Mendelian Randomization Analysis of Fertility Phenotypes and Endometrial Cancer Risk in the UK-Biobank

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Introduction

Observational studies have shown a link between several fertility phenotypes and endometrial cancer (EC). Here, we use Mendelian Randomisation (MR) to investigate if these observational associations are causal.

Research Objectives

Use univariable MR and multivariable MR (MVMR) to assess causal effects of fertility phenotypes on EC risk.

Methods

We performed three genome-wide association (GWAS) analysis using FastGWA[1] in the UK Biobank[2]:
-Years ovulating(N=118,227)
-Age at last birth (N=203,153)
-Years on contraceptive pill (N=178,233).

Two sample Inverse variance weighted (IVW) MR were performed to assess causal effect of fertility phenotypes on EC risk.

MVMR analysis was performed with fertility phenotypes significantly associated with EC in univariate analyses, in addition to other confounding phenotypes.

Results

We found 13 independent genetic variants associated with age at last birth and 20 with years ovulating, but none for years taking the contraceptive pill.

The IVW MR analysis found evidence of a causal effect of number of live births (P=0.006) and years ovulating (P=0.015) on EC risk.

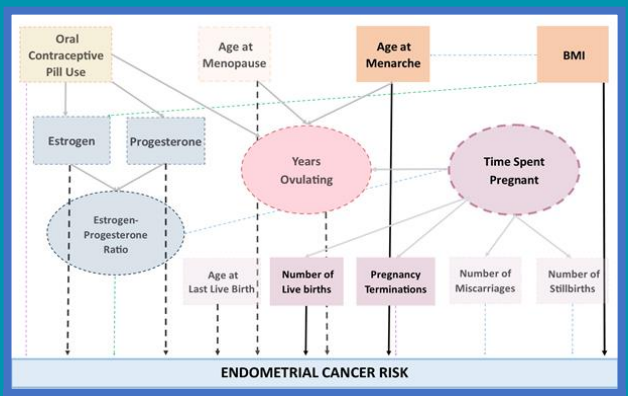

Figure 1: Causal and observational relationships between fertility phenotypes and endometrial cancer (EC) risk: causal relationships are represented by solid black arrows, causal relationships that did not reach statistical significance are represented by dotted black arrows. Negative observational relationships found in the present study are indicated by purple dotted arrows, previously reported observational relationships are indicated by green dotted (positive) and blue dotted (negative) arrows. Grey arrows represent closely connected phenotypes. BMI: Body mass index

Table 1: Results from the MVMR analysis of fertility phenotypes on EC risk.

Exposure	Number of SNPs	Estimate	Standard Error	P-Value
Age at Menarche	96	-0.126	0.048	0.008
Age at Menopause	36	0.024	0.019	0.203
Body Mass Index	558	0.498	0.059	0.00
Number of live births	5	-0.251	0.105	0.017
Years ovulating	5	0.011	0.015	0.455

MVMR analysis showed a significant causal effect of number of live births on EC risk (P=0.017), independent of confounding phenotypes (Table1).

Discussion

We have found that number of live births may causally decrease a woman's risk of EC, independently of age at menarche, age at menopause and BMI.

Years ovulating showed a possible causal increase in EC risk through univariable MR, however the MVMR analysis did not show this to be an independent risk factor.

Limitations

We could not perform MR on years using the oral contraceptive pill as we did not find any genetic variants for this trait.

Additionally, several genetic variants associated with years ovulating were either unavailable in the other summary statistics or highly associated with age at menopause, meaning only a subset were available for the MVMR.

Conclusion

We show that number of live births has an independent, protective effect on EC risk, even when accounting for confounding phenotypes.

This provides insight into the various hypotheses
surrounding fertility risk factors and EC risk and has
important implications for public health initiatives.

Selected References

[1] Yang, J., *et.al.* GCTA: a tool for genome-wide complex trait analysis. *AJHG* **88**, 76-82 (2011).
[2] Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203-209 (2018).

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