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Original Article

Gut microbiome associated with PARP inhibitor efficacy in patients with ovarian cancer

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ABSTRACT

Objective: To investigate an association between the gut microbiome and efficacy of poly(ADP-ribose) polymerase inhibitors (PARPi) in ovarian cancer.
Methods: This study conducted fecal microbiome analysis (16S rRNA gene sequencing) and circulating tumor DNA (ctDNA) profiling for ovarian cancer patients who underwent PARPi maintenance therapy. Fecal and blood samples were collected at the baseline and the progressive disease (PD) or last follow-up. The relative abundance of gut microbes and progression-free survival (PFS) were analyzed using linear discriminant analysis of effect size and the Cox proportional hazard model according to *BRCA1/2* mutation (*BRCA1/2*mut) status detected by ctDNA sequencing.

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Conflict of Interest

Mika Okazawa-Sakai declares no competing interests. Shunsuke A. Sakai declares no competing interests. Ichinosuke Hyodo reports advisory roles for Asahi-Kasei, Ono, Taiho, Chugai, and Eisai Pharmaceutical Companies. Satoshi Horasawa declares no competing interests. Kentaro Sawada declares no competing interests. Takao Fujisawa reports honoraria from Amelieff Co. Ltd. Yasuko Yamamoto declares no competing interests. Shogen Boku reports

Results: Baseline samples were available from 23 *BRCA1/2*mut-positive patients and 33 *BRCA1/2*mut-negative patients. The microbes enriched in the baseline samples with long PFS were *Bifidobacterium*, *Roseburia*, *Dialister*, *Butyricicoccus*, and *Bilophila* for *BRCA1/2*mut-positive patients and *Phascolarctobacterium* for *BRCA1/2*mut-negative patients. In multivariate analyses dividing patients by the median values of relative abundances, no bacteria were associated with PFS in *BRCA1/2*mut-positive patients, whereas high *Phascolarctobacterium* abundances (≥1.11%) was significantly associated with longer PFS in *BRCA1/2*mut-negative patients (median 14.0 vs. 5.9 months, hazard ratio=0.28; 95% confidence interval=0.11–0.69; p=0.014). In the last samples, the relative abundances of *Phascolarctobacterium* were significantly higher in patients without PD (n=5) than those with PD (n=15) (median 1.25% vs. 0.06%; p=0.016).
Conclusion: High fecal composition of *Phascolarctobacterium* was associated with prolonged PFS in patients with *BRCA1/2*mut-negative ovarian cancer receiving PARPi therapy. Our results would provide new insights for future research.

Keywords: Gut Microbiome; Circulating Tumor DNA; Ovarian Cancer; PARP Inhibitor; Maintenance; Progression-Free Survival

Synopsis

Fecal bacterial composition was analyzed in 56 patients with ovarian cancer treated with poly(ADP-ribose) polymerase inhibitors. *BRCA1/2* mutations (*BRCA1/2*mut) were detected in 23 patients by circulating tumor DNA analysis. No bacteria relevant to progression-free survival (PFS) was found in *BRCA1/2*mut-positive patients. High composition of *Phascolarctobacterium* was associated with longer PFS in *BRCA1/2*mut-negative patients.

INTRODUCTION

Ovarian cancer is the deadliest gynecological cancer [1]. Approximately a half of ovarian cancers have DNA homologous recombination deficiency (HRD), commonly caused by mutations in *BRCA1/2* [1]. Poly(ADP-ribose) polymerase inhibitors (PARPi) target HRD tumors via a synthetic lethal approach [2]. PARPi was developed as a maintenance therapy for patients who responded to platinum-based chemotherapy and showed remarkable improvement in progression-free survival (PFS) in ovarian cancer [1,2]. However, short-term responders are often observed especially in patients without *BRCA1/2* mutations (*BRCA1/2*mut), and even long-term responders acquire resistance to PARPi [2]. Resistance mechanisms are not fully understood [2]. Recent studies have revealed another mechanism of action for PARPi: an induction of antitumor immune cell responses via the activation of DNA-sensing type I interferon pathway [3].

The gut microbiome promotes host immune responses by interacting with immunocompetent cells using microbiota-derived metabolites such as short-chain fatty acids (SCFAs), and influences cancer treatment efficacy across various cancers [4]. Previous studies have suggested that commensal microbiomes might contribute to the etiology, disease severity, and treatment outcomes of ovarian cancer [5,6]. However, the gut microbiome profile implicated in PARPi efficacy remains unclear.

This study is a prospective observational multicenter study of patients enrolled in SCRUM-Japan MONSTAR-SCREEN, a nationwide plasma genomic and fecal microbiome profiling study involving 31 institutions in Japan [7]. Here, we report the landscape of the

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gut microbiome in patients with ovarian cancer and the distinct gut microbiome profile associated with PARPi efficacy using 16S rRNA gene sequencing and circulating tumor DNA (ctDNA) analyses.

MATERIALS AND METHODS

1. Study design and patients

We recruited patients with ovarian cancer from July 2019 to September 2021, who were age ≥20 years, received systemic chemotherapy for advanced disease, and provided written informed consent. We excluded patients who had no response to platinum-based chemotherapy, no PARPi therapy, and no baseline samples. All patients were followed up until the data cutoff. The data-cutoff date was June 2023. Patients with lost to follow-up, consent withdrawal, or missing data were removed from analysis.

Fecal and blood samples were collected at two points: 1) before or immediately after the start of PARPi treatment (baseline sample) and 2) at progressive disease (PD) or the last follow-up during the period from December 2021 to January 2022 (last sample).

Anonymized clinicopathological and genotyping data were collected using an electronic data-capture system. Nucleotide and amino acid sequences were referenced to the RefSeq Reference Sequence. Disease progression was assessed according to the Response Evaluation Criteria in Solid Tumors v1.1. More details are provided in the study protocol (**Method S1**).

This study was conducted in accordance with the Declaration of Helsinki and Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study protocol was approved by the Institutional Review Boards of the participating institutions and was registered in the University Hospital Medical Information Network (UMIN000036749).

2. Fecal microbiome analysis

Sample collection, DNA extraction, and 16S rRNA gene sequencing were performed as described previously [8]. After 16S rRNA gene sequencing, taxonomic annotation (FASTQ files) using QIIME2 (v2022.4) was performed [9]. Low-quality sequences in the FASTQ data were filtered, and the DADA2 algorithm [10] was used to correct errors in the sequences, followed by the generation of a read count table of amplicon sequence variants (ASVs). The reads were rarefied to 38807 reads, the minimum number of reads for all samples. Next, a phylogenetic analysis was conducted using the SILVA database (v138) [11] to obtain the number of reads through taxonomy. The microbial metadata in the database were added to the taxonomy in the following order: species, genus, order, class, and phylum. If it did not exist in the database, it was classified as 'unknown.' Unweighted UniFrac distance matrices were obtained using the QIIME2 command. A principal coordinate analysis (PCoA) was performed on the matrices. Alpha-diversity was calculated using the number of ASVs [8].

3. ctDNA genotyping

Next-generation sequencing analysis of ctDNA was performed using FoundationOne® Liquid CDx (Foundation Medicine, Boston, MA, USA), which targets 324 gene alterations as well as biomarkers such as microsatellite instability and blood tumor mutation burden [12].

Author Contributions

Conceptualization: O.M.; Data curation: O.M., S.S.A.; Formal analysis: O.M., S.S.A.; Funding acquisition: O.M.; Methodology: O.M., S.S.A.; Project administration: H.I., H.S., S.K., F.T., Y.Y., H.K., N.Y., Y.R.; Resources: B.S., H.Y., I.M., S.D., H.K., E.T., I.K., I.K., W.H., T.K., Y.H., K.K., C.T., Y.T., A.D.; Software: S.S.A.; Supervision: H.I., H.S., S.K., F.T., Y.Y., H.K., N.Y., Y.R.; Visualization: O.M., S.S.A.; Writing - original draft: O.M., S.S.A.; Writing - review & editing: H.I., H.S., S.K., F.T., Y.Y., B.S., H.Y., I.M., S.D., H.K., E.T., I.K., I.K., W.H., T.K., Y.H., K.K., C.T., H.K., N.Y., Y.R., Y.T., A.D.

4. Statistical analysis

For fecal microbiome analysis, patients were divided into long-term responders (LTR) and short-term responders (STR) according to the median PFS in patients with *BRCA1/2*mut detected by baseline ctDNA sequencing (*BRCA1/2*mut-positive) and in patients without the mutations (*BRCA1/2*mut-negative), respectively. The linear discriminant analysis (LDA) of effect size (LEfSe) was used to estimate the effect size of each differentially abundant feature with the threshold of an LDA score (log10) of ±2.0 [13]. Alpha diversity was compared between the 2 groups using the Mann–Whitney U test. Permutation multivariate analysis of variance was performed to test for beta diversity.

The clinicopathological factors relevant to gut bacterial composition were assessed using a binary logistic regression model. The magnitude of statistical significance was expressed as odds ratio (OR) and 95% confidence interval (CI). The clinicopathological factors included in the analyses were age, body mass index, history of lifestyle-related diseases, histology, and maintenance therapy setting, and medication use.

PFS was measured from the date of initiation of PARPi therapy to the date of PD or death. The PFS rate was estimated using the Kaplan–Meier method, and the difference in PFS between the two groups was analyzed using the log-rank test. Multivariate analysis of PFS was performed using the Cox proportional hazards model and hazard ratios (HRs) and 95% CI were calculated. Patients were classified into 2 groups with high and low relative abundances of gut microbes based on the median value in each of the *BRCA1/2*mut-positive and *BRCA1/2*mut-negative patients. The clinicopathological factors included in the analyses were age, histology, and maintenance therapy setting.

To compare the distribution of factors between 2 groups, Fisher's exact test for categorical variables and Mann–Whitney U test for continuous variables were used. A 2-sided p-value of <0.05 was set as significant in all analyses. Adjustment of multiple comparison was not applied because of the exploratory nature of the study. All statistical analyses other than fecal microbiome analyses were performed using EZR (Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) [14].

RESULTS

1. Patients

Among 110 patients with ovarian cancer enrolled in the MONSTAR-SCREEN study, 56 patients were included in the analyses (**Fig. 1A**). The clinical characteristics of the 56 patients are presented in **Table 1**. All patients were Japanese female with a median (interquartile range; IQR) age of 58 years (50, 66 years). The median (IQR) body mass index was 21 kg/m^2 (18, 24 kg/m^2), and approximately 20% of patients had a history of lifestyle-related diseases such as diabetes, hypertension, and hyperlipidemia. All patients underwent maintenance therapy with a PARPi after responding to platinum-based chemotherapy. Most patients (n=54) underwent PARPi monotherapy, and the remaining patients underwent combination of PARPi and bevacizumab (n=2). Only 4 patients had HRD test results for their tumors, and 2 were positive. Twelve patients (21.4%) received antibiotics prior to PARPi treatment and 3 (5.4%) during PARPi treatment. Information on medications other than antibiotics prior to PARPi treatment was collected through a patient questionnaire, and the answers were obtained from 39 of the 56 patients (69.6%). Of these, proton pump inhibitors were used in 3 (7.7%) and probiotics in 9 (23.1%).

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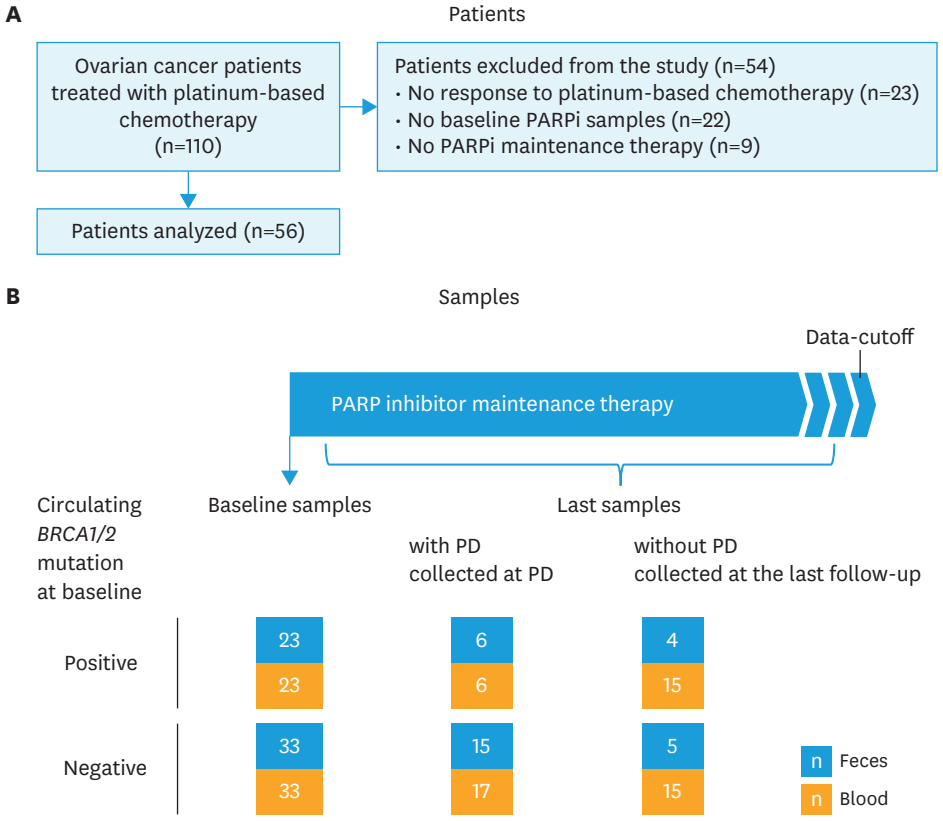

Fig. 1. Patients and samples. (A) Patients. Among 110 patients with ovarian cancer enrolled in the MONSTAR-SCREEN study, 56 patients who underwent PARPi maintenance therapy after the response to platinum-based chemotherapy and provided baseline blood and fecal samples were analyzed. (B) Samples. Baseline samples were collected before or immediately after the start of PARPi treatment. Last samples were collected at PD or the last follow-up during the period from December 2021 to January 2022.
PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease.

The median day from the start of PARPi treatment to baseline-sample submission was 0 (IQR, −3, +13) for fecal samples and 0 (IQR, −3, 0) for blood samples.

Thirty-four (60.7%) patients had PD at a median (IQR) follow-up of 28.4 (25.4, 32.4) months. Thirty fecal and 48 blood last samples were obtained (**Fig. 1B**).

2. ctDNA analysis

The most frequently detected gene at baseline was *TP53* (n=27, 48%), followed by *BRCA1* (n=15, 27%), *CHEK2* (n=9, 16%), *BRCA2* (n=8, 14%), and *ATM* (n=4, 7%). The median (IQR) variant allele fraction of *BRCA1/2*mut was 49.3% (48.4%–51.5%), suggesting a germline origin. The variant allele fraction of other genes was below 20%, except for one *RAD51C* mutation (48.8%).

In the baseline samples, *BRCA1/2*mut were not detected in 33 samples (59%), including three samples (5%) without valid results from ctDNA sequencing. Biomarkers of blood tumor mutation burden and microsatellite instability were low or unavailable in all 56 samples, probably because the tumor response to prior chemotherapy resulted in low plasma tumor fractions at the time of sample collection.

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Table 1. Baseline characteristics of patients

Characteristics	Overall (n=56)	*BRCA* mutation status		
		Negative (n=33)	Positive (n=23)	p-value*
Age (yr)	58 (50, 66)	60 (50, 70)	55 (50, 65)	0.193
Body mass index (kg/m²)†	21 (18, 24)	21 (19, 23)	21 (18, 24)	0.780
Lifestyle-related diseases				
No	44 (78.6)	28 (84.8)	16 (69.6)	
Yes	12 (21.4)	5 (15.2)	7 (30.4)	
Histology				0.383
High-grade serous carcinoma	47 (83.9)	26 (78.8)	21 (91.3)	
Endometrioid carcinoma	2 (3.6)	2 (6.1)	0 (0.0)	
Clear cell carcinoma	2 (3.6)	2 (6.1)	0 (0.0)	
Mucinous carcinoma	1 (1.8)	1 (3.0)	0 (0.0)	
Other	4 (7.1)	2 (6.1)	2 (8.7)	
Drug				0.416
Olaparib	52 (92.9)	29 (87.9)	23 (100.0)	
Niraparib	2 (3.6)	2 (6.1)	0 (0.0)	
Olaparib plus bevacizumab	2 (3.6)	2 (6.1)	0 (0.0)	
Maintenance therapy setting				0.229
First line chemotherapy	16 (28.6)	7 (21.2)	9 (39.1)	
Second or later line chemotherapy	40 (71.4)	26 (78.8)	14 (60.9)	
Antibiotic use prior to PARPi treatment†				0.742
No	42 (75.0)	25 (75.8)	17 (73.9)	
Yes	12 (21.4)	6 (18.2)	6 (26.1)	
Antibiotic use during PARPi treatment				0.067
No	53 (94.6)	33 (100.0)	20 (87.0)	
Yes	3 (5.4)	0 (0.0)	3 (13.0)	
Baseline sample submission (day)‡				
Feces	0 (−3, +13)	0 (−2, +13)	−1 (−4, +12)	0.894
Blood	0 (−3, 0)	0 (−3, 0)	0 (−5, 0)	0.590
Homologous recombination-related gene alterations in ctDNA				
ATM	4 (7.1)	2 (6.1)	2 (8.7)	1.000
BRCA1	15 (26.8)	0 (0.0)	15 (65.2)	-
BRCA2	8 (14.3)	0 (0.0)	8 (34.8)	-
CHEK2	9 (16.1)	7 (21.2)	2 (8.7)	0.282
PALB2	1 (1.8)	0 (0.0)	1 (4.3)	0.411
RAD51C	1 (1.8)	1 (3.0)	0 (0.0)	1.000

Values are presented as median (interquartile range) or number (%).
ctDNA, circulating tumor DNA; PARPi, poly(ADP-ribose) polymerase inhibitors.
*p-values were calculated using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables comparing the distribution of the factors between the 2 columns (patients without *BRCA1/2* mutations vs. patients with *BRCA1/2* mutations).
†Data on body mass index and antibiotic use prior to PARPi treatment was missing in two patients.
‡Based on the start date of PARPi.

Baseline clinical characteristics did not differ according to *BRCA1/2*mut status (**Table 1**). Other homologous recombination-related gene mutations (n=15) were found in ten *BRCA1/2*mut-negative patients. Ten *BRCA1/2*mut-positive patients (44%) and 24 *BRCA1/2*mut-negative patients (73%) had PD. The median PFS was unattained and 9.2 months in *BRCA1/2*mut-positive and *BRCA1/2*mut-negative patients, respectively (HR=0.35; 95% CI=0.16–0.73; p<0.01) (**Fig. S1**).

All of the last samples had valid results from ctDNA sequencing. Twenty-one *BRCA1/2*mut-positive patients submitted the last samples, in which the same *BRCA1/2*mut were detected as those in the baseline samples, with a median (IQR) variant allele fraction of 49.6% (49.1%, 50.2%). Secondary reversion mutations in *BRCA1* were detected in 2 of 6 (33.3%) *BRCA1/2*mut-positive patients with PD (**Fig. S2**). No other gene alterations known to contribute to resistance were identified in patients with PD [2].

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3. Fecal microbiome analysis

First, fecal baseline samples were examined to determine whether the composition of the gut microbiota differed according to *BRCA1/2*mut status. Antibiotic use prior to PARPi treatment was 6 (19%) in *BRCA1/2*mut-positive patients and 6 (26%) in *BRCA1/2*mut-negative patients, with no difference between the 2 groups (p=0.742). Alpha diversity (**Fig. 2A**), beta diversity (**Fig. 2B**), and phylum-level composition (**Fig. 2C**) did not differ according to the *BRCA1/2*mut

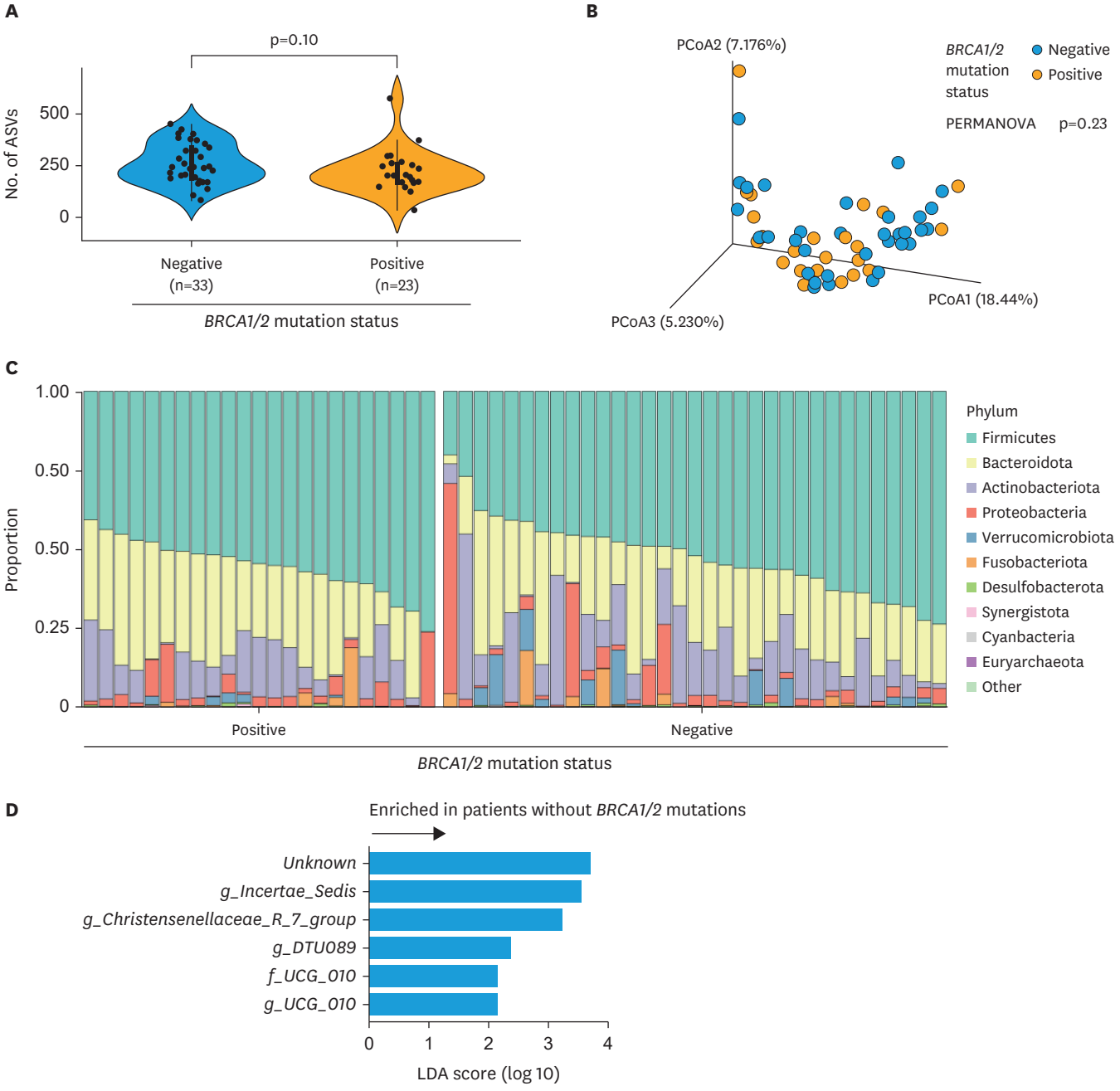

Fig. 2. Landscape of gut microbiome based on *BRCA1/2*mut status. (A) Violin plot of the number of amplicon sequence variants to compare taxonomic richness (alpha diversity). (B) PCoA plot (beta diversity). (C) Phylum-level microbial composition. (D) LEfSe representation of microbial relative abundance comparing between patients with and without *BRCA1/2*mut.
ASVs, amplicon sequence variants; *BRCA1/2*mut, *BRCA1/2* mutation; *f*, family; *g*, genus; LDA, linear discriminant analysis; LEfSe, linear discriminant analysis of effect size; PCoA, principal coordinate analysis; PERMANOVA, permutation multivariate analysis of variance.

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status. LEfSe analysis revealed genus-level compositional difference between *BRCA1/2*mut-positive and *BRCA1/2*mut-negative patients; *Incertae Sedis*, *Christensenellaceae R-7 group*, *DTU089*, and *UCG-010* were enriched in *BRCA1/2*mut-negative patients, whereas no enriched genera were detected in *BRCA1/2*mut-positive patients (**Fig. 2D**). The median (IQR) relative abundance of genus enriched in *BRCA1/2*mut-negative patients was 0.68% (0.19%, 2.26%), 0.24% (0.01%, 0.68%), 0.03% (0.01%, 0.11%), and 0% (0%, 0.02%), respectively.

Next, the relative abundance of microbes in the fecal baseline samples was analyzed separately in *BRCA1/2*mut-positive and *BRCA1/2*mut-negative patients. In *BRCA1/2*mut-positive patients, the cutoff PFS was set at 18 months based on the results of previous studies [2], because the actual median PFS was unattained; *Bifidobacterium*, *Roseburia*, *Dialister*, *Butyricicoccus*, and *Bilophila* were enriched in the LTR, and *Faecalicoccus* and *Enorma* were enriched in the STR (**Fig. 3A**). In *BRCA1/2*mut-negative patients, the median PFS of 9 months was used as the cutoff; *Phascolarctobacterium* and *Rothia* were enriched in the LTR, and *Merdibacter*, *DTU089*, *Gordonibacter*, and *Subdoligranulum* were enriched in the STR (**Fig. 3B**). Of these bacteria, *Dialister*, *Faecalicoccus*, *Enorma,* and *Rothia* were not detected in over 50% of the fecal samples, and their median abundances could not be obtained. Multivariate analyses excluding these bacteria showed that no bacteria were associated with PFS in *BRCA1/2*mut-positive patients (**Fig. 3C**), while high relative abundances of *Phascolarctobacterium* (≥median of 1.11%) was significantly associated with a long PFS in *BRCA1/2*mut-negative patients (median PFS 14.0 vs. 5.9 months, HR=0.28; 95% CI=0.11–0.69; p=0.014) (**Fig. 3D**). Antibiotic use during PARPi treatment was 3 (13%) in *BRCA1/2*mut-positive patients, but none in *BRCA1/2*mut-negative patients.

Furthermore, the multivariate analysis including age, histology, maintenance therapy setting, and *Phascolarctobacterium* relative abundance, showed that the high relative abundance of *Phascolarctobacterium* was independently associated with longer PFS (HR=0.37; 95% CI=0.16–0.85; p=0.019) (**Table S1**).

The actual PFS plots according to the relative abundance of *Phascolarctobacterium* is shown in **Fig. 4**. The accuracy of the cutoff value of 1.11% was 0.73 (95% CI=0.64–0.96) with sensitivity of 75% and specificity of 71% for predicting the PFS over 9 months.

The genus of *Phascolarctobacterium* was not detected in one-third of the *BRCA1/2*mut-negative fecal samples (n=11). We performed another analysis in the same way dividing patients into undetected and detected for *Phascolarctobacterium* and obtained the similar result (median PFS 14.0 vs. 5.2 months, HR=0.27; 95% CI=0.12–0.63; p=0.001) (**Fig. S3**). No factors, such as age, body mass index, history of lifestyle-related diseases, histology, maintenance therapy setting, and antibiotic use prior to PARPi treatment, were associated with the detection of *Phascolarctobacterium* (**Table S2**).

Finally, compositional changes of *Phascolarctobacterium* were analyzed in paired samples from 20 *BRCA1/2*mut-negative patients (**Fig. 1**). Five patients without PD submitted the samples at the last follow-up and 15 patients submitted them at PD. The median (IQR) intervals between the initiation of PARPi therapy and last-sample submission were 10.0 (7.8, 11.1) months in the patients without PD (n=5) and 5.5 (4.2, 9.8) months in the patients with PD (n=15). The *Phascolarctobacterium* relative abundances showed no consistent dynamics in both samples with and without PD (**Fig. 5A**), while they were significantly higher in the last samples of patients without PD than in those of patients with PD (median [IQR], 1.25% [1.16%, 2.37%] vs. 0.06% [0%, 0.99%]; p=0.016) (**Fig. 5B**). The relative abundances of other

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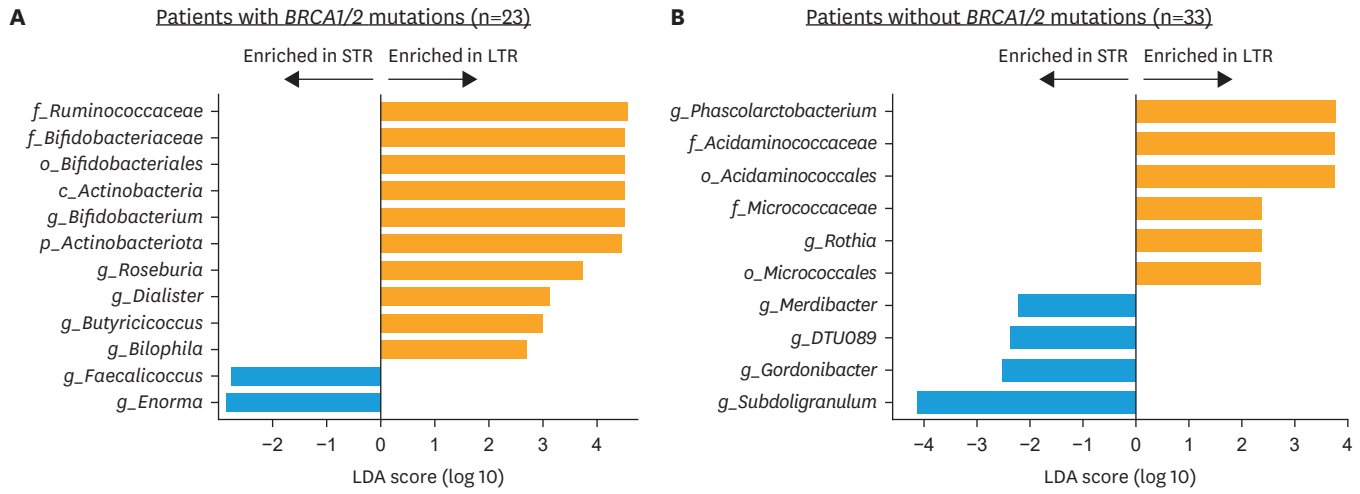
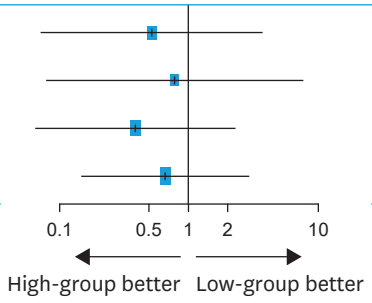


C Patients with BRCA1/2 mutations (n=23)

Gut microbe	Median relative abundance % [IQR]	Relative abundance High-group, Low-group No. of events/No. of patients	HR (95% CI)	p-value
Bifidobacterium	4.10 [0.09–10.0]	3/12, 7/11	0.52 (0.07–3.73)	0.51
Roseburia	0.60 [0–1.12]	3/12, 7/11	0.78 (0.08–7.64)	0.83
Butyricicoccus	0.19 [0.09–0.43]	3/12, 7/11	0.39 (0.06–2.34)	0.30
Bilophila	0.14 [0–0.25]	4/12, 6/11	0.66 (0.15–2.97)	0.59



D Patients without BRCA1/2 mutations (n=33)

Gut microbe	Median relative abundance % [IQR]	Relative abundance High-group, Low-group No. of events/No. of patients	HR (95% CI)	p-value
Phascolarctobacterium	1.11 [0–1.93]	10/17, 14/16	0.28 (0.11–0.69)	0.01
Merdibacter	0.02 [0–0.04]	15/17, 9/16	1.98 (0.80–4.86)	0.14
DTU089	0.03 [0.01–0.11]	14/17, 10/16	1.56 (0.60–4.05)	0.36
Gordonibacter	0.03 [0–0.04]	13/17, 11/16	1.44 (0.49–4.24)	0.50
Subdoligranulum	0.61 [0.01–2.41]	12/17, 12/16	1.36 (0.57–3.26)	0.49

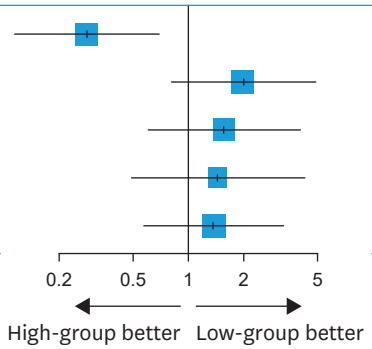


Fig. 3. Microbial compositions and PFS. LEfSe representation of microbial relative abundance between LTR (green) and STR (red) in fecal baseline samples of (A) patients with *BRCA1/2*mut and (B) patients without *BRCA1/2*mut. Multivariate analyses of enriched bacteria for PFS in (C) patients with *BRCA1/2*mut and (D) patients without *BRCA1/2*mut.
*BRCA1/2*mut, *BRCA1/2* mutation; *c*, class; CI, confidence interval; *f*, family; *g*, genus; HR, hazard ratio; LDA, linear discriminant analysis; LEfSe, linear discriminant analysis of effect size; LTR, long-term responder; *o*, order; *p*, phylum; PFS, progression-free survival; STR, short-term responder.

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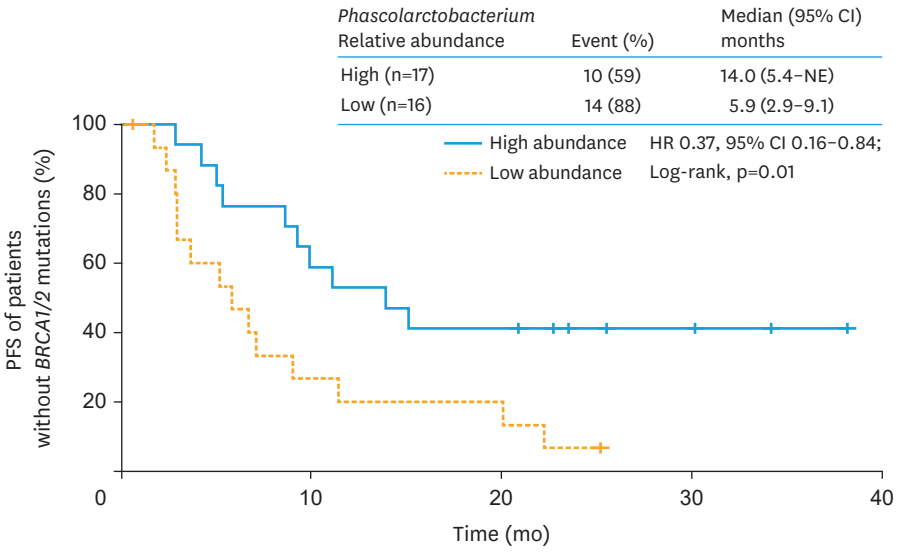

No. at risk					
High abundance	17	11	7	3	0
Low abundance	16	4	3	0	0

Fig. 4. Kaplan–Meier estimate plots of PFS according to relative abundances of *Phascolarctobacterium* in patients without *BRCA1/2*mut.
*BRCA1/2*mut, *BRCA1/2* mutation; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

bacteria did not show any consistent changes between the baseline and last samples (**Fig. 5A**) and any differences between samples with and without PD in the last samples (**Fig. 5B**).

The number of paired samples in the *BRCA1/2*mut-positive patients was too small as 10 to analyze.

DISCUSSION

This study revealed that a high composition of *Phascolarctobacterium* in the fecal microbiome was associated with a long PFS of PARPi therapy in *BRCA1/2*mut-negative patients with ovarian cancer. The patient characteristics, prevalence of *BRCA1/2*mut, and PFS of PARPi therapy in this study were consistent with those of previous studies conducted in Europe and the United States [2].

*BRCA1/2*mut are potent predictive factors of PARPi efficacy through synthetic lethality targeting HRD [2], and indeed a large difference of PFS was observed between *BRCA1/2*mut-positive and *BRCA1/2*mut-negative patients in this study. Microbial diversity in the baseline fecal samples did not differ between *BRCA1/2*mut-positive and *BRCA1/2*mut-negative patients, although some genus-level compositions were different. *BRCA1/2*mut carriers are reported to have a progesterone–estrogen imbalance that may lead to commensal microbial differences in *BRCA1/2*mut status [6]. Further research is required to clarify the association between germline *BRCA1/2*mut and the gut microbiome, with respect to carcinogenesis and tumor progression in ovarian cancer.

A profile of the gut microbiome associated with the efficacy of PARPi was not found in *BRCA1/2*mut-positive patients. Antibiotic use during PARPi treatment was recognized in

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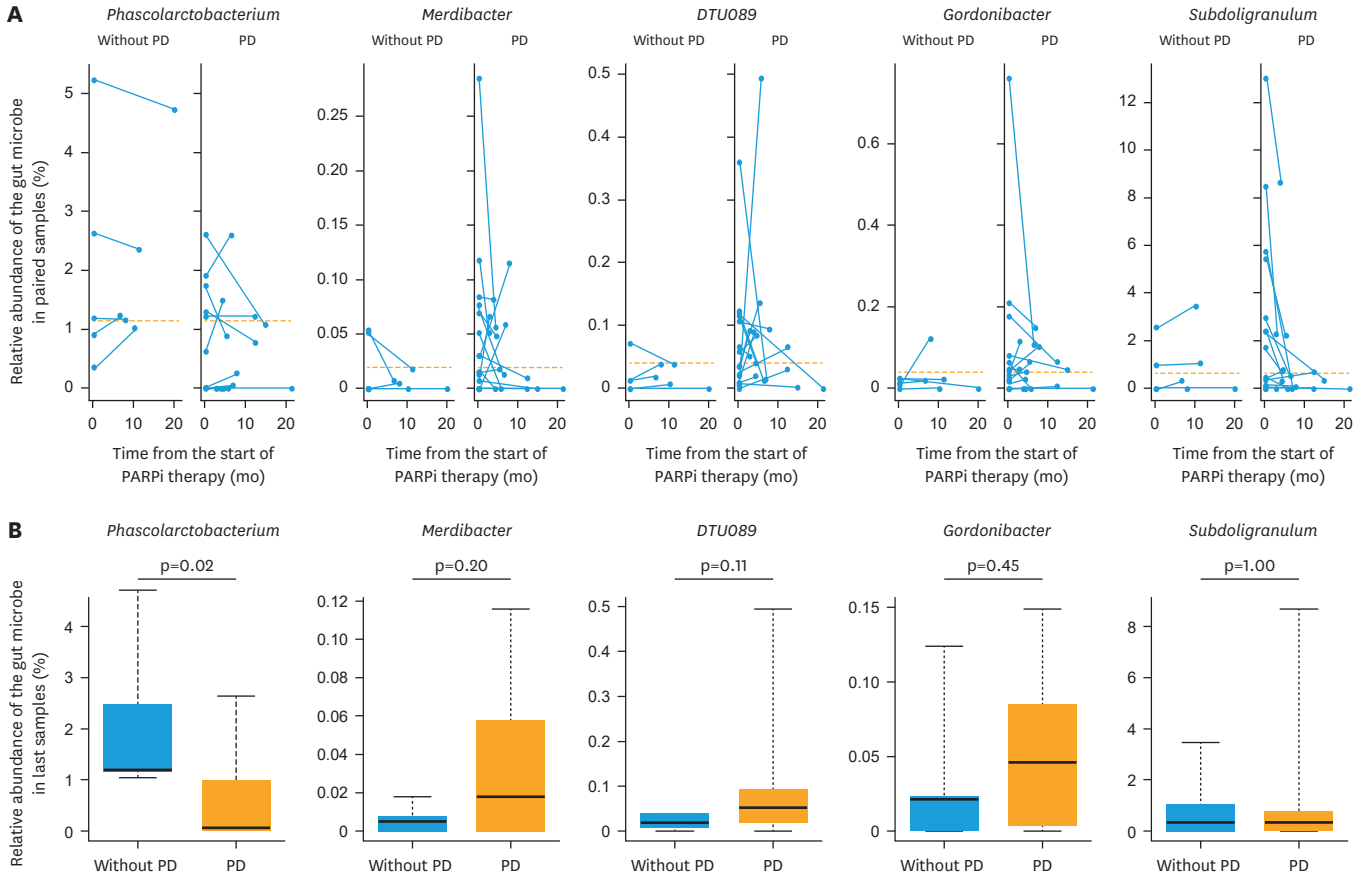

Fig. 5. Paired-sample analysis for gut microbes in patients without *BRCA1/2* mutations. (A) Changes in relative abundances between baseline and last samples of patients without PD (n=5) and with PD (n=15). Red dotted lines indicate the median value of relative abundances in baseline samples used in the multivariate analyses. (B) Boxplots for the relative abundances in the samples at the last follow-up without PD (n=5) and at PD (n=15).
PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease.

a part of *BRCA1/2*mut-positive patients (13%), which may have altered the gut microbiota composition and influenced the results. However, our *BRCA1/2*mut-positive patients exhibited excellent long-term PFS with a median of 24 months or more, and the impact of antibiotic use on our results seemed small. *Bifidobacterium*, *Roseburia*, and *Butyricicoccus* enriched in the LTR can produce SCFAs enhancing the antitumor activity of $CD8^+$ T-cells [4,15], and these bacteria might contribute to prolonged PFS. Further studies with larger sample sizes and longer observation periods are needed for *BRCA1/2*mut-positive patients.

High relative abundance of *Phascolarctobacterium* was substantially associated with a long PFS in *BRCA1/2*mut-negative patients. In the analysis, we used a median relative abundance of 1.11% as the cutoff to divide patients into 2 groups: high and low abundances. Multivariate analysis showed that the high relative abundance of *Phascolarctobacterium* was independently associated with longer PFS. These findings imply that *Phascolarctobacterium* is a pivotal gut bacterium that predicts the efficacy of PARPi therapy in ovarian cancer. In addition, the result of the last sample analyses, the higher relative abundance in patients without PD than those with PD, supported this inference.

Phascolarctobacterium are commensal bacteria in the gut and play a role in the fermentation of carbohydrates [16]. They are known to produce SCFAs, particularly propionate and acetate,

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which are associated with various beneficial effects on the host metabolism and immunity [4,16]. In a preclinical study, *Phascolarctobacterium* induce local and systemic accumulation of interferon-γ^+ $CD8^+$ T cell [17]. *Phascolarctobacterium* are associated with the response to immune checkpoint inhibitors in patients with various cancers [18-21]. We speculate that a high composition of *Phascolarctobacterium* may promote host antitumor immunity and enhance the efficacy of PARPi. However, further research is needed to elucidate its cellular and molecular mechanisms.

Our analysis also revealed that certain bacteria, such as *Subdoligranulum*, *Gordonibacter*, *DTU089*, and *Merdibacter* tended to be present in higher abundance in patients who experienced particularly short PFS. This finding suggests that testing for fecal abundances of these bacteria might be valuable in identifying patients who are potentially resistant to PARPi therapy. However, this observation requires further validation through preclinical models and additional patient cohorts.

To date, various clinical factors, such as age, dietary fiber intake, individual genetic variations, and medical history, are known to affect gut microbiome [4]. Antibiotics, proton pump inhibitors, and probiotics can alter gut microbiota composition [4]. In this study, however, information on the medication other than antibiotics was insufficient to analyze. We conducted a multivariate analysis examining the association between *Phascolarctobacterium* detection and factors including age, BMI, histology, presence of lifestyle-related diseases, treatment setting, and antibiotic use prior to PARPi treatment. This analysis revealed no significant associations. However, future studies with larger cohorts and more detailed medical information could help clarify the relationship between *Phascolarctobacterium* abundance, patient characteristics, and clinical outcomes.

The patients in this study received platinum-based chemotherapy before the submission of fecal samples. Previous studies have reported a possible association between the response to chemotherapy and the commensal microbiome in patients with ovarian cancer [22,23]. However, the gut microbiome associated with platinum sensitivity remains unknown, and its association with tumor HRD status is unclear. Only 4 patients in our cohort had available HRD test results for their tumors, of which 2 were positive. Due to this small sample size with known HRD status, we were unable to conduct a meaningful analysis of how tumor HRD status might have influenced our results. However, all patients in our study were platinum-sensitive, which may suggest that the impact of HRD status on our findings could be limited.

Several large-scale analyses demonstrated that ethnicity contributes to variations in microbiota composition [4,24]. The gut microbiome of Asian populations is characterized by remarkable diversity and richness, with prominent genera including *Prevotella*, *Bacteroides*, *Lactobacillus*, *Faecalibacterium*, *Ruminococcus*, *Subdoligranulum*, *Coprococcus*, *Collinsella*, *Megasphaera*, *Bifidobacterium*, and *Phascolarctobacterium* [24]. This profile differs from those typically observed in European and African ethnicities. However, a Norwegian study on gut microbiome associated with colorectal cancer detected *Phascolarctobacterium* as commensal bacteria, suggesting some commonalities across different ethnic groups [25]. Thus, differences in the gut microbiome between ethnic groups are evident, and the results of this study should be validated in non-Asian ethnic groups.

We suggest that specific gut microbiome profiles, particularly the abundance of *Phascolarctobacterium*, could potentially serve as predictive biomarkers for PARPi efficacy.

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With further validation, this could lead to the development of a microbiome-based test to help identify patients most likely to benefit from PARPi therapy. Patients with favorable microbiome profiles might be prioritized for PARPi treatment, while those with less favorable profiles might be considered for alternative therapies.

Numerous intervention trials targeting the gut microbiome are currently ongoing in patients undergoing immune checkpoint inhibitor therapy, including fecal microbiota transplantation and combination with butyrate-producing bacteria [4,26-28]. Our results suggest that similar interventions may be effective in enhancing PARPi efficacy. Potential strategies include probiotic supplementation to increase beneficial bacteria like *Phascolarctobacterium*, dietary interventions to promote a favorable gut microbiota composition, and fecal microbiota transplantation from patients who responded well to PARPi treatment.

Regarding the introduction of stool-based microbiome testing into clinical practice, there are concerns about its feasibility and acceptability. However, rapid progress in sequencing technologies and bioinformatics is making microbiome testing more cost-effective and scalable for clinical use [29]. Unlike a colonoscopy or blood draw, stool samples can be collected at home, minimizing discomfort and inconvenience. In recent years, growing evidence has suggested that the gut microbiome modulates the efficacy and toxicity of cancer therapy [4]. As the importance of the microbiome in health becomes more widely recognized, patients would gradually accept such tests.

Other limitations of this study include: the small sample size without a validation cohort, lack of analyses of tumor samples, such as the presence of tumor-infiltrating lymphocytes, and the possibility of ethnic disparity in the gut microbiome. Further studies are needed to address these limitations.

In conclusion, this study demonstrated a favorable association between the fecal composition of *Phascolarctobacterium* and PARPi efficacy in *BRCA1/2*mut-negative patients with ovarian cancer. Our results provide a microbial foundation for future studies that impact PARPi treatment strategies.

SUPPLEMENTARY MATERIALS

Method S1
SCRUM-Japan MONSTAR-SCREEN Protocol.

Table S1
Multivariate analysis of clinicopathological factors associated with PFS in patients without *BRCA1/2* mutations

Table S2
Clinicopathological factors associated with *Phascolarctobacterium* detection

Fig. S1
PFS stratified using *BRCA1/2*mut status. PFS was significantly different between patients with and without *BRCA1/2*mut.

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Fig. S2

Secondary reversion mutations of *BRCA1* in the circulating DNA of patients with disease progression. In Patient #1, the presumed germline variant (c.3640G>T) changes glycine to a terminal codon, and the secondary mutation (c.3640_3641>TG) changes it to tryptophan, which is predicted to restore *BRCA1*. In Patient #2, the presumed germline variant (c.3477_3480del) causes a frameshift, resulting in truncation of *BRCA1*, and the secondary mutation (c.3474_3485del) cause a deletion of 12 bases including this site, which restores the open reading frame and is predicted to restore *BRCA1*.

Fig. S3

PFS stratified by *Phascolarctobacterium*-detection status (undetected vs. detected) in patients without *BRCA1/2*mut. PFS was significantly different between patients with *Phascolarctobacterium* undetected and patients with *Phascolarctobacterium* detected in fecal baseline samples.

REFERENCES

1. Kobayashi Y, Shimada M, Tamate M, Cho HW, Zhu J, Chou HH, et al. Current treatment strategies for ovarian cancer in the East Asian Gynecologic Oncology Trial Group (EAGOT). J Gynecol Oncol 2024;35:e87. PUBMED | CROSSREF
2. Miller RE, El-Shakankery KH, Lee JY. PARP inhibitors in ovarian cancer: overcoming resistance with combination strategies. J Gynecol Oncol 2022;33:e44. PUBMED | CROSSREF
3. Kandalaft LE, Dangaj Laniti D, Coukos G. Immunobiology of high-grade serous ovarian cancer: lessons for clinical translation. Nat Rev Cancer 2022;22:640-56. PUBMED | CROSSREF
4. Fernandes MR, Aggarwal P, Costa RG, Cole AM, Trinchieri G. Targeting the gut microbiota for cancer therapy. Nat Rev Cancer 2022;22:703-22. PUBMED | CROSSREF
5. Sipos A, Ujlaki G, Mikó E, Maka E, Szabó J, Uray K, et al. The role of the microbiome in ovarian cancer: mechanistic insights into oncobiosis and to bacterial metabolite signaling. Mol Med 2021;27:33. PUBMED | CROSSREF
6. Nené NR, Reisel D, Leimbach A, Franchi D, Jones A, Evans I, et al. Association between the cervicovaginal microbiome, *BRCA1* mutation status, and risk of ovarian cancer: a case-control study. Lancet Oncol 2019;20:1171-82. PUBMED | CROSSREF
7. Nakamura Y, Fujisawa T, Taniguchi H, Bando H, Okamoto W, Tsuchihara K, et al. SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN: Path to the realization of biomarker-guided precision oncology in advanced solid tumors. Cancer Sci 2021;112:4425-32. PUBMED | CROSSREF
8. Sakai SA, Aoshima M, Sawada K, Horasawa S, Yoshikawa A, Fujisawa T, et al. Fecal microbiota in patients with a stoma decreases anaerobic bacteria and alters taxonomic and functional diversities. Front Cell Infect Microbiol 2022;12:925444. PUBMED | CROSSREF
9. Bolyen E, Rideout JR, Dillon MR, Bokulich NA, Abnet CC, Al-Ghalith GA, et al. Reproducible, interactive, scalable and extensible microbiome data science using QIIME 2. Nat Biotechnol 2019;37:852-7. PUBMED | CROSSREF
10. Callahan BJ, McMurdie PJ, Rosen MJ, Han AW, Johnson AJ, Holmes SP. DADA2: high-resolution sample inference from Illumina amplicon data. Nat Methods 2016;13:581-3. PUBMED | CROSSREF
11. Quast C, Pruesse E, Yilmaz P, Gerken J, Schweer T, Yarza P, et al. The SILVA ribosomal RNA gene database project: improved data processing and web-based tools. Nucleic Acids Res 2013;41:D590-6. PUBMED | CROSSREF
12. Woodhouse R, Li M, Hughes J, Delfosse D, Skoletsky J, Ma P, et al. Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. PLoS One 2020;15:e0237802. PUBMED | CROSSREF
13. Segata N, Izard J, Waldron L, Gevers D, Miropolsky L, Garrett WS, et al. Metagenomic biomarker discovery and explanation. Genome Biol 2011;12:R60. PUBMED | CROSSREF
14. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-8. PUBMED | CROSSREF

15. Chang SC, Shen MH, Liu CY, Pu CM, Hu JM, Huang CJ. A gut butyrate-producing bacterium *Butyricicoccus pullicaecorum* regulates short-chain fatty acid transporter and receptor to reduce the progression of 1,2-dimethylhydrazine-associated colorectal cancer. Oncol Lett 2020;20:327. PUBMED | CROSSREF
16. Wu F, Guo X, Zhang J, Zhang M, Ou Z, Peng Y. *Phascolarctobacterium faecium* abundant colonization in human gastrointestinal tract. Exp Ther Med 2017;14:3122-6. PUBMED | CROSSREF
17. Tanoue T, Morita S, Plichta DR, Skelly AN, Suda W, Sugiura Y, et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. Nature 2019;565:600-5. PUBMED | CROSSREF
18. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018;359:97-103. PUBMED | CROSSREF
19. Lee KA, Thomas AM, Bolte LA, Björk JR, de Ruijter LK, Armanini F, et al. Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma. Nat Med 2022;28:535-44. PUBMED | CROSSREF
20. Peng Z, Cheng S, Kou Y, Wang Z, Jin R, Hu H, et al. The gut microbiome is associated with clinical response to anti-PD-1/PD-L1 immunotherapy in gastrointestinal cancer. Cancer Immunol Res 2020;8:1251-61. PUBMED | CROSSREF
21. Wu Z, Zhang S, Li L, Huang Z, Huang D, Hu Y. The gut microbiota modulates responses to anti-PD-1 and chemotherapy combination therapy and related adverse events in patients with advanced solid tumors. Front Oncol 2022;12:887383. PUBMED | CROSSREF
22. Asangba AE, Chen J, Goergen KM, Larson MC, Oberg AL, Casarin J, et al. Diagnostic and prognostic potential of the microbiome in ovarian cancer treatment response. Sci Rep 2023;13:730. PUBMED | CROSSREF
23. D'Amico F, Perrone AM, Rampelli S, Coluccelli S, Barone M, Ravegnini G, et al. Gut microbiota dynamics during chemotherapy in epithelial ovarian cancer patients are related to therapeutic outcome. Cancers (Basel) 2021;13:3999. PUBMED | CROSSREF
24. Syromyatnikov M, Nesterova E, Gladkikh M, Smirnova Y, Gryaznova M, Popov V. Characteristics of the gut bacterial composition in people of different nationalities and religions. Microorganisms 2022;10:1866. PUBMED | CROSSREF
25. Bucher-Johannessen C, Birkeland EE, Vinberg E, Bemanian V, Hoff G, Berstad P, et al. Long-term follow-up of colorectal cancer screening attendees identifies differences in *Phascolarctobacterium* spp. using 16S rRNA and metagenome sequencing. Front Oncol 2023;13:1183039. PUBMED | CROSSREF
26. Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science 2021;371:602-9. PUBMED | CROSSREF
27. Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin JM, Morrison RM, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science 2021;371:595-602. PUBMED | CROSSREF
28. Dizman N, Meza L, Bergerot P, Alcantara M, Dorff T, Lyou Y, et al. Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. Nat Med 2022;28:704-12. PUBMED | CROSSREF
29. Wensel CR, Pluznick JL, Salzberg SL, Sears CL. Next-generation sequencing: insights to advance clinical investigations of the microbiome. J Clin Invest 2022;132:e154944. PUBMED | CROSSREF