overall, both physiological and psychological changes with reproductive events may be partial pathways to determine the women's longevity. The prolonged effect of lactation against mortality suggests the need for vigorous promotion of breastfeeding from the perspective of maternal health. I hope that this study provides a better understanding of how reproductive history influences long-term health, and help women in making informed choices and decision.