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Duration of ovarian hormone exposure and gynecological cancer risk in Korean women: the Korean Heart Study

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ABSTRACT

Background: Although reproductive and hormonal factors – such as early menarche and late menopause – have been reported as independent risk factors for cancer, few studies have examined these factors in East Asian populations.
Methods: We performed a large prospective cohort study of 66,466 women. Ovarian hormone exposure was defined as length of time between menarche and menopause. Incidence rates for breast, ovarian, endometrial and cervical cancers were examined separately in relation to reproductive lifespan defined as age at menopause minus age at menarche. Multivariable adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated using the Cox proportional hazards model.
Results: Women with early menarche were at increased risk for developing breast cancer (HR, 1.57, 95% CI, 1.17–2.10) for age at menarche ≤12 years compared to women with age at menarche ≥17 years. Women with late age at menopause (≥52 years) had increased risks for cancers of the breast (HR, 1.59, 95%CI, 1.11–2.28) and ovary (HR, 3.22, 95% CI, 1.09–9.55) compared to women with early menopause (≤45 years of age). Women with longer duration of ovarian hormone exposure (≥40 years) were at increased risk for developing breast cancer (HR, 2.23, 95% CI, 1.35–3.68) as well as endometrial cancer (*p* for trend, 0.0209).
Conclusions: We showed that longer reproductive spans are associated with an increased risk of breast and endometrial cancer in Korean women.

1. Introduction

Hormone-related cancers include breast cancer, ovarian cancer, endometrial cancer and cervical cancer. In particular, breast cancer has become the most common cancer and the major cause of cancer-related mortality among women worldwide [1]. In 2012, the incidence of breast cancer per 100,000 persons in Korea was second to that of thyroid cancer and increased from 24.5 in 1999 to 50.7 in 2012 [2]. Early menarche, late menopause, a late full-term delivery, and never having breast-fed a child are related to the cohort effect of breast cancer mortality [3].

Although there have been great advances in the understanding of the etiology of hormone-related cancer among women, large studies of Asian populations are lacking. Given the different environmental exposures, genetic backgrounds, body types, and socioeconomic histories among Asian populations relative to their Western counterparts, there are strong *prima facie* reasons to anticipate that different risk factor/disease associations will emerge in this group.

Currently, there are well-established reproductive risk factors for the development of breast cancer [4–7] and endometrial cancer [8]. The key reproductive risk factors – timing of menarche and menopause and age at first pregnancy – are considered drivers of ovarian hormone exposure. Early menarche and late menopause increase the cumulative number of ovulatory cycles [9] which act to increase the exposure of breast epithelial tissue to estrogen and progesterone [4]. In contrast to breast cancer, early age at first childbirth and multiple pregnancies were found to increase the risk of cervical cancer [10,11]

Studies have not, however, addressed cancer risk in relation to the specific duration of exposure to ovarian hormones in Korean women. Although many studies have established early menarche and late menopause as independent risk factors for cancer [4–11], the time period in years between menarche and menopause has not been extensively investigated in relation to cancer risk.

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According to the Korean National Health and Nutrition Survey, the average age at menarche decreased from 15.2 years in 2005 to 14.8 years in 2012, whereas the average of age at menopause increased from 48.7 years in 2001 to 49.9 years in 2012 [12–15]. The average duration of ovarian hormone exposure by birth cohort has increased among Korean women born after 1945 (Fig. 1).

The objectives of this study were to examine the effect of age at menarche, age at menopause, and length of time between menarche and menopause on cancer incidence in the Korean Heart Study (KHS) population.

2. Material and methods

2.1. Study participants

The KHS included 430,920 individuals (266,782 men and 164,138 women) who had voluntarily undergone private health examinations in 18 centers located in the capital Seoul and six provinces in South Korea between 1996 and 2004. A full description of the KHS population has been published previously [16,17].

Of the 164,138 female participants in the KHS, 9458 women who were diagnosed with cancer at the time of enrolment were excluded from this analysis. In addition, 1121 participants with an extremely low body mass index (BMI) ($<16\ kg/m^2$), weight ≤ 30 kg, or height ≤ 130 cm, and missing data on menarche ($n = 86{,}820$) and others ($n = 9{,}731$) were excluded. Therefore, the final analytical cohort comprised 66,466 Korean women for the analysis for age at menarche and 19,033 for the analysis for length of time between menarche and menopause. Mean follow-up period was 12.1 years.

2.2. Data collection

Each participant was asked to complete a structured questionnaire to collect the following details: age at menarche, age at menopause, smoking history (never-smoker, ex-smoker, or current smoker), alcohol drinking (non-drinker or consumer of any amount of alcohol on a regular basis), regular exercise (yes or no), and exogenous hormone use (menopausal hormone only). Participant height and weight were measured while the participants were wearing light clothing. BMI was calculated as the weight (kg) divided by the height squared (m^2). Systolic and diastolic blood pressures were measured after a rest period of at least 15 min. Our measure of socioeconomic status was the health insurance premium per year in South Korean won (1129 won = 1.00 US dollar) paid by the employees to their medical insurance scheme. This financial mean is calculated on the basis of the employee's income plus assets, such as ownership of property and automobiles [18].

For clinical chemistry assays, serum – separated from peripheral venous blood – was obtained from each participant after a minimum fasting period of 12 h. Levels of fasting serum glucose and total cholesterol were measured using a COBAS INTEGRA 800 and a Hitachi-7600 analyzer (Hitachi, Tokyo, Japan).

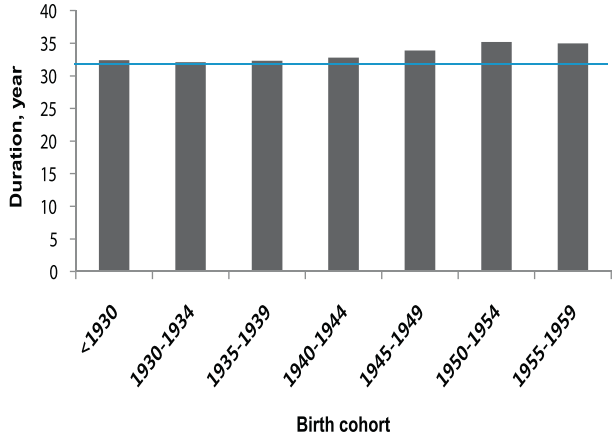

Fig. 1. Average duration of ovarian hormone exposure by birth cohort in Korean women.

2.3. Follow-up for hospital admissions

Using computerized searches of data provided by the National Health Insurance Service (NHIS) in Korea, outcomes were ascertained from diagnoses noted on hospital discharge summaries. With rare emigration rates from South Korea, follow-up for linkage was likely to be close to 100% complete. The principal outcomes were morbidity from (1) all cancers (International Classification of Diseases, Tenth Revision [ICD-10] codes C00–C97); (2) breast cancer (ICD-10 codes C50); (3) cervical cancer (ICD-10 codes C53), (4) ovarian cancer (ICD-10 codes C56), and (5) endometrial cancer (ICD-10 codes C54). The follow-up period was from January 1997 to December 2012.

2.4. Statistical analysis

Age at menarche was categorized as ≤ 12, 13–14, 15–16, and ≥ 17 years. Age at menopause was categorized as ≤ 45, 46–48, 49–51, and ≥ 52 years. Duration between menarche and menopause was categorized as <30, 30–34, 35–39, and ≥ 40 years. For some analyses, the lower categories of age at menarche, age at menopause and duration between menarche and menopause were combined into a single stratum because of small numbers. We computed hazard ratios (HRs; the hazard for incidence in a specific category divided by the corresponding hazard in the reference category) using Cox proportional hazards models adjusted for age and other potentially confounding factors. We did not adjust for parity in our main models because information on this variable was available for only a small proportion of women. However, we conducted sensitivity analyses with adjustment for this information when available. We used the adjusted relative risk values to calculate population-attributable risk. All analyses were conducted using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

3. Results

The average age of the study population was 47.4 years for participants at menarche and 55.6 years for participants at menopausal age. Based on self-reports, the baseline prevalence of early menarche (≤ 12 years) and short duration between menarche and menopause (≤ 30 years) were 5.4% and 20.9%, respectively (Table 1). The study population had on average a low BMI, and only 25.0% and 2.4% of women had BMIs of ≥ 25 or >30 kg/m^2, respectively. Smoking was uncommon among Korean women (5% at baseline prevalence).

During the 12.1 years of follow-up, a total of 5251 incident cases of all cancers – including breast (989), cervical (151), ovarian (135), and endometrial cancers (117) – occurred among the participants. In general, hazard ratio estimates for all cancers were above unity for participants in the lower strata of age at menarche (Table 2). We observed positive linear trends in incident cancer with decreasing age at menarche for all cancers ($p = 0.020$). As compared to the reference category (≥ 17 years), women with an age at menarche of ≤ 12 years had significantly increased risk for breast cancer (HR = 1.57, 95% CI = 1.17–2.10). In the combined category of women with age at menarche ≤ 14 years, increasedrisks