Leveraging genetically correlated traits improves the detection of susceptibility loci for endometrial cancer

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Background

Endometrial cancer is the fifth most common female cancer worldwide and the most common gynaecological tumour in industrialised countries, accounting for 380,000 new cases diagnosed and nearly 90,000 deaths in 2018[1]. Identification of susceptible loci lays the foundation for the understanding of the aetiology of endometrial cancer. We recently conducted the largest genome-wide association study (GWAS) for endometrial cancer (12,906 cases), identifying 16 genetic loci associated with disease risk[2]. However, these risk loci together explained nearly a quarter of the portion of the familial relative risk attributable to common, readily-imputable variants. Another crucial way to the prevention and the reduction of mortalities of endometrial cancer is to identify and understand its risk factors. Many risk factors of endometrial cancer have been identified observational studies and Mendelian Randomisation analyses.

In this study, we leveraged the availability of GWAS summary-level data of diverse traits from the UKB Biobank and other consortia to identify risk factors of endometrial cancer.

Methods

Fig. 1 Diagram of the analyses.

Result 1 – Genetic correlations

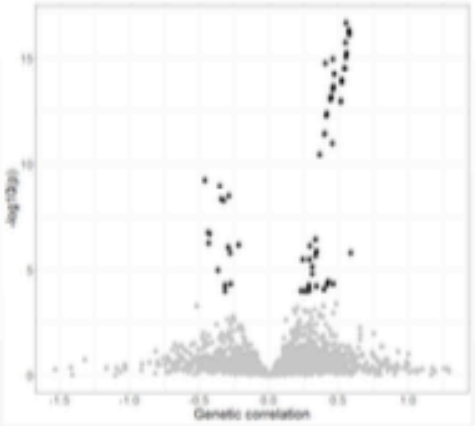


Fig. 2 Volcano plot of genetic correlations between EC and all traits tested. Black points represent 67 traits, which had a rg to all EC with FDR < 0.01; whereas those grey points were traits having a rg with FDR >= 0.01.

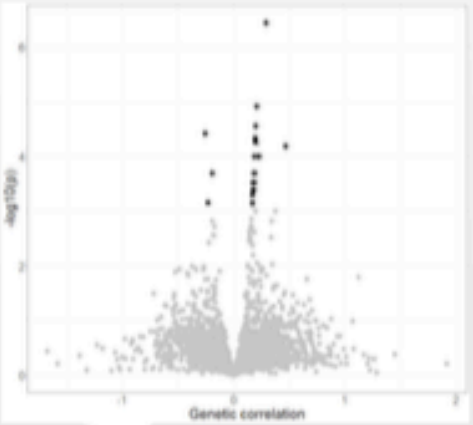


Fig. 3 Volcano plot of genetic correlations between EC_BMI-adj and all traits tested. Black points represent traits having a significant genetic correlation at the level of p<7.46 × 10-4, whereas grey points are traits not passing this significance threshold.

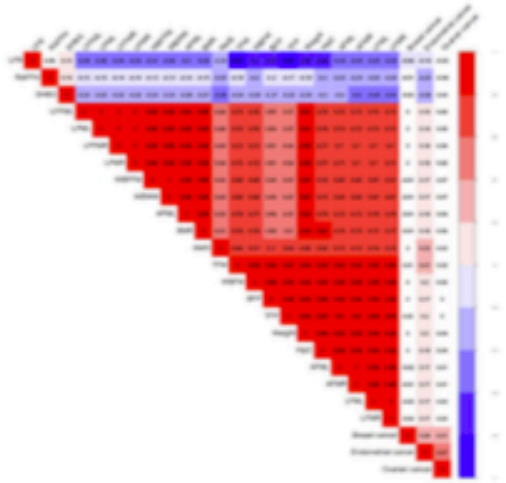


Fig. 4 Heatmap of pairwise correlations of the 34 traits that remained significantly correlated with endometrial cancer adjusted for BMI.

Result 2 – Risk factors detected by MR analysis

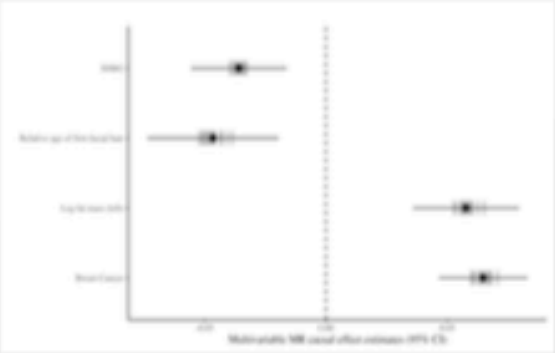
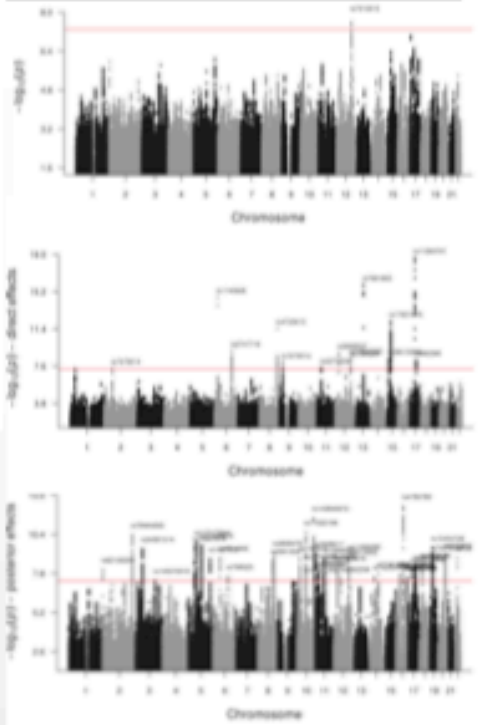


Fig. 5 Coefficients plot of four risk factors causally affecting EC in multivariable MR analysis. The black dot is the multivariable causal effect estimate and the horizontal line the 95% interval from the multivariable MR model using all chromosomes for each risk factor; whereas grey vertical bars represents the 22 per-chromosome estimates.

Result 3 – risk loci detected



References

1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., and Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68, 394-424.

2. O'Mara, T.A., Glubb, D.M., Amant, F., Annibali, D., Ashton, K., Attia, J., Auer, P.L., Beckmann, M.W., Black, A., Bolla, M.K., et al. (2018). Identification of nine new susceptibility loci for endometrial cancer. Nature Communications 9.

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