Abstract GS2-06: Exploring the causal role of the human gut microbiome in breast cancer risk using mendelian randomization FREE

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Abstract

Background: Variation in the human gut microbiome may influence cancer progression and therapy response through various mechanisms including modulation of both immune and cell signalling pathways. Whilst observational epidemiological studies have provided evidence that the gut microbiome may play a role in cancer risk, such studies are prone to residual confounding, reverse causation, and other forms of bias. Therefore, the nature of these associations still remains unclear. Mendelian randomization (MR) is a causal methodology that uses genetic variants as instruments ("proxies") for risk factors to eliminate such biases when questioning causality in observational epidemiological associations. The statistical power and precision of MR analyses can be increased by employing a "two-sample MR" (2SMR) framework in which summary data – usually from large, independent, genome-wide association studies (GWASs) reporting associations of genetic variants with exposures (here, the gut microbiome) and outcomes (here, cancer) – are synthesised to estimate causal effects of each exposure on each outcome of interest. In this study, we utilised 2SMR to interrogate causal relationships between the gut microbiome and breast cancer (BC) risk using the largest published GWASs of the gut microbiome and of clinically utilised subtypes of BC.

Methods: We performed 2SMR using summary-level data from the GWAS of the host genetic contribution to gut microbiome variation amongst European individuals (the Flemish Gut Flora Project and two German cohorts (n=3890)) combined with summary-level data from the GWAS of BC risk (Breast Cancer Association Consortium (133,384 cases stratified by Luminal A, Luminal B, Human Epidermal Growth Factor 2 (Her2) positive, Her2 negative and triple negative status and 113,789 controls, plus

18,908 BRCA1 mutation carriers (9,414 with BC)). Sensitivity analyses were also conducted to assess pleiotropy of genetic variants on BC risk, independent of gut microbiota. Analyses were conducted in R Studio using the TwoSampleMR and the MR-TRYX packages.

Results: Of the 14 microbial traits (MTs) with evidence for a host genetic contribution in the GWAS of the gut microbiome, we found evidence that abundance of a genus within a certain bacterial order decreased the risk of triple negative BC (odds ratio per standard deviation increase: 0.84; 95% CI: 0.71, 0.9; p=0.03). In addition, we demonstrated that the risk of all molecular subtypes of BC may be altered by variation in these MTs, and that these relationships differed according to subtype. Sensitivity analyses demonstrated that pleiotropy was unlikely to explain these relationships

Conclusions: In our study, we utilised two recent and novel GWASs in an MR context to appraise causality in relationships between the gut microbiome and BC risk and found evidence that certain bacteria may alter BC risk, effects of which vary according to molecular subtype. These important results generate hypotheses about mechanisms underlying the causal biology of BC subtypes and potentially facilitate the design of BC risk-reducing interventions and prevention strategies.

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