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Genetic causal relationships between menarche, menopause age, and breast, ovarian, and endometrial cancers in East Asian women.

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The risks of breast cancer (BrC), ovarian cancer (OvC), and endometrial cancer (EnC), are known to be influenced by the duration of exposure to female hormones, which is determined by key reproductive milestones like the ages at menarche and menopause. However, the causal relationships between key reproductive ages and the risk of these cancers remain unknown. Leveraging large-scale cohort data from East Asian populations, we investigated the causal relationships between age at menarche, age at menopause, and the risk of BrC, OvC, and EnC in East Asian women using the Mendelian Randomization (MR) approach. We utilized recent genome-wide association study (GWAS) summary statistics for age at menopause from the Korean Genome and Epidemiology Study (KoGES, n=28,212) and Taiwan Biobank (TWB, n=41,066), as well as for age at menarche (KoGES, n=45,615; TWB, n=87,844), and cancer phenotypes from the BioBank Japan (BBJ) GWAS. Several rounds of two-sample MR based on summary statistics were employed to assess the causal relationships between age at menarche/menopause and cancer risks. Univariable MR was used to estimate the direct effects, while bidirectional MR was conducted to investigate potential reverse causality. Our MR results suggested a significant causal relationship between age at menopause and EnC. In the KoGES dataset, univariable MR revealed that a 1(SD) increase in age at menopause was associated with a more than threefold increased risk of EnC (OR = 3.20, 95% CI: 1.56–6.58, p = 0.0015). The results of bidirectional MR indicated no reverse causal effect of EnC on menopause age. Similarly, the TWB dataset supported these findings, showing that an increase in age at menopause was associated with an elevated risk of EnC (OR = 1.98, 95% CI: 1.15–3.42, p = 0.0136). In conclusion, our study provides evidence for a potential genetic link between age at menopause and endometrial cancer. No significant associations were found between age at menarche and the risk of female cancers. Despite the common belief that later menopause might be linked to an increased risk of breast cancer, our results did not support a significant causal association in this population. These findings may guide prevention strategies and interventions for women at higher genetic risk of endometrial cancer based on menopause timing.