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Body Mass Index and Risk of Female Reproductive System Tumors Subtypes: A Meta-analysis of Mendelian Randomization Study

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 April 2024 and was last updated on 06 April 2024.

INTRODUCTION

Review question / Objective Previous studies have found a strong link between BMI and female reproductive system tumors, but the precise causal relationship still needs to be determined due to varying literature. We conducted a Mendelian randomisation (MR) study to explore this association further.

Condition being studied In this study, we used BMI as an exposure factor, related subtypes of breast cancer and four other common female reproductive system tumor subtypes as outcome indicators, and the study mainly followed the following five steps:(1)Determination of IVs (selection of IVs and verification of IVs);(2)Sorting out and extracting relevant data before analysis; (3)TSMR analysis;(4)Analyze the data and map them;(5)Further meta-analysis of the TSMR results was performed to integrate the TSMR results from the currently available prospective evidence.

METHODS

Participant or population Sample inclusion criteria: Have GWAS sequencing data and corresponding clinical information, including data release year, race, gender, research institution, sample size, PMID number, etc.

Intervention There must be some difficult to avoid random errors in the selection and inclusion of IVs. Therefore, it is necessary to carry out "Leave-one-out" analysis of the data, eliminate one SNP in turn, and calculate the Mendelian randomisation analysis effect of the remaining SNP. Through the display of forest maps, we can intuitively judge the

influence of each SNP on the results, so as to judge the stability of TSMR analysis results.

Comparator There must be some difficult to avoid random errors in the selection and inclusion of IVs. Therefore, it is necessary to carry out "Leave-one-out" analysis of the data, eliminate one SNP in turn, and calculate the Mendelian randomisation analysis effect of the remaining SNP. Through the display of forest maps, we can intuitively judge the influence of each SNP on the results, so as to judge the stability of TSMR analysis results.

Study designs to be included A Meta-analysis based on the TSMR.

Eligibility criteria None.

Information sources The genetic information utilized in determining BMI derives from a genome-wide association study (GWAS) that has been formally published. The genetic links to five prevalent Female Reproductive System tumors were derived from the FinnGen and UK Biobank studies, along with other extensiveconsortia.

Main outcome(s) Genetic predisposition towards BMI exhibits a significant association with multiple tumors of the female reproductive system. Specifically, for every 1-unit increase in BMI log-transformed odds ratio (OR), The OR fluctuations for overall breast cancer patients ranged from 0.661 to 0.996 (95% CI,0.544-1, P <0.05). When stratified by estrogen receptor (ER) status, the OR for ER (+) breast cancer patients ranged from 0.782 to 0.844 (95% CI,0.616-0.994, P <0.05) and the OR for ER (-) breast cancer patients ranged from 0.663 to 0.789 (95% CI,0.498-0.991, P <0.05).1.577-1.908(95% CI,1.049-2.371, P<0.05) for endometrial carcinoma.1.216-1.303 (95% CI,1.021-1.591, P <0.05) for high-grade serous ovarian cancer,1.217 (95% CI,1.034-1.432, P<0.05) for low-grade malignant serous ovarian cancer and 1.502 (95% CI,1.112-2.029, P<0.05) for endometrioid ovarian carcinoma. Furthermore, our findings indicated that genetic predisposition towards BMI did not exhibit a causal association with uterine fibroids, cervical precancerous lesions, or cervical cancer itself.

Quality assessment / Risk of bias analysis To determine the comprehensive causal relationship between body mass index and different types of cancer, we performed a further meta-analysis of the TSMR results for all tumors and their associated subtypes of GWAS data included in the study. When at least three independent studies were identified assessing whether there was a causal effect between BMI and risk of disease with female tumors and their subtypes, data were pooled into the meta-analysis. We pooled the risk ratios for all TSMRs with a fixed-effects model and assessed the heterogeneity across studies by examining the funnel plot of the risk ratios estimates and using the Cochrane Q test and I2 statistic (P≤0.1, or I2 ≥50% for any heterogeneity ; P＞0.1, or I2 ＜50% without heterogeneity).For research data with heterogeneity, we explored the source of heterogeneity from the perspective of clinical and methodological heterogeneity, and further conducted subgroup analysis based on the attribute characteristics causing heterogeneity existed in the results in order to eliminate heterogeneity.

Strategy of data synthesis The study mainly followed the following five steps:(1)Determination of IVs (selection of IVs and verification of IVs); (2)Sorting out and extracting relevant data before analysis;(3)TSMR analysis;(4)Analyze the data and map them;(5)Further meta-analysis of the TSMR results was performed to integrate the TSMR results from the currently available prospective evidence.

Subgroup analysis Genetic information for BMI comes from a currently published genome-wide association study (GWAS) including 339,224 participants.GWAS summary data for the five female cancer outcomes (breast, endometrial, cervical, ovarian and uterine fibroids) and their subtypes were selected from the largest cancer-specific GWAS (107endometrial cancer to 122977 breast cancer) database.In the univariate MR (UVMR) analysis, inverse variance weighting (IVW) was used as the main method, and robust adjusted Weighted median, Simple mode, Weighted mode, and MR-Egger were used as supplementary methods to this causal inference. Sensitivity analyses included the Cochran-Q test, the Egger intercept test, and the Leave one out analysis to verify the robustness of the MR results.At last,A meta-analysis of TSMR results of female breast and multiple female reproductive system tumor-related subtypes from different databases was performed to integrate the currently available prospective evidence.

Sensitivity analysis There must be some difficult to avoid random errors in the selection and inclusion of IVs. Therefore, it is necessary to carry out "Leave-one-out" analysis of the data, eliminate one SNP in turn, and calculate the Mendelian randomisation analysis effect of the remaining SNP. Through the display of forest maps, we can

intuitively judge the influence of each SNP on the results, so as to judge the stability of TSMR analysis results.

Country(ies) involved China.

Keywords body mass index; obesity; tumors of the female reproductive system; Mendelian randomisation; meta-analysis.

Contributions of each author

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