World Journal of Surgical Oncology

RESEARCH

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Causal effect of gut microbiota on the risk of cancer and potential mediation by inflammatory proteins

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Abstract

Background While growing evidence highlights the role of gut microbiota and inflammatory proteins in cancer, with cancer-related inflammation now considered the seventh hallmark of cancer, the direct causal relationships between specific microbiota, cancer, and the potential mediating effects of inflammatory proteins have not been fully established.

Methods We employed Mendelian randomization (MR) to assess the causal relationships between gut microbiota, inflammatory proteins, and eighteen distinct cancers using data from extensive genome-wide association studies (GWAS). The primary statistical method utilized was inverse variance weighting (IVW). We also investigated whether inflammatory proteins could mediate the effects of gut microbiota on cancer development.

Results Our findings revealed 42 positive and 49 inverse causal impacts of gut microbiota on cancer risk ($P < 0.05$). Additionally, we identified 32 positive and 28 inverse causal relationships between inflammatory proteins and cancer risk. Moreover, genus *Collinsella* decreased the risk of lung cancer by decreasing levels of T-cell surface glycoprotein CD5 (mediating effect = 16.667%), while genus *Ruminococcaceae UCG005* increased the risk of mesothelioma by increasing levels of CCL4 (mediating effect = 5.134%).

Conclusions Our study provides evidence for a causal association between gut microbiota, inflammatory proteins, and eighteen different cancer types. Notably, the T-cell surface glycoprotein CD5 and CCL4 were identified as mediators linking the genus *Collinsella* with lung cancer and the genus *Ruminococcaceae UCG005* with mesothelioma, respectively.

Keywords Gut microbiota, Cancer, Inflammatory proteins, Two-sample mendelian randomization, Univariable MR

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Background

The gut microbiota refers to the complex community of microbial species residing in the human gastrointestinal tract, which represents the largest and most diverse microbial reservoir in the body, comprising approximately 10^{14} microorganisms [1]. Gastrointestinal microbiota are crucial for maintaining physiological balance and metabolic functions, such as immune system maturation, vitamin synthesis, and nutrient absorption [2]. Research has linked gut microbiota with various cancers [3] and highlighted its significant role in modulating inflammation, particularly in the context of cancer [4]. Cancer-related inflammation is recognized as the seventh hallmark of cancer, with inflammatory cells and mediators playing pivotal roles in the tumor microenvironment [5, 6]. The systemic inflammatory response (SIR), assessed through circulating markers such as serum proteins and blood cell counts, has been linked to survival outcomes across various cancers. Key markers, including C-reactive protein, the Glasgow Prognostic Score, the neutrophil-to-lymphocyte ratio, and the prognostic nutrition index, have been extensively investigated for their prognostic and predictive value in multiple cancers. Both gut microbiota and inflammatory proteins appear to influence cancer progression, with inflammatory proteins potentially acting as mediators in the microbiota-cancer axis.

While randomized controlled trials (RCTs) could establish a causal relationship between gut microbiota or circulating inflammatory proteins and cancer, such studies are challenging to conduct in humans due to logistical constraints, such as the difficulty of screening gut microbiota [7, 8] and circulating inflammatory proteins [9]. As a result, most current findings are based on observational studies examining the composition and alterations of gut microbiota in the feces of cancer [10]. Several cohort studies have suggested a potential link between gut microbiota and cancer. Research indicates that gut microbiota plays a crucial role in modulating the immune response to systemic inflammation, and disruption of this symbiotic relationship may increase susceptibility to cancer [11, 12].

Mendelian randomization (MR), a technique in genetic epidemiology, employs genetic variants as instrumental variables to assess causal relationships between exposures and outcomes [13–15]. Since genetic markers are established at conception, MR is less susceptible to confounding by environmental factors or reverse causality, which are common limitations in observational studies. By leveraging large-scale summary statistics, MR strengthens the analytical rigor in investigating the connections between gut microbiota, inflammatory proteins, and cancer.

In this study, we perform an extensive MR analysis to investigate the causal interactions between the gut microbiota, inflammatory proteins, and multiple types of cancer, focusing particularly on the mediating role of inflammatory proteins in the microbiota-to-cancer pathway.

Methods

Study design

This study comprises three main components as depicted in Fig. 1: Firstly, we explored the causal effects of 211

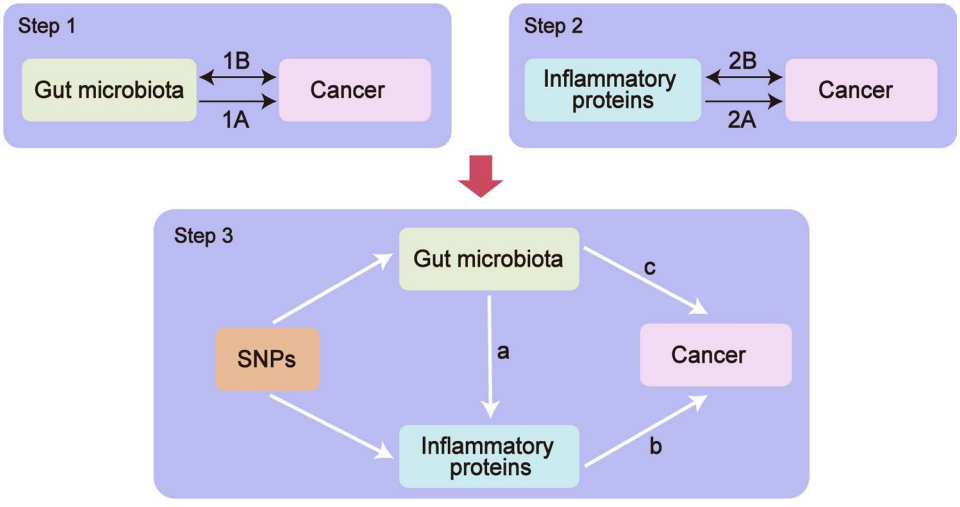

Fig. 1 This figure illustrates the framework of our analysis. "SNPs" denotes a set of single-nucleotide polymorphisms, each linked to one or more exposures. Step 1 A assesses the causal impacts of gut microbiota on cancer, while Step 1B examines the bidirectional causal relationships between gut microbiota and cancer. Step 2 A explores the causal effects of inflammatory proteins on cancer, and Step 2B investigates the bidirectional causal effects between inflammatory proteins and cancer. Step 3 outlines the mediation analysis, where path a represents the causal effect of gut microbiota on inflammatory proteins, path b denotes the causal effect of inflammatory proteins on cancer, and path c illustrates the total effect of gut microbiota on cancer

gut microbiota on eighteen types of cancer (Step 1 A); secondly, we examined the causal effects of 91 inflammatory proteins on eighteen types of cancer (Step 2 A); and thirdly, we conducted a mediation analysis to investigate the role of inflammatory proteins in the pathway linking gut microbiota to cancers (Step 3). We employed single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) for these analyses MR relies on three fundamental assumptions: (1) IVs must be robustly associated with the exposure; (2) IVs are independent of any confounding factors; and (3) IVs influence the outcome solely through their effect on the exposure [16].

Data sources

SNPs associated with human gut microbiota composition were selected as instrumental variables (IVs) from the MiBioGen GWAS dataset [17], available at https://mibiogen.gcc.rug.nl/. This large-scale, multi-ethnic GWAS integrated 16 S ribosomal RNA gene sequencing data and genotyping information from 18,340 participants across 24 cohorts in the USA, Canada, Israel, South Korea, Germany, Denmark, the Netherlands, Belgium, Sweden, Finland, and the UK, aiming to explore the relationship between autosomal genetic variants and gut microbiota composition. The dataset included 211 taxa, encompassing 131 genera, 35 families, 20 orders, 16 classes, and 9 phyla. Detailed descriptions of participant recruitment criteria and genetic data quality control are provided in the original publication [17] (Table S1). The rationale for using the 16 S rRNA processing pipeline was previously outlined [18]; in brief, divergence in the 16 S rRNA gene domains between cohorts hindered OTU-level analysis. Instead, direct taxonomic classification of the reads, using an up-to-date reference database, facilitated improved concordance in taxonomic composition across domains and a higher mapping rate.

Data on 91 circulating inflammatory proteins were obtained from the EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/downloads/summary-statistics, accession numbers GCST90274758 to GCST90274848), measured using the Olink Target Inflammation panel across 11 cohorts, including 14,824 participants of European ancestry (Table S1) [19].

We extracted genetic variant data for 18 cancer types from large-scale consortia (Table S1). The Finnish Genetics dataset included 304 liver cancer and 633 gastric cancer samples. The International Lung Cancer Consortium contributed data from 27,209 lung cancer samples. The Breast Cancer Association Consortium provided data on 228,951 breast cancer samples. The Prostate Cancer Association Group supplied information on 140,254 prostate cancer samples. The Medical Research Council-Integrative Epidemiology Unit (MRC-IEU) contributed data for 463,010 kidney cancer and 462,933 cervical cancer samples. Data on colorectal cancer (407,746 samples) and pancreatic cancer (196,187 samples) were also included. The Ovarian Cancer Association Consortium provided data on 66,450 ovarian cancer samples. Additional datasets, including from the Neale Lab, covered lymphoma (361,194 samples) and melanoma (361,194 samples). The UK Biobank provided data on esophageal cancer (372,756 samples) and mesothelioma (133 samples). Data on endometrial cancer (121,885 samples), thyroid cancer (989 samples), bladder cancer (1,279 samples), and basal cell carcinoma (392,871 samples) were also included. Since this study utilized publicly available summary data, no additional ethical approval or consent was required. The GWAS data for multiple cancers were sourced from the MRC-IEU GWAS Database (https://gwas.mrcieu.ac.uk/). The data sources and published PMID numbers for these 18 cancers are provided in Table S1.

Genetic instrument selection

First, based on previous studies, linear regression analysis was performed for each genetic variant, employing a less stringent threshold ($P < 1 \times 10^{-5}$) as a screening.

criterion [17, 20]. This method was intended to evaluate and mitigate potential IVs bias within the MR analysis. To maximize the number of available instruments for each inflammatory protein, we set the threshold for SNPs selection at a P-value of 5×10^{-6} [20, 21]. Next, SNPs in linkage disequilibrium (LD) were excluded from the analysis. LD clustering was performed using an interlocking imbalance threshold of 10,000 kb and an r^2 value of 0.001 [22, 23]. To assess potential weak instrument bias, we computed the F-statistic, with an F-statistic above 10 indicating a low likelihood of weak instrument bias.

MR analysis

Two-sample mendelian randomization

To assess the causal relationships between gut microbiota, inflammatory proteins, and cancers, we conducted two-sample Mendelian Randomization (MR) analyses as outlined in steps 1 A and 2 A of Fig. 1. The primary analytical method used was the Inverse Variance Weighted (IVW) approach, supplemented by the Wald ratio test for features with only one instrumental variable (IV) [24]. MR findings were reported as odds ratios (ORs) with 95% confidence intervals (CIs), considered statistically significant when the IVW P-values were below 0.05 and the directional consistency between IVW and MR-Egger results was observed.

Bidirectional causality analysis

To assess the bi-directional causal relationships between cancers, gut microbiota, and inflammatory proteins, we designated cancers as the "exposure" and both gut microbiota and inflammatory proteins linked to cancers as the

"outcome" (Step 1B and Step 2B in Fig. 1). We identified SNPs that are significantly associated with various cancers ($P < 1 \times 10^{-5}$) [25, 26]. SNPs with *F*-statistic values below 10 were deemed weak instruments [23].

Mediation analysis

We conducted a detailed two-sample bidirectional MR analysis to explore the reciprocal causal relationships between gut microbiota and cancer, referred to as the 'total effect'. Subsequently, we employed a multivariable MR method to perform a mediation analysis aimed at identifying inflammatory proteins that mediate the interaction between gut microbiota and cancer.

The direct effects of gut microbiota on cancer were determined using multivariable MR, adjusting for the presence of inflammatory proteins. Mediation analysis is permissible only under specific statistical thresholds: Initially, for Step 1 A, the resultant *P*-value must be below 0.05, whereas for Step 1B, it should exceed 0.05. Correspondingly, in Step 2 A, the *P*-value associated with the results must be less than 0.05, and for Step 2B, greater than 0.05. Furthermore, in Step 3, the *P*-value for outcomes derived from multivariable MR should also fall below 0.05. The indirect effects mediated by inflammatory proteins were calculated as $\beta_a \times \beta_b$, where β_a represents the MR effect of gut microbiota on the mediators, and β_b represents the MR effect of inflammatory proteins on cancer, adjusted for the influence of gut microbiota. Standard errors for these indirect effects were estimated using the delta method [27].

Statistical analysis

For each exposure, our primary MR analysis employed the Inverse Variance Weighted (IVW) method within a multiplicative random-effects model [24]. This approach aggregates the Wald ratio estimates from each SNP to produce a consolidated causal estimate for each risk factor. Each SNP's causal impact is calculated by dividing its association with the outcome by its association with the exposure [28]. Given that IVW estimates can be skewed by pleiotropic instrumental variables [24], we conducted several sensitivity analyses to address potential pleiotropy. Cochran's Q test was used to assess heterogeneity among SNPs, and scatter plots of SNP-exposure and SNP-outcome associations were generated to visualize the MR results [29]. A leave-one-out analysis was conducted to determine the influence of each individual SNP on the results by sequentially excluding each SNP and re-running the IVW method on the remaining SNPs [30]. Additionally, MR-PRESSO and MR-Egger regression were applied to test for horizontal pleiotropy. MR-PRESSO was used to identify significant outliers and correct for horizontal pleiotropy by removing these outliers [31]. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for outcomes corresponding to a one-SD increase in lipid-related traits. To enhance the rigor of our results, the Benjamini-Hochberg procedure (FDR) was applied to adjust *P* -values when evaluating the associations between a single gut microbiota or inflammatory protein and multiple cancer types. Differences were considered statistically significant if the *P* -value remained below 0.05 after FDR correction [32, 33].

All analyses were conducted using R statistical software (version 4.2.1). MR was performed using the "TwoSampleMR" package in R. For multiplicity tests, the "MR_PRESSO" package was utilized [34].

Results

Causal effects of gut microbiota and inflammatory proteins on multiple cancer

Liver cancer

Analysis identified six gut microbiota with significant associations to liver cancer risk (Fig. 2 and Table S2). Specifically, the genus *Anaerofilum* (OR = 1.742, 95% CI = 1.027–2.958, *P* = 0.040), genus *Paraprevotella* (OR = 1.849, 95% CI = 1.095–3.124, *P* = 0.022), and genus *Ruminococcus gnavus group* (OR = 2.018, 95% CI = 1.070–3.806, *P* = 0.030), along with the order *Mollicutes RF9* (OR = 2.314, 95% CI = 1.072–4.992, *P* = 0.033) and the phylum *Verrucomicrobia* (OR = 2.119, 95% CI = 1.025–4.380, *P* = 0.043), were associated with an increased risk of liver cancer. Conversely, the family *Rhodospirillaceae* (OR = 0.571, 95% CI = 0.328–0.995, *P* = 0.048) was associated with a reduced risk.

Additionally, elevated levels of Fibroblast Growth Factor 19 (FGF19) (OR = 1.967, 95% CI = 1.209–3.201, *P* = 0.01), Interleukin-17 A (IL-17 A) (OR = 2.429, 95% CI = 1.098–5.371, *P* = 0.028), and Osteoprotegerin (OPG) (OR = 1.792, 95% CI = 1.028–3.127, *P* = 0.040) significantly increased the incidence of liver cancer, as illustrated in Fig. 3 and detailed in Table S3.

Colorectal cancer

Our analysis revealed five gut microbiota linked to colorectal cancer (CRC) risk, as shown in Fig. 2 and Table S2. Specifically, the genus *Adlercreutzia* (OR = 1.256, 95% CI = 1.013–1.558, *P* = 0.038) was found to significantly increase the risk of colorectal cancer. Conversely, reductions in risk were observed with the genus *Bilophila* (OR = 0.777, 95% CI = 0.629–0.960, *P* = 0.020), genus *Clostridium sensustricto 1* (OR = 0.770, 95% CI = 0.603–0.985, *P* = 0.037), genus *Coprococcus 2* (OR = 0.649, 95% CI = 0.476–0.884, *P* = 0.012), and genus *Ruminococcaceae UCG-002* (OR = 0.843, 95% CI = 0.713–0.997, *P* = 0.046).

Figure 3 details associations between various inflammatory proteins and colorectal cancer. Elevated levels of Glial Cell-Derived Neurotrophic Factor (GDNF) (OR = 1.159, 95% CI = 1.001–1.342, *P* = 0.049) significantly

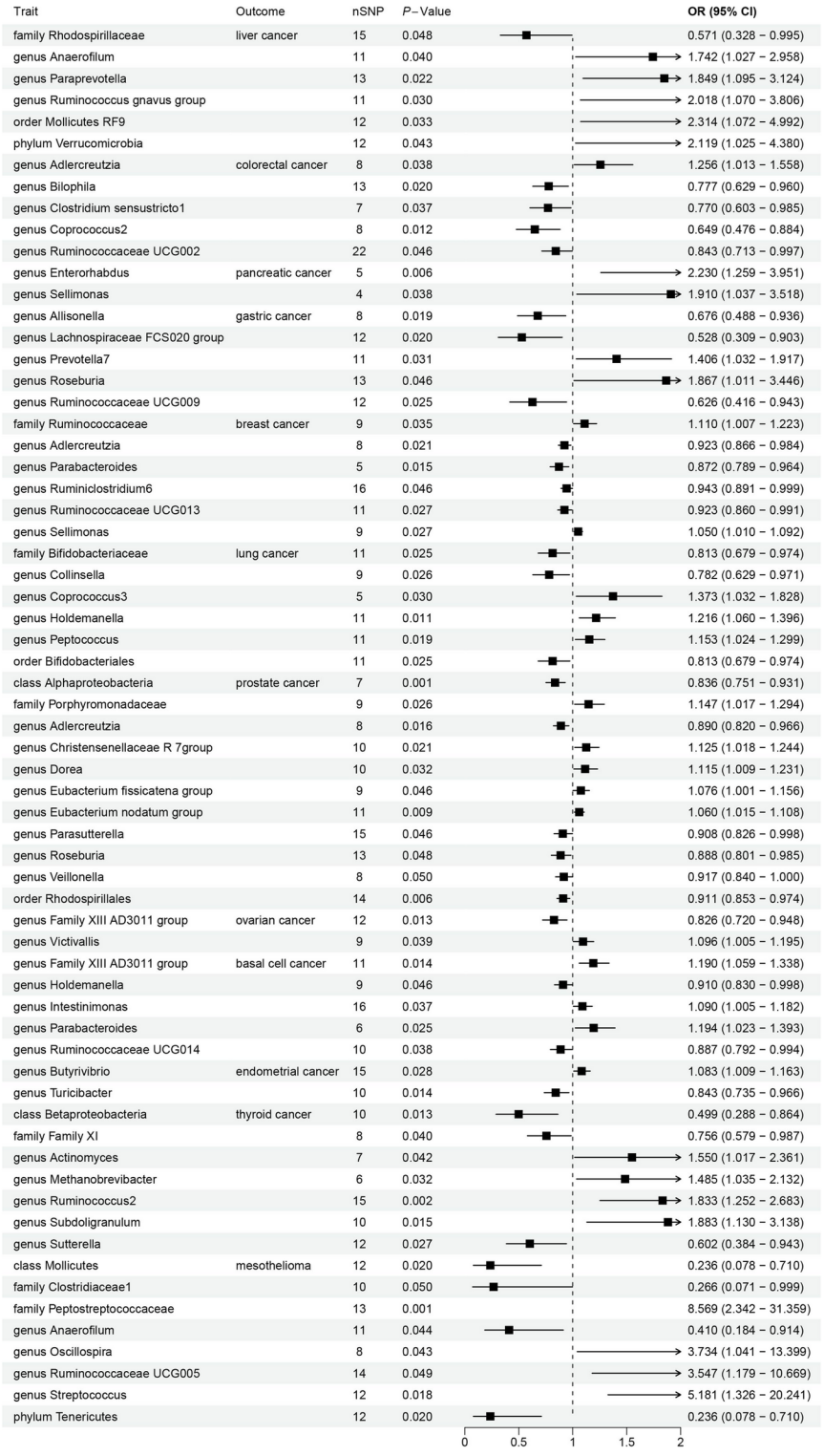

Fig. 2 MR results of gut microbiota and liver, colorectal, pancreatic, gastric, breast, lung, prostate, ovarian, basal cell, endometrial, thyroid, mesothelioma cancer

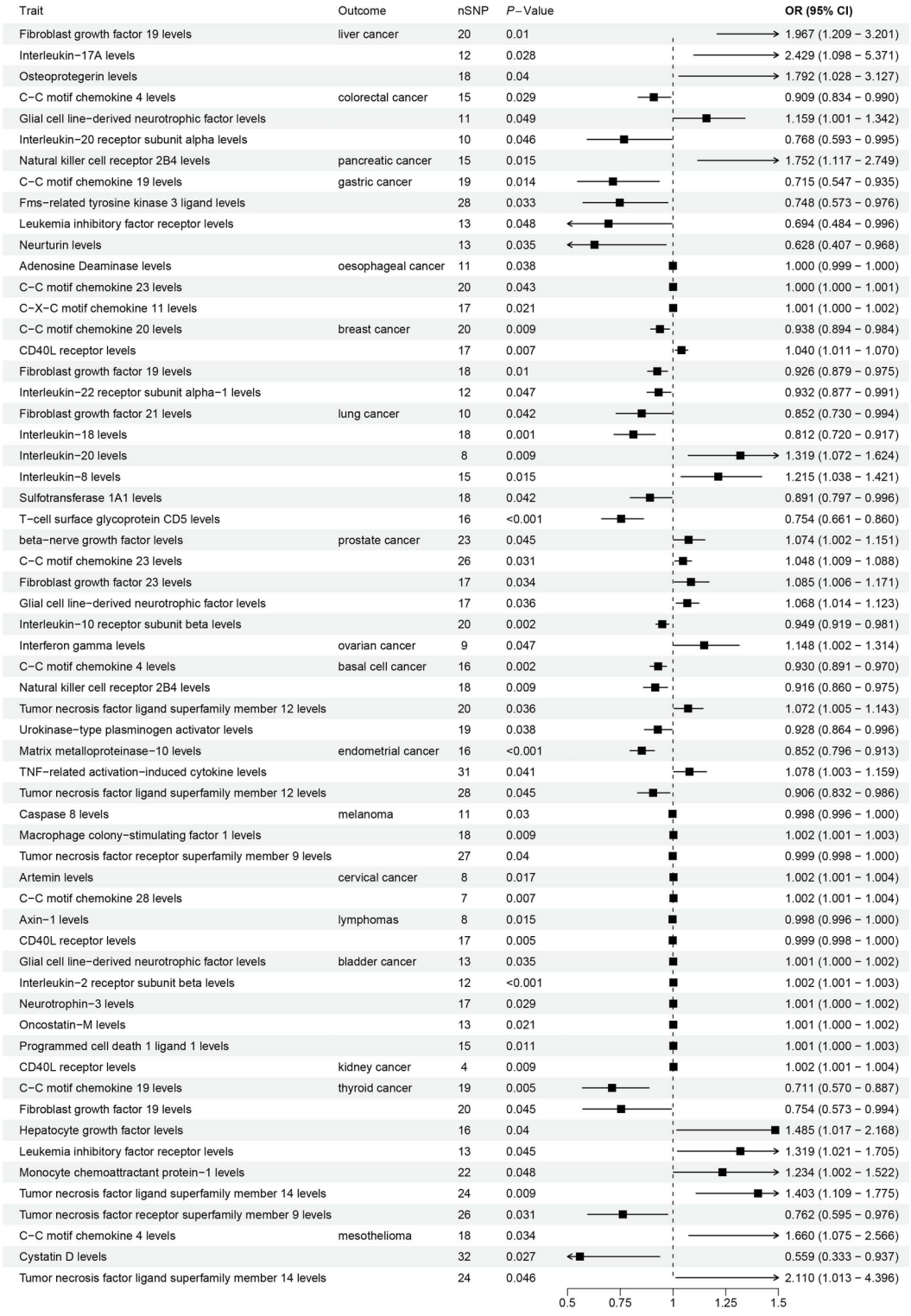

Fig. 3 MR results of inflammatory protein and cancer

increased the risk of colorectal cancer. In contrast, C-C Motif Chemokine 4 (CCL4) (OR = 0.909, 95% CI = 0.834–0.990, $P = 0.029$) and Interleukin-20 Receptor Subunit Alpha (IL20RA) (OR = 0.768, 95% CI = 0.593–0.995, $P = 0.046$) were associated with a decreased risk, as detailed in Table S3.

Pancreatic cancer

Our study identified two gut microbiota associated with pancreatic cancer risks (Fig. 2 and Table S2). The genus *Enterorhabdus* (OR = 2.230, 95% CI = 1.259–3.951, *P* = 0.006) and genus *Sellimonas* (OR = 1.910, 95% CI = 1.037–3.518, *P* = 0.038) were significantly linked to an increased risk of pancreatic cancer.

Additionally, elevated levels of the Natural Killer Cell Receptor 2B4 (NKR2B4) were found to significantly increase the risk of pancreatic cancer (OR = 1.752, 95% CI = 1.117–2.749, *P* = 0.015), as detailed in Fig. 3 and Table S3.

Gastric cancer

Our analysis identified five gut microbiota associated with gastric cancer risk, detailed in Table S2 and illustrated in Fig. 2. Notably, the genus *Prevotella7* (OR = 1.406, 95% CI = 1.032–1.917, *P* = 0.031), and genus *Roseburia* (OR = 1.867, 95% CI = 1.011–3.446, *P* = 0.046) were linked to an increased risk of gastric cancer. In contrast, genus such as *Allisonella* (OR = 0.676, 95% CI = 0.488–0.936, *P* = 0.019), *Lachnospiraceae FCS020 group* (OR = 0.528, 95% CI = 0.309–0.903, *P* = 0.020), and *Ruminococcaceae UCG009* (OR = 0.626, 95% CI = 0.416–0.943, *P* = 0.025) were associated with a decreased risk.

Figure 3 and Table S3 also show that reduced levels of several inflammatory proteins, including C-C motif chemokine 19 (CCL19) (OR = 0.715, 95% CI = 0.547–0.935, *P* = 0.014), Fms-related tyrosine kinase 3 ligand (Flt-3 L) (OR = 0.748, 95% CI = 0.573–0.976, *P* = 0.033), leukemia inhibitory factor receptor (OR = 0.694, 95% CI = 0.484–0.996, *P* = 0.048) and Neurturin (OR = 0.628, 95% CI = 0.407–0.968, *P* = 0.035) significantly decreased the risk of gastric cancer (Table S3).

Oesophageal cancer

Our study identified six gut microbiota linked to oesophageal cancer, as detailed in Table S4 and depicted in Fig. 4. The genus *Coprobacter* (OR = 1.001, 95% CI = 1.000-1.002, *P* = 0.028), genus *Oxalobacter* (OR = 1.001, 95% CI = 1.000-1.001, *P* = 0.049), genus *Senegalimassilia* (OR = 1.002, 95% CI = 1.000-1.003, *P* = 0.006), and genus *Veillonella* (OR = 1.001, 95% CI = 1.000-1.002, *P* = 0.027) were associated with an increased risk of oesophageal cancer. Conversely, the genus *Romboutsia* (OR = 0.999, 95% CI = 0.998-1.000, *P* = 0.048) and genus *Turicibacter*

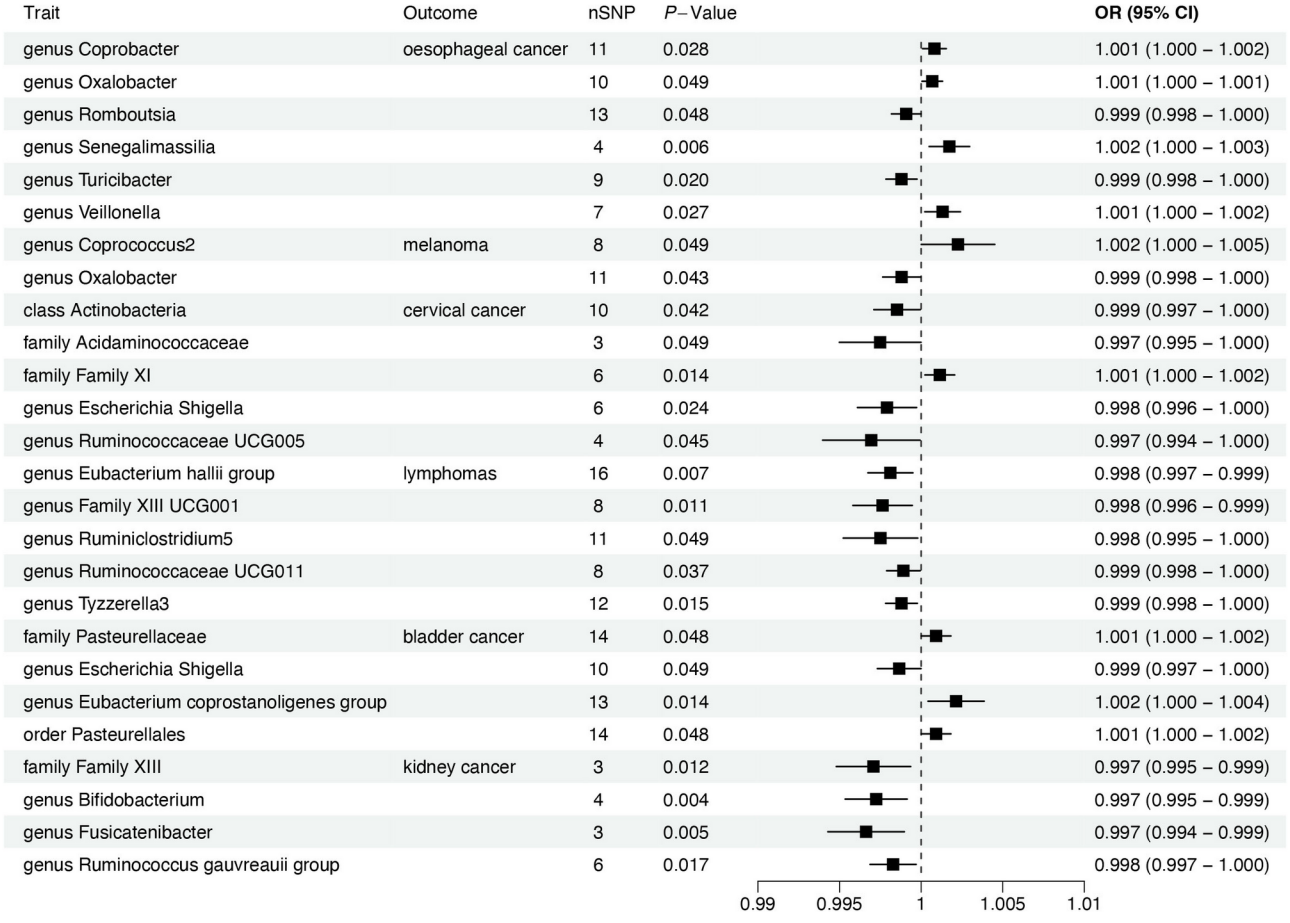

Fig. 4 MR results of gut microbiota and oesophageal, melanoma, cervical, lymphomas, bladder, kidney cancer

(OR = 0.999, 95% CI = 0.998-1.000, $P = 0.020$) were found to significantly decrease the risk.

Breast cancer

Analysis identified six gut microbiota with associations to breast cancer, as detailed in Table S2 and shown in Fig. 2. The family *Ruminococcaceae* (OR = 1.110, 95% CI = 1.007–1.223, $P = 0.035$) and the genus *Sellimonas* (OR = 1.050, 95% CI = 1.010–1.092, $P = 0.027$) were found to increase the risk of breast cancer. In contrast, the genus *Adlercreutzia* (OR = 0.923, 95% CI = 0.866–0.984, $P = 0.021$), genus *Parabacteroides* (OR = 0.872, 95% CI = 0.789–0.964, $P = 0.015$), genus *Ruminiclostridium 6* (OR = 0.943, 95% CI = 0.891–0.999, $P = 0.046$), and genus *Ruminococcaceae UCG013* (OR = 0.923, 95% CI = 0.860–0.991, $P = 0.027$) were associated with a decreased risk.

Additionally, Fig. 3 indicates that elevated levels of the CD40 ligand receptor (OR = 1.040, 95% CI = 1.011–1.070, $P = 0.007$) significantly increased the incidence of breast cancer. Conversely, lower levels of C-C motif chemokine 20 (CCL20) (OR = 0.938, 95% CI = 0.894–0.984, $P = 0.009$), FGF19 (OR = 0.926, 95% CI = 0.879–0.975, $P = 0.01$), and IL22 receptor alpha 1 (IL22Rα1) (OR = 0.932, 95% CI = 0.877–0.991, $P = 0.047$) were associated with a reduced incidence of breast cancer (Table S3).

Lung cancer

Our analysis identified six gut microbiota linked to lung cancer risk, as outlined in Table S2 and illustrated in Fig. 2. The genus *Coprococcus3* (OR = 1.373, 95% CI = 1.032–1.828, $P = 0.030$), genus *Holdemanella* (OR = 1.216, 95% CI = 1.060–1.396, $P = 0.011$), and genus *Peptococcus* (OR = 1.153, 95% CI = 1.024–1.299, $P = 0.019$) were found to increase the risk of lung cancer. Conversely, the family *Bifidobacteriaceae* (OR = 0.813, 95% CI = 0.679–0.974, $P = 0.025$) and genus *Collinsella* (OR = 0.782, 95% CI = 0.629–0.971, $P = 0.026$) were associated with a decreased incidence of lung cancer.

Figure 3 reveals that elevated levels of Interleukin-20 (IL-20) (OR = 1.319, 95% CI = 1.072–1.624, $P = 0.009$) and Interleukin-8 (IL-8) (OR = 1.215, 95% CI = 1.038–1.421, $P = 0.015$) significantly raised the risk of lung cancer. In contrast, lower levels of T-cell surface glycoprotein CD5 (OR = 0.754, 95% CI = 0.661–0.860, $P < 0.001$), Fibroblast growth factor 21 (FGF21) (OR = 0.852, 95% CI = 0.730–0.994, $P = 0.042$), Interleukin-18 (IL-18) (OR = 0.812, 95% CI = 0.720–0.917, $P = 0.001$), and Sulfotransferase 1A1 (SULT1A1) (OR = 0.891, 95% CI = 0.797–0.996, $P = 0.042$) significantly reduced the incidence of lung cancer (Table S3).

Prostate cancer

Our analysis revealed eleven gut microbiota associated with prostate cancer risk, as detailed in Table S2 and illustrated in Fig. 2. The family *Porphyromonadaceae* (OR = 1.147, 95% CI = 1.017–1.294, $P = 0.026$), genus *Christensenellaceae R-7 group* (OR = 1.125, 95% CI = 1.018–1.244, $P = 0.021$), genus *Dorea* (OR = 1.115, 95% CI = 1.009–1.231, $P = 0.032$), genus *Eubacterium fissicatena group* (OR = 1.076, 95% CI = 1.001–1.156, $P = 0.046$), and genus *Eubacterium nodatum group* (OR = 1.060, 95% CI = 1.015–1.108, $P = 0.009$) were found to significantly increase the risk of prostate cancer. Conversely, the class *Alphaproteobacteria* (OR = 0.836, 95% CI = 0.751–0.931, $P = 0.001$), genus *Adlercreutzia* (OR = 0.890, 95% CI = 0.820–0.966, $P = 0.016$), genus *Parasutterella* (OR = 0.908, 95% CI = 0.826–0.998, $P = 0.046$), genus *Roseburia* (OR = 0.888, 95% CI = 0.801–0.985, $P = 0.048$), genus *Veillonella* (OR = 0.917, 95% CI = 0.840-1.000, $P = 0.050$), and order *Rhodospirillales* (OR = 0.911, 95% CI = 0.853–0.974, $P = 0.006$) were associated with a decreased risk.

Figure 3 indicates that elevated levels of Beta-nerve growth factor (β-NGF) (OR = 1.074, 95% CI = 1.002–1.151, $P = 0.045$), C-C motif chemokine 23 (CCL23) (OR = 1.048, 95% CI = 1.009–1.088, $P = 0.031$), Fibroblast growth factor 23 (FGF23) (OR = 1.085, 95% CI = 1.006–1.171, $P = 0.034$), and GDNF (OR = 1.068, 95% CI = 1.014–1.123, $P = 0.036$) significantly increased the risk of prostate cancer. Meanwhile, l Interleukin-10 receptor subunit beta (IL-10Rβ) (OR = 0.949, 95% CI = 0.919–0.981, $P = 0.002$) was linked to a decreased risk (Table S3).

Ovarian cancer

Analysis presented in Fig. 2 indicates that the genus *Victivallis* (OR = 1.096, 95% CI = 1.005–1.195, $P = 0.039$) was significantly associated with an increased risk of ovarian cancer. Conversely, the genus *Family XIII 3011 group* (OR = 0.826, 95% CI = 0.720–0.948, $P = 0.013$) was found to decrease the risk significantly.

Further findings shown in Fig. 3 reveal that elevated levels of Interferon gamma (INF-γ) (OR = 1.148, 95% CI = 1.002–1.314, $P = 0.047$) also significantly raised the risk of ovarian cancer, as detailed in Table S3.

Basal cell cancer

As illustrated in Fig. 2, our analysis identified several gut microbiota associated with basal cell cancer risk. The genus *Family XIII AD3011 group* (OR = 1.190, 95% CI = 1.059–1.338, $P = 0.014$), genus *Intestinimonas* (OR = 1.090, 95% CI = 1.005–1.182, $P = 0.037$), and genus *Parabacteroides* (OR = 1.194, 95% CI = 1.023–1.393, $P = 0.025$) were found to significantly increase the risk. In contrast, the genus *Holdemanella* (OR = 0.910, 95% CI = 0.830–0.998, $P = 0.046$) and *Ruminococcaceae UCG014* (OR = 0.887, 95% CI = 0.792–0.994, $P = 0.038$) were associated with a reduced risk.

Figure 3 reports that elevated levels of Tumor necrosis factor ligand superfamily member 12 (TNFSF12) (OR = 1.072, 95% CI = 1.005–1.143, $P = 0.036$) significantly increased the risk of basal cell cancer. Conversely, lower levels of CCL4 (OR = 0.930, 95% CI = 0.891–0.970, $P = 0.002$), NKR2B4 (OR = 0.916, 95% CI = 0.860–0.975, $P = 0.009$), and urokinase-type plasminogen activator (OR = 0.928, 95% CI = 0.864–0.996, $P = 0.038$) were linked to a decreased risk of basal cell cancer, as detailed in Table S3.

Endometrial cancer

Analysis depicted in Fig. 2 reveals that genus *Butyrivibrio* (OR = 1.083, 95% CI = 1.009–1.163, $P = 0.028$) was associated with an increased risk of endometrial cancer. Conversely, the genus *Turicibacter* (OR = 0.843, 95% CI = 0.735–0.966, $P = 0.014$) was linked to a decreased risk.

Further findings from Fig. 3 indicate that elevated levels of TNF-related activation-induced cytokine (TRANCE) (OR = 1.078, 95% CI = 1.003–1.591, $P = 0.041$) significantly increased the risk of endometrial cancer. On the other hand, Matrix metalloproteinase-10 (MMP10) (OR = 0.852, 95% CI = 0.796–0.913, $P < 0.001$), and Tumor necrosis factor ligand superfamily member 12 (TNFLSF12) (OR = 0.906, 95% CI = 0.832–0.986, $P = 0.045$) significantly decreased the risk, as detailed in Table S3.

Melanoma

According to Fig. 4, the genus *Coprococcus2* (OR = 1.002, 95% CI = 1.000-1.005, $P = 0.049$) was found to significantly increase the risk of melanoma. Conversely, the genus *Oxalobacter* (OR = 0.999, 95% CI = 0.998-1.000, $P = 0.043$) was associated with a decreased risk (Table S4).

Further insights from Fig. 3 indicate that elevated levels of M-CSF1 (OR = 1.002, 95% CI = 1.001–1.003, $P = 0.009$) significantly increased the risk of melanoma. In contrast, lower levels of Caspase 8 (OR = 0.998, 95% CI = 0.996-1.000, $P = 0.030$) and Tumor necrosis factor receptor superfamily member 9 (TNFRSF9) (OR = 0.999, 95% CI = 0.998-1.000, $P = 0.040$) significantly reduced the risk, as detailed in Table S3.

Cervical cancer

Figure 4 shows that family *Family XI* (OR = 1.001, 95%CI = 1.000-1.002, $P = 0.014$) significantly increased the risk of cervical cancer. Class *Actinobacteria* (OR = 0.999, 95%CI = 0.997-1.000, $P = 0.042$), family *Acidaminococcaceae* (OR = 0.997, 95%CI = 0.995-1.000, $P = 0.049$), genus *Escherichia Shigella* (OR = 0.998, 95%CI = 0.996-1.000, $P = 0.024$), genus *Ruminococcaceae UCG005* (OR = 0.997, 95%CI = 0.994-1.000, $P = 0.045$) significantly decreased the risk of cervical cancer (Table S4).

Figure 3 shows that artemin levels (OR = 1.002, 95%CI = 1.001–1.004, $P = 0.017$) and.

C-C motif chemokine 28 levels (CCL28) (OR = 1.002, 95%CI = 1.001–1.004, $P = 0.007$) significantly decreased the risk of cervical cancer (Table S3).

Lymphomas

Figure 4 reveals that several genus were linked to a decreased risk: *Eubacterium hallii group* (OR = 0.998, 95% CI = 0.997–0.999, $P = 0.007$), *Family XIII UCG001* (OR = 0.998, 95% CI = 0.996–0.999, $P = 0.011$), *Ruminiclostridium5* (OR = 0.998, 95% CI = 0.995-1.000, $P = 0.049$), *Ruminococcaceae UCG011* (OR = 0.999, 95% CI = 0.998-1.000, $P = 0.037$), and *Tyzzerella3* (OR = 0.999, 95% CI = 0.998-1.000, $P = 0.015$) (Table S4).

Additional findings from Fig. 3 indicate that lower levels of Axin-1 (OR = 0.998, 95% CI = 0.996-1.000, $P = 0.015$) and the CD40 ligand receptor (CD40L) (OR = 0.999, 95% CI = 0.998-1.000, $P = 0.005$) also significantly reduced the risk of lymphomas, as detailed in Table S3.

Bladder cancer

Figure 4 identifies multiple microbial groups associated with bladder cancer risk. Specifically, the family *Pasteurellaceae* (OR = 1.001, 95% CI = 1.000-1.002, $P = 0.048$), the genus *Eubacterium coprostanoligenes group* (OR = 1.002, 95% CI = 1.000-1.004, $P = 0.014$), and the order *Pasteurellales* (OR = 1.001, 95% CI = 1.000-1.002, $P = 0.048$) were found to significantly increase the risk of bladder cancer. Conversely, the genus *Escherichia Shigella* (OR = 0.999, 95% CI = 0.997-1.000, $P = 0.049$) was associated with a decreased risk (Table S4).

Additionally, Fig. 3 indicates that increased levels of several biomarkers also significantly raised the risk of bladder cancer. These include GDNF (OR = 1.001, 95% CI = 1.000-1.002, $P = 0.035$), Interleukin-2 receptor subunit beta (IL-2Rβ) (OR = 1.002, 95% CI = 1.001–1.003, $P < 0.001$), Neurotrophin-3 (OR = 1.001, 95% CI = 1.000-1.002, $P = 0.029$), Oncostatin-M (OR = 1.001, 95% CI = 1.000-1.002, $P = 0.021$), and Programmed cell death 1 ligand 1 (OR = 1.001, 95% CI = 1.000-1.003, $P = 0.011$), as detailed in Table S3.

Kidney cancer

Figure 4 highlights several gut microbiota associated with a reduced risk of kidney cancer. Specifically, the family *Family XIII* (OR = 0.997, 95% CI = 0.995–0.999, $P = 0.012$), and the genus *Bifidobacterium* (OR = 0.997, 95% CI = 0.995–0.999, $P = 0.004$), *Fusicatenibacter* (OR = 0.997, 95% CI = 0.994–0.999, $P = 0.005$), and *Ruminococcus gauvreauii group* (OR = 0.998, 95% CI = 0.997-1.000, $P = 0.017$) were found to significantly decrease the risk of developing kidney cancer (Table S4).

Figure 3 indicate that higher levels of CD40L receptor (OR = 1.002, 95% CI = 1.001–1.004, *P* = 0.009) significantly increased the risk of kidney cancer, as detailed in Table S3.

Thyroid cancer

Figure 2 indicates that several gut microbiota were linked with an increased risk of thyroid cancer. The genus *Actinomyces* (OR = 1.550, 95% CI = 1.017–2.361, *P* = 0.042), *Methanobrevibacter* (OR = 1.485, 95% CI = 1.035–2.132, *P* = 0.032), *Ruminococcus2* (OR = 1.833, 95% CI = 1.252–2.683, *P* = 0.002), and *Subdoligranulum* (OR = 1.883, 95% CI = 1.130–3.138, *P* = 0.015) all significantly raised the risk. In contrast, the class *Betaproteobacteria* (OR = 0.499, 95% CI = 0.288–0.864, *P* = 0.013), family *Family XI* (OR = 0.756, 95% CI = 0.579–0.987, *P* = 0.040), and genus *Sutterella* (OR = 0.602, 95% CI = 0.384–0.943, *P* = 0.027) significantly lowered the risk.

Figure 3 shows that certain biomarkers significantly influenced the risk of thyroid cancer. Elevated levels of Hepatocyte growth factor (HGF) (OR = 1.485, 95% CI = 1.017–2.168, *P* = 0.040), Leukemia inhibitory factor receptor (LIFR) (OR = 1.319, 95% CI = 1.021–1.705, *P* = 0.045), Monocyte chemoattractant protein-1 (MCP-1) (OR = 1.234, 95% CI = 1.002–1.522, *P* = 0.048), and Tumor necrosis factor ligand superfamily member 14 (TNFLSM14) (OR = 1.403, 95% CI = 1.109–1.775, *P* = 0.009) increased the risk. Conversely, lower levels of C-C motif chemokine 19 (CCL19) (OR = 0.711, 95% CI = 0.570–0.887, *P* = 0.005), FGF19 (OR = 0.754, 95% CI = 0.573–0.994, *P* = 0.045), and TNFRSM9 (OR = 0.762, 95% CI = 0.595–0.976, *P* = 0.031) decreased the risk, as detailed in Table S3.

Mesothelioma

Figure 2 demonstrates significant associations between various gut microbiota and the risk of mesothelioma. The family *Peptostreptococcaceae* (OR = 8.569, 95% CI = 2.342–31.359, *P* = 0.001), and the genus *Oscillospira* (OR = 3.734, 95% CI = 1.041–13.399, *P* = 0.043), *Ruminococcaceae UCG005* (OR = 3.547, 95% CI = 1.179–10.669, *P* = 0.049), and *Streptococcus* (OR = 5.181, 95% CI = 1.326–20.241, *P* = 0.018) were found to significantly increase the risk. Conversely, the class *Mollicutes* (OR = 0.236, 95% CI = 0.078–0.710, *P* = 0.020), family *Clostridiaceae1* (OR = 0.266, 95% CI = 0.071–0.999, *P* = 0.050), genus *Anaerofilum* (OR = 0.410, 95% CI = 0.184–0.914, *P* = 0.044) and phylum *Tenericutes* (OR = 0.236, 95% CI = 0.078–0.710, *P* = 0.020) significantly decreased the risk.

Figure 3 highlights the elevated levels of C-C motif chemokine 4 (CCL4) (OR = 1.660, 95% CI = 1.075–2.566, *P* = 0.034) and TNFLSM14 (OR = 2.110, 95% CI = 1.013–4.396, *P* = 0.046) significantly increased the risk of mesothelioma. In contrast, lower levels of cystatin D (OR = 0.559, 95% CI = 0.333–0.937, *P* = 0.027) were associated with a decreased risk, as detailed in Table S3.

Mediation analysis of gut microbiota, inflammatory protein, and cancer

This study evaluated the causal effects of gut microbiota and inflammatory proteins on cancer, emphasizing their mediating roles in cancer pathways. We established causal associations with six gut microbiota and six inflammatory proteins for lung cancer, and eight gut microbiota and three inflammatory proteins for mesothelioma, as detailed in Figs. 2, 3 and 4 and Table S2,S3,S4.

Specifically, a mediation MR analysis was conducted to explore the pathway from the genus *Collinsella* to lung cancer *via* T-cell surface glycoprotein CD5. The mediation effect of genus *Collinsella* on lung cancer, accounting for T-cell surface glycoprotein CD5, was β = 0.041 (95% CI = 0.007 to 0.068). The mediation analysis revealed that T-cell surface glycoprotein CD5 accounted for approximately 16.667% of the effect (*P* = 8.61E-05) (Fig. 5; Table 1). No reverse causation was observed between genus *Collinsella*, T-cell surface glycoprotein CD5, and lung cancer (Table S5 and S6). The MR-PRESSO analysis did not indicate any heterogeneity, horizontal pleiotropy (Table S7-S12).

Similarly, the mediation effect of genus *Ruminococcaceae UCG005* on mesothelioma *via* CCL4 was β = 0.065 (95% CI = 0.001–0.151), with CCL4 mediating 5.134% of the effect (*P* = 0.000346121) (Fig. 5; Table 2). There was no reverse causation found between genus *Ruminococcaceae UCG005*, CCL4, and mesothelioma (Table S5 and S6). The MR-PRESSO analysis did not indicate any heterogeneity, horizontal pleiotropy (Table S7-12).

Discussion

The human gut, a complex network populated by trillions of microorganisms including bacteria, archaea, fungi, protists, and viruses-with bacteria being predominant-has been the focus of extensive research [35]. For decades, scientists have sought to unravel the intricate connections between human microbiota and various diseases. There is growing evidence suggesting that gut microbiota may influence a range of cancers, potentially paving the way for novel cancer therapies that target the gut microbiota [36, 37]. Nonetheless, the diversity of cancer types and the complexity of the gut microbiota pose significant challenges in summarizing their impact on cancer through observational studies alone. In this study, we employed MR to investigate the potential causal relationships between gut microbiota and cancer. Our analysis across eighteen cancer types revealed that specific gut microbiotas could act as either risk factors or protective agents, depending on the cancer in question.

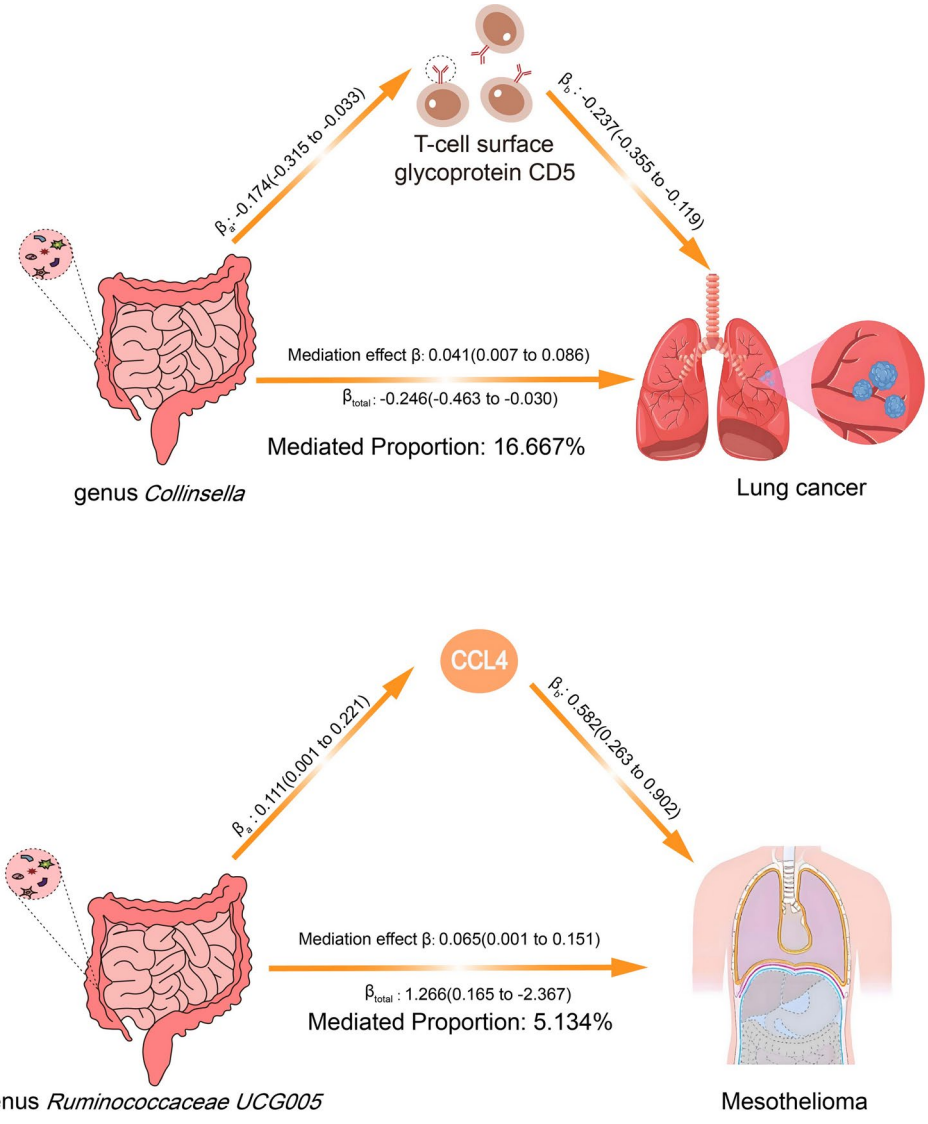

Fig. 5 An overview chart of mediation analysis. A: Genus *Collinsella* decreased the risk of lung cancer by decreasing levels of T-cell surface glycoprotein CD5. B: Genus *Ruminococcaceae UCG005* increased the risk of mesothelioma by increasing levels of CCL4

Table 1 The mediation effect of genus *Collinsella* on lung cancer *via* T-cell surface glycoprotein CD5

Mediator	Total effect β (95%CI)	Direct effect a β(95%CI)	Direct effect b β(95%CI)	Mediation effect β (95%CI)	Mediated Proportion (%)
T-cell surface glycoprotein CD5	-0.246(-0.463 to -0.030)	-0.174(-0.315 to -0.033)	-0.237(-0.355 to -0.119)	0.041 (0.007 to 0.086)	16.667

'Total effect' indicates the effect of genus *Collinsella* on lung cancer, 'direct effect a' indicates the effect of genus *Collinsella* on T-cell surface glycoprotein CD5, 'direct effect b' indicates the effect of T-cell surface glycoprotein CD5 on lung cancer and 'mediation effect' indicates the effect of genus *Collinsella* on lung cancer through T-cell surface glycoprotein CD5. Total effect, direct effect a and b were analyzed by IVW; mediation effect was analyzed by delta method

Table 2 The mediation effect of genus *Ruminococcaceae UCG005* on mesothelioma *via* CCL4

Mediator	Total effect β (95%CI)	Direct effect a β(95%CI)	Direct effect b β(95%CI)	Mediation effect β (95%CI)	Mediated Proportion (%)
CCL4	1.266(0.165 to -2.367)	0.111(0.001 to 0.221)	0.582(0.263 to 0.902)	0.065(0.001 to 0.151)	5.134

'Total effect' indicates the effect of genus *Ruminococcaceae UCG005* on mesothelioma, 'direct effect a' indicates the effect of genus *Ruminococcaceae UCG005* on CCL4, 'direct effect b' indicates the effect of CCL4 on mesothelioma and 'mediation effect' indicates the effect of genus *Ruminococcaceae UCG005* on mesothelioma through CCL4. Total effect, direct effect a and b were analyzed by IVW; mediation effect was analyzed by delta method

Research has demonstrated that high abundance of the genus *Ruminococcus gnavus group* [38] and the phylum *Verrucomicrobia* [39] are linked to elevated inflammation levels, suggesting a mechanism through which they may increase liver cancer risk. Conversely, the family *Rhodospirillaceae* was associated with a decreased risk of liver cancer. In CRC, the genus *Bilophila* has been associated with a reduced risk of the disease. Previous studies have suggested that *Bilophila* modulates CRC risk through the production of hydrogen sulfide (H_2S) [40]. Interestingly, some research indicates that H_2S can protect and even restore the disrupted mucus layer, potentially preventing inflammation [41, 42]. This effect has been confirmed in studies involving novel non-steroidal anti-inflammatory drugs (NSAIDs) that release H_2S [43]. H_2S-releasing compounds have demonstrated significant anticancer effects, including the inhibition of CRC cell proliferation and the induction of apoptosis. However, the underlying mechanisms remain unclear, with some evidence suggesting that H_2S may act by inhibiting nuclear factor-κB (NF-κB) signaling and increasing intracellular Ca^{2+} levels, leading to cell cycle arrest [44, 45]. Despite these findings, the role of H_2S in CRC remains controversial, and further investigation into its mechanistic pathways is needed.

Studies from Korea have identified *Prevotella* as a causative agent of gastric cancer, while *Lactococcus lactis* appears to protect against it [46]. Our analysis also found that a genetically higher abundance of the genus *Sellimonas* correlates with increased breast cancer risk, highlighting a need for further research into its underlying mechanisms and potential pathways to cancer. Similarly, shifts in gut microbiota composition have been observed in patients with breast [47] and lung cancers compared to controls, indicating a possible microbial influence on cancer development [48]. In lung cancer, the presence of family *Bifidobacteriaceae*, genus *Clostridium sensustricto1*, genus *Collinsella*, genus *Ruminiclostridium6*, and order *Bifidobacteriales* is associated with decreased incidence, supporting potential protective roles. Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) are widely used in the treatment of lung cancer. Studies have indicated that the genus *Collinsella* plays a role in modulating the response to ICIs in lung cancer [49]. Regarding prostate cancer, extracts from *Alphaproteobacteria* have been found to mitigate risks linked with benign prostate hyperplasia [50], and their anti-invasion properties further substantiate their protective potential against cancer [51]. However, the precise relationship between *Alphaproteobacteria* and prostate cancer remains to be fully elucidated [52]. For ovarian cancer, the genus *Victivallis*, a Gram-negative anaerobe isolated from human feces [53], is linked with a reduced cancer incidence [54]. Additionally, the abundance of Family XI correlates with hepatovisceral fat [55], a risk factor for basal cell cancer, while *Turicibacter* may confer protective effects against endometrial cancer by influencing host bile acid and lipid metabolism genes [56].

Our MR analysis identified the genus *Eubacterium coprostanoligenes group* as a risk factor for bladder cancer, while genus *Fusicatenibacter* emerged as a protective factor for kidney cancer. This supports the concept that a healthy gut microbiota not only benefits immune system activity but also maintains thyroid function. Indeed, our study found that genus *Actinomyces*, genus *Methanobrevibacter*, genus *Ruminococcus2*, and genus *Subdoligranulum* increase the risk of thyroid cancer. Although the associations between mesothelioma and microbiota are less explored, our analysis suggests that family *Peptostreptococcaceae*, genus *Oscillospira*, genus *Ruminococcaceae UCG005*, and genus *Streptococcus* may increase mesothelioma risk. Conversely, class *Mollicutes*, family *Clostridiaceae1*, genus *Anaerofilum*, and phylum *Tenericutes* appear to exert protective effects. While genus *Ruminococcaceae UCG005* is identified as a potential biomarker for colorectal adenomas [57], its role in mesothelioma has not been previously reported. Our study finds that genus *Ruminococcaceae UCG005* may increase mesothelioma risk through the modulation of CCL4.

Overall, this study contributes to understanding the complex interactions between gut microbiota and disease, particularly in how certain microbes may influence the risk of various cancers. The role of inflammatory proteins as potential mediators between gut microbiota and cancer development remains an area ripe for further investigation.

Our MR analysis revealed significant associations between inflammatory proteins and cancer risk. Specifically, IL-20 and IL-8 were found to increase the risk of lung cancer, whereas T-cell surface glycoprotein CD5, FGF21, IL-18, and SULT1A1 appeared to decrease it. Notably, T-cell surface glycoprotein CD5, recognized as a prognostic marker in lung cancer [58], may mediate the influence of the gut microbiota on the immune system. We observed an indirect effect of genus *Collinsella* on lung cancer *via* T-cell surface glycoprotein CD5. Similarly, genus *Ruminococcaceae UCG005* impacted mesothelioma through its effect on CCL4. CCL4, also known as macrophage inflammatory protein, plays a crucial role in the CC chemokine family. Its interaction with CCR5 and its role as a suppressive factor for HIV, secreted by $CD8^+$ T-cells [59], are well documented. Furthermore, CCL4's activation of PI3K [59] may explain its role in promoting the proliferation of mesothelial cells [60, 61], shedding light on its potential contribution to mesothelioma pathogenesis.

While this study utilizes MR to explore causal relationships between gut microbiota, inflammatory proteins,

and various types of cancer. However, there are several limitations. Firstly, potential breaches of the independence and exclusion restriction assumptions, particularly with regard to pleiotropy, cannot be entirely dismissed [62].

Secondly, as the GWAS data used in this study is predominantly derived from European populations, the generalizability of the findings to other ethnic groups may be limited. Future research should incorporate independent datasets from diverse populations and research settings to validate the robustness and broader applicability of the observed causal relationships. Furthermore, the incomplete data collection impedes further statistical adjustments for confounders, a prevalent issue in MR studies. Thirdly, this study employs 16 S rRNA sequencing for gut microbiota GWASs, which, due to its lower taxonomic resolution compared to shotgun metagenomics and the complex nature of gut microbiota, may affect the reliability of causal inferences. In the future, we will further design clinical studies to investigate the mechanism of T-cell surface glycoprotein CD5 and CCL4 as mediators linking the genus *Collinsella* with lung cancer and the genus *Ruminococcaceae UCG005* with mesothelioma (Fig. 5).

Conclusion

In this study, we comprehensively explored the causal effects between gut microbiota, inflammatory proteins, and cancer. There were 42 positive and 49 inverse causal effects between genetic liability in the gut microbiota and cancer. There were 32 positive correlations and 28 inverse causal effects between inflammatory proteins and cancer. In addition, inflammatory proteins seemed to act as a mediating factor in the pathway from gut microbiota to lung cancer and mesothelioma.

Abbreviations

MR	Mendelian randomization
GWAS	Genome-wide association studies
IVW	Inverse variance weighting
SNPs	Single nucleotide polymorphisms
IVs	Instrumental variables
LD	Linkage disequilibrium
FGF19	Fibroblast Growth Factor 19
IL-17 A	Interleukin-17A
CRC	Colorectal cancer
OPG	Osteoprotegerin
GDNF	Glial Cell-Derived Neurotrophic Factor
CCL4	C-C Motif Chemokine 4
IL20RA	Interleukin-20 Receptor Subunit Alpha
NKR2B4	Natural Killer Cell Receptor 2B4
CCL19	C-C motif chemokine 19
Flt-3 L	Fms-related tyrosine kinase 3 ligand
CCL20	C-C motif chemokine 20
IL22Rα1	IL22 receptor alpha 1
IL-20	Interleukin-20
IL-8	Interleukin-8
FGF21	Fibroblast growth factor 21
IL-18	Interleukin-18
SULT1A1	Sulfotransferase 1A1
β-NGF	Beta-nerve growth factor
CCL23	C-C motif chemokine 23
FGF23	Fibroblast growth factor 23
M-CSF	Macrophage colony-stimulating factor 1
IL-10Rβ	Interleukin-10 receptor subunit beta
M-CSF1	Macrophage colony-stimulating factor 1
TNFSF12	Tumor necrosis factor ligand superfamily member 12
TRANCE	TNF-related activation-induced cytokine
MMP10	Matrix metalloproteinase-10
TNFLSF12	Tumor necrosis factor ligand superfamily member 12
TNFRSF9	Tumor necrosis factor receptor superfamily member 9
CCL28	C-C motif chemokine 28 levels
CD40L	CD40 ligand receptor
IL-2Rβ	Interleukin-2 receptor subunit beta
HGF	Hepatocyte growth factor
LIFR	Leukemia inhibitory factor receptor
TNFLSM14	Tumor necrosis factor ligand superfamily member 14
CCL19	C-C motif chemokine 19
INF-γ	Interferon gamma
CCL4	C-C motif chemokine 4

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03822-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

Supplementary Material 12

Supplementary Material 13

Acknowledgements

Not applicable.

Author contributions

The study was conceptualized and designed by Cantu Fang, in collaboration with Huanhuan Luo and Yanli He, who also oversaw the research. Yao Wang and Wanli Liu were responsible for data collection, organization, and analysis. Liwen Liu made significant contributions to the creation of figures, which enhanced both the analytical depth and visual clarity of the manuscript. The initial draft was authored by Yao Wang, with Wanli Liu providing critical reviews. Yao Wang get the fundings.

Funding

National Natural Science Foundation of China (82405214), Postdoctoral Fellowship Program of CPSF (GZC20240344), China Postdoctoral Science Foundation (2024M760668), National Demonstration Pilot Project for the Inheritance and Development of Traditional Chinese Medicine -Construction project between Guangzhou University of Chinese Medicine and Zhongshan Hospital of Traditional Chinese Medicine (GZYZS2024U02), National Demonstration Pilot Project for the Inheritance and Innovative Development of Traditional Chinese Medicine (YN2024B001), Guangdong Provincial Bureau of Traditional Chinese Medicine (20251434).

Data availability
The datasets analysed during the current study are available in the MiBioGen(www.mibiogen.org), EBI GWAS Catalog(https://www.ebi.ac.uk/gwas/) and IEU OpenGWAS (https://gwas.mrcieu.ac.uk/).

Declarations

Ethics approval and consent to participate
Not applicable. All data sets used in this study are publicly accessible and were obtained from research that had already received patient consent and ethical approval. Therefore, no further ethical approval or informed consent was required for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 19 December 2024 / Accepted: 15 April 2025
Published online: 26 April 2025

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