Does physical activity associate with gut microbiome and survival outcomes of Chinese metastatic colorectal cancer patients? A secondary analysis of a randomized controlled trial

Lingyun Sun a,*, Yunzi Yan b, Shaohua Yan c, Yufei Yang a, **

a Oncology Department, Xiyuan Hospital, China Academy of Chinese Medical Sciences, #1 Xiyuan Caochang Road, Haidian District, 100091, Beijing, PR China
b Graduate School, Beijing University of Chinese Medicine, #11 East Road of North Third Ring Road, 100029, Chaoyang District, Beijing, PR China
c Oncology Department, Dongfang Hospital, Beijing University of Chinese Medicine, #6 Fangzhuang Xingyuan, Fengtai District, 100078, Beijing, PR China

ARTICLE INFO

Keywords:
Colorectal cancer
Intestinal microbiology
Physical activity
Colorectal metastases

ABSTRACT

Background: This study aimed to evaluate associations between physical activities, gut microbiome and survival outcomes among Chinese metastatic colorectal cancer (mCRC) patients.

Methods: We conducted a secondary analysis nested in a randomized controlled clinical trial (RCT) of a traditional Chinese herbal medicine for mCRC patients (ChiCTR2000029599). After one-month intervention, we followed up patients every six months for survival outcomes and the last follow-up was in August 2022 (median follow-up time 28.6 months). We assessed patients’ physical activity (PA) through short form of the International Physical Activity Questionnaire (IPAQ-SF) and collected patients’ stool samples at baseline. Kaplan–Meier survival analyses and Cox regression models were used to evaluate the association between PA level and overall survival outcomes. 16S rRNA sequencing approaches were utilized for the gut microbiome analysis.

Results: Among 40 mCRC patients enrolled in the original RCT, 15 patients were still alive at the time of the last follow-up. The mean IPAQ score was 2569.5 MET-min/week for all patients, indicating a moderate PA level. Specifically, there were 7 patients in high PA level group, 2 patients in low PA level group and the rest were in middle PA group. Gut microbiome community difference analysis showed that patients with high PA levels had a significantly higher alpha diversity than that of the middle PA group (131.53 vs. 98.12, p = 0.04), an increased abundance of Phascolarctobacterium and Ruminococcaceae and a decreased abundance of Megasphaera at the genus level. Cox regression model showed that after controlling for the original tumor site and TCM treatment, high PA level was independently associated with a lower risk of death (relative risk 0.13, p = 0.014).

Conclusions: High PA level could be associated with survival benefits among Chinese mCRC patient through its potential role on modulating gut microbiome. Our results could be referred to patients’ education and future clinical study design.

1. Background

The latest global statistics showed that colorectal cancer (CRC) is the third most common malignant tumor and the second leading cause of cancer-related death worldwide [1]. Over the past few decades, the incidence of CRC has decreased in most developed countries, and it has been predicted that by 2035, the CRC mortality rate will decrease by 20–60% in these countries [2]. In many developing countries, however, both the incidence and mortality rates are still increasing rapidly, especially in China (age-standardized incidence rate rose from 64% to 102.5% from 1990 to 2017, per 100 000 person-years [3, 4]). According to a retrospective study conducted among 384 thousand newly diagnosed Chinese CRC patients in 2012, 45.5% of the cases were attributable to obesity, physical inactivity and other lifestyle factors such as smoking, alcohol intake and dietary factors [5].

Both NCCN and ASCO clinical guidelines have recommended that CRC survivors ameliorate obesity and increase physical activity levels to promote their health condition [6]. An Australian 10-year cohort study showed that exercise was independently associated with lower risk of cancer related death among stage II CRC patient [7]. Nonetheless, data
from Chinese cancer patients’ population in Singapore and US showed that they were less likely to engage in physical activities but spent more time on television watching compared with other ethnic groups [8, 9]. However, to date, there is still lack of evidence on Chinese CRC patients’ PA level in China mainland and whether they could benefit from physical activities.

Existing studies have illustrated the potential benefits of physical activities for cancer control and health promotion might be explained through certain mechanisms [10]. These mechanisms included regulating insulin-like growth factor 1 and other metabolic, modulating sex hormones, reducing oxidative stress and inflammation, and enhancing host immunity [11, 12]. Among them, gut microbiome is a new field and hotspot to further investigate the association between lifestyle and CRC prognosis [13, 14]. In healthy population, sedentary behavior and less physical activity were found to be related with lower diversity of the gut microbiome [15]. Whether physical activity could impact on gut microbiome of CRC patients was still not clear. Thus, the current study aimed to evaluate Chinese metastatic CRC (mCRC) patients’ physical activities level, as well as its association with their survival outcomes and gut microbiome diversity.

2. Method

2.1. Study design

The current study is a secondary analysis and follow-up data of a randomized double-blind placebo-controlled trial which was conducted between April 2018 and March 2019 in Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing, China (Registration number: ChiCTR2000029599; URL: https://www.chictr.org.cn/showproj.aspx?proj=48950). In the original randomized controlled trial (RCT), we enrolled 40 stage IV colorectal cancer patients with unresectable metastatic diseases who had not received chemotherapy, radiotherapy, targeted therapy, or immunotherapy for at least one month and were not receiving antibiotic or probiotic treatments at the time of enrollment. All patients were randomly assigned to the Quxie capsule group (a traditional Chinese herbal medicine compound) or placebo capsule group. The intervention lasted for one month. For more details on the Quxie capsule and study design, please refer to the original paper [16].

2.2. Ethics statement

The original RCT study was approved by the Ethics Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (2016XLA122-1). All patients signed informed consent forms before enrollment.

2.3. Physical activity level assessment

We used the validated Mandarin version of the International Physical Activity Questionnaire-7 (IPAQ-7) to evaluate the patients’ physical activity (PA) levels [17] (supplement table 1). The IPAQ-7 includes 6 questions asking patients whether they perform high-intensity PA (metabolic equivalent intensity, MET = 8), mild PA (MET = 4) or walking activities (MET = 3.3) and the specific time spent on these activities during the past seven days. The 7th question asked about how much time the patients spent sitting during working days. The physical activity level was measured by an individual’s PA level per week, which was calculated by summing each level of PA by the MET \( \times \) frequency per week (d/w) \( \times \) daily time spent (min/d). Then, we defined the high, middle, and low PA groups according to the IPAQ scoring standard (high PA level = total PA level over 3000 MET-min/W; middle PA level = total PA level over 600 MET-min/W but lower than 3000 MET-min/W; low PA level = not meeting any of these standards).

We collected information on the patients’ health behaviors, including smoking status, alcohol intake, sedentary behavior and habits of staying up late. We asked whether the patients had ever smoked/drank alcohol, quit smoking/drinking alcohol or currently smoked/drank alcohol at the time of enrollment. We used the 7th question of the IPAQ to define whether the patient had sedentary behavior. More than 5 h of sitting was defined as sedentary behavior, and less than or equal to 5 h of sitting was defined as non-sedentary behavior.

2.4. Patients’ information

For the secondary analysis, we obtained patient information from the baseline assessment of the original RCT, including sex, age and body mass index (BMI, calculated from patients’ weight and height), as well as disease information, including the original tumor site, time since the stage IV disease diagnosis, metastatic site and whether the patients had undergone colostomy.

2.5. Follow-up and survival outcomes

After patients completed the one-month intervention in the original RCT, we started to follow up all patients every 6 months for survival outcomes. The last follow-up was in August 2022 and the median follow-up time was 28.6 ± 17.50 months. The observed event was defined as all causes of death.

2.6. Gut microbiome analysis

We collected patients’ stool samples at baseline and stored them in DNA stabilizer tube. Majorbio Bio-Pharm Technology Co. Ltd. (Shanghai, China) performed gut microbiome 16SrRNA analysis. Through Majorbio Cloud (Majorbio Bio-Pharm Technology Co. Ltd., Shanghai, China), an online bioinformation analysis platform, alpha diversity at the operational taxonomic unit (OTU) level was measured by the Chao, Shannon, and ACE indices and compared between patients with different PA levels. Principal Component analysis (PCA) was used to detect beta diversity between the groups. Community difference analysis among the groups was tested at the phylum level, and the LEfSe multilevel FDR method was used for multiple hypothesis correction. We used heatmap correlation analysis by using OS and IPAQ score as environmental factors on genus level.

2.7. Statistical analysis

The secondary analysis was based on full analysis set (FAS) basis, including all participants being randomized (n = 40), regardless of whether they had adhered to the study protocol. We used an analysis of variance, chi-square test or t test to compare IPAQ scores between patients with different basic and disease characteristics. Kaplan–Meier and log-rank tests were used to compare the overall survival of patients with different physical activity levels. A multivariable-adjusted Cox regression model was used to evaluate independent impact factors (QX or placebo treatments, original tumor sites, PA level and gut microbiome diversity index) on OS. All analyses were performed using SPSS 21 (IBM Corp. USA). Missing data was deleted for final analysis. Differences were considered statistically significant if the p value was lower than 0.05 on both sides.

3. Results

3.1. Disease and basic information

Among 40 mCRC patients enrolled in the original RCT, the mean age was 65 ± 11 years old, and 27.5% of them were female. Seventy-five percent of the patients’ original tumor sites were the left colon or rectum. Among the 35 patients who underwent surgery, 7 had received colostomy. The mean BMI was 22.8 ± 3.6, 47.5% of them had BMI over 23 which could be considered overweight (Table 1).
2.2. Physical activity level and sedentary behavior among mCRC patients

The total mean IPAQ score of 34 patients who completely answered the questionnaire was 2569.5 ± 2504.7, indicating a moderate PA level (Table 1). CRC patients who had undergone colostomy tended to have significantly higher PA levels than those who had not (3577.5 vs. 2324.4, p = 0.022, Table 1). After categorized by the IPAQ scoring standard, there were 7 patients in high PA level group, 25 patients in moderate PA group, and 2 patients in low PA group respectively.

We used the 7th item of the IPAQ to evaluate the patients’ sedentary behavior. Among the 38 patients who answered this question, the mean daily sitting time was 4.3 ± 1.8 h (Table 1), with 22.5% of the patients regarded as having sedentary behavior (8 h per weekday).

3.3. Gut microbiome diversity in different PA level groups

We finally collected 39 patients’ stool samples for 16SrRNA test on gut microbiome and acquired 2179026 sequencing data. Rarefaction curve was flat which indicated that the sequencing data amount was enough (Figure 1 A). Alpha diversity showed that the Ace Index of the high physical activity group was significantly higher than that of the middle PA level (131.53 vs. 98.12, p = 0.04, Figure 1B). PCA on genus level showed that the composition of gut microbiome in middle and high PA level groups were different in beta diversity analysis (Figure 1C). The interpretation degree of PC1 axis and PC2 axis was 36.35% and 24.95% respectively. Community difference analysis at the genus level showed that patients with a high PA level had a significantly higher abundance of Phascolarctobacterium (2.1%, 0.8% vs. 0.1%, p = 0.04), Ruminococcaceae_UCG-01 (1.4%, 1.0% vs. 0%, p = 0.01), norank_o_Mollicutes_RF39 (0.5%, 0.3% vs. 0%, p = 0.04) and a significantly lower abundance of Megabacter (0.4%, 0.4% vs. 1.8%, p = 0.01) than the patients in the middle and low PA groups (Figure 1D). LEfSe analysis from phylum to species level between middle and high PA groups showed that middle PA group was enriched of Flavonifractor_plautii (specie, LDA3.12), Coprobacter (genus, LDA 2.99) and Oscillibacter (genus, LDA 2.83), while high PA group was enriched of Prevotellaceae (family, LDA4.66), Agathobacter (genus, LDA4.23) and Subdoligranulum (genus, LDA4.01) (Figure 1E).

3.4. Overall survival outcomes in different PA level groups and factor analysis

Until August 2022, the median follow-up time after enrollment was 28.6 ± 17.50 months. Fifteen patients were still alive at the time of the last follow-up, three patients lost follow-up and could not find out their recent status. The estimated median OS for middle and low PA levels was 4 and 16 months respectively, whereas median OS had not been reached in high PA so far. Kaplan–Meier survival analysis showed that there was no statistically significant difference on overall survival outcomes among different PA levels (p = 0.28, Figure 2).

Since original tumor site and treatment group (QX or placebo group) in the original RCT might influence the survival outcomes, we used multivariate COX regression model for further analysis. After controlling for these confounders, high physical activity level was independently associated with a lower risk of death than low and middle physical activity level (relative risk 0.13, 95% CI 0.03, 0.66, p = 0.014, Table 2). The omnibus test of model coefficient showed that the -2 Log Likelihood of the model was 23.44 (p = 0.001), indicating a well fitness and significance.

Heatmap correlation analysis on genus level showed that OS was positively related with the abundance of Escherichia-Shigella (p = 0.003), and negatively related with the abundance of Oscillibacter (p = 0.03), Ruminoclostridium (p = 0.04), and unclassified_f_Lachnospiraceae (p = 0.008), IPAQ score was found to be positively related with the abundance of Mollicutes, Ruminococcaceae, Paraprevotella, Christensenellaceae and Phascolarctobacterium, while negatively related with the abundance of Lachnospiraceae (all p < 0.05, Figure 3).

4. Discussion

In this study, we found that the majority of Chinese mCRC patients in the cohort kept a moderate physical activity level such as walk and housework. However, only few of them engaged in vigorous physical activities such as running and ball game. Compared with middle PA level groups, mCRC patients in high PA group had more diverse gut microbiome composition as well as elevated abundance of beneficial bacteria Phascolarctobacterium and Ruminococcaceae. In addition, high PA level was independently associated with significant less risk of death among mCRC patients after controlling original tumor site, TCM intervention in the original RCT and gut microbiome diversity index.

Previously, systematic review on several observational studies revealed that an increased physical activity level was associated with lower recurrence and mortality risk among CRC survivors after radical treatments [18]. In 2019, a prospective cohort study with 1218 mCRC patients who were enrolled in SWOG 80405 study, a phase III clinical trial, showed that a higher physical activity level was associated with

---

Table 1. Patients’ information, IPAQ scores and sitting hours.

| Patients’ information (n = 40) | IPAQ Score (n = 34) | MET-min/W (n = 38) | Sitting Hours (n = 38) |
|-------------------------------|-------------------|--------------------|-----------------------|
| Gender                        |                   |                    |                       |
| Male (n = 29)                 | 2549.0 (2751.3)   | 0.27               | 4.0 (3.3)             |
| Female (n = 11)               | 2612.5 (2011.5)   | 4.2 (0.6)          |                       |
| Age(years)                    |                   |                    |                       |
| <65 (n = 16)                  | 2994.9 (3031.3)   | 0.26               | 4.6 (0.4)             |
| ≥65 (n = 24)                  | 2144.2 (1834.7)   | 4.1 (0.4)          |                       |
| BMI                           |                   |                    |                       |
| ≤18 (n = 4)                   | 2835.0 (1806.6)   | 0.77               | 3.8 (1.0)             |
| 18-23 (n = 17)                | 2877.9 (841.1)    | 4.5 (0.6)          |                       |
| ≥23 (n = 19)                  | 2228.9 (383.9)    | 4.3 (0.3)          |                       |
| Original tumor site           |                   |                    |                       |
| Right colon (n = 10)          | 1392.0 (660.1)    | 0.30               | 4.1 (0.6)             |
| Left colon (n = 9)            | 2664.0 (2421.1)   | 5.1 (0.6)          |                       |
| Rectum (n = 21)               | 3050.9 (2946.7)   | 4.1 (0.4)          |                       |
| Time since stage IV diagnosis (years, n = 34) | 2084.2 (1956.8)   | 0.23               | 4.3 (0.5)             |
| ≤1 (n = 16)                   | 2507.5 (2995.0)   | 4.1 (0.4)          |                       |
| 1-3 (n = 12)                  | 4599.0 (3071.9)   | 5.5 (0.9)          |                       |
| Colostomy (n = 35)            |                   |                    |                       |
| Yes (n = 7)                   | 3577.5 (4080.4)   | 0.022              | 2.9 (0.6)             |
| No (n = 28)                   | 2324.4 (2001.6)   | 4.8 (0.3)          |                       |
| Metastatic site               |                   |                    |                       |
| Liver (n = 14)                | 2576.5 (2204.4)   | 0.86               | 4.8 (0.5)             |
| Lung (n = 14)                 | 3232.3 (3246.1)   | 3.2                | 3.9 (0.4)             |
| Other (n = 12)                | 1816.5 (1820.4)   | 4.7                | 4.7 (0.7)             |
| Treatment group in Original RCT |                    |                    |                       |
| QX (n = 20)                   | 2476.8 (2994.4)   | 0.85               | 4.8 (0.4)             |
| Placebo (n = 20)              | 2642.7 (2124.8)   | 3.9 (0.4)          |                       |
| Total                         | 2569.5 (2504.7)   | 4.3 (1.8)          |                       |

Abbreviations: SD, standard deviation;

1 Diet scores, IPAQ scores and sitting hours are described as the mean (standard deviation), and we used t test to compare the mean differences between the groups.

2 Statistical significance was set at P = 0.05.

3 Missing data exists for this information.

4 Metastatic sites were calculated separately (one patient might have multiple metastasis tumor sites), paired t-test was done between patients had these certain metastatic sites or not, for example, patients who had lung metastasis and who did not.

4
better progression-free survival (PFS) [19]. Unfortunately, none of those studies involved data from China and Chinese population. Our results were consistent with the previous findings on the positive association between physical activity level and survival outcomes among mCRC patients. To the best of our knowledge, this is one of the first studies to prove that Chinese CRC patients could also benefit from physical activities and to provide valuable evidence on education and lifestyle guidance to patients and their caregivers.

The World Health Organization (WHO) recommends that adults complete at least 150 min of moderate-intensity physical activity each week (about 900 MET-min/week). For CRC patients, the level of PA could be impacted by many factors such as different treatment phases, ethnic, and other socioeconomic backgrounds. In SWOG 80405 study, for example, PA level was assessed during chemotherapy and 47% of enrolled mCRC patients’ physical activity levels were lower than 3 MET-h/week (180 MET-min/week), which was significantly lower than the average PA level of mCRC patients in our study who were not under active cancer treatments [19]. Similarly, a Turkish study on early-stage CRC patients showed that the mean PA level (measured by IPAQ-SF) was 1560.72 MET-min/week which was also lower than the Chinese data [20]. However, when compared the mean BMI of the two cohorts together (Turkish 27.4 versus Chinese 22.8), we could infer that such

---

**Figure 1.** A: Rarefaction curve among three PA level groups (low: 2 samples; middle: 25 samples; high: 7 samples); B: Alpha diversity analysis (ACE Index) among the different physical activity level groups; C: Beta diversity analysis on PCA between middle and high physical activity level groups; D: Community difference analysis at the genus level among the different physical activity level groups; E: LEfSe analysis from phylum to species level between middle and high physical activity level groups.

**Figure 2.** Kaplan–Meier survival analysis among the mCRC patients in different physical activity groups.
disparity might be related with different lifestyles between the two countries. In the future, it necessary to carry out clinical guideline on how to provide more individualized and detailed recommendations for CRC patients based on existed evidence.

According to our results, physical activity might benefit mCRC patients through modulating gut bacteria, especially increasing the abundance of beneficial bacteria *Phascolarctobacterium* and *Ruminococcaceae* while reducing pathogenic bacterium *Megasphaera*. In 2018, researchers from the Mayo Clinic found that overweight adults were more likely to successfully lose weight if they had a higher abundance of *Phascolarctobacterium* [21]. In addition to its role in energy metabolism [22], *Phascolarctobacterium* could reduce the availability of luminal succinate and therefore prevent the growth of *Clostridoides difficile* in the human body, which could cause severe intestinal inflammation [23]. *Ruminococcaceae* is another beneficial bacterium that can maintain human digestive function and reduce the risk of gastrointestinal tumor growth. In contrast, *Megasphaera* is a pathogenic bacterium that has been found to be associated with gastric cancer development [24]. In future studies, metagenomics and metabolomics analyses are necessary to explore the functional pathways of the gut microbiome that are affected by physical activity among CRC patients and their predictive role on survival outcomes.

There are certain limitations in our study. First, the physical activity level might be related to patients’ performance status since all participants enrolled in our study had stage IV cancer. However, the average KPS of all participants at the time of enrollment was 80, indicating comparable health condition levels. In addition, the physical activity assessment tool in this study (IPAQ-SF) were based on patients’ self-report, which might lead to some information bias [25]. We also need to mention that the gut microbiome could be impacted by many other environmental factors, such as the original CRC tumor site and previous

| Factors                        | Regression coefficient | Relative Risk (95% CI) | P value |
|-------------------------------|------------------------|------------------------|---------|
| Treatment group               | 0                      | 1.00                   | -       |
| Placebo                       | 0.86                   | 2.37 (0.86, 6.52)      | 0.094   |
| QX                            | 0.77                   | 2.16 (0.40, 12.1)      | 0.35    |
| **Original Tumor site**       |                        |                        |         |
| Rectum                        | 0                      | 1.00                   | 0.11    |
| Left colon                    | -1.37                  | 0.25 (0.06, 1.04)      | 0.057   |
| Right colon                   | 0.77                   | 2.16 (0.40, 12.1)      | 0.35    |
| **Physical activity level**   |                        |                        |         |
| Low & middle                  | 0                      | 1.00                   | -       |
| High                          | -2.04                  | 0.13 (0.03, 0.66)      | 0.014   |
| **Ace index of alpha diversity** | 0.038                | 1.039 (1.013, 1.065)   | 0.03    |

Abbreviations: RR, relative risk; 95% CI, 95% confidential interval.

1 Relative risk of event (death) is exp (regression coefficient).

2 Since there were only two patients in the low PA cohort, we merged low and middle PA groups together in this model.

3 Ace index of gut microbiome alpha diversity analysis.
cancer treatment, such as chemo- or radiotherapy. Relatively small sample size that generated from the original RCT was also an important limitation of the current study. For example, there were only two patients in low PA group which made it difficult for survival and gut microbiome analysis within this group. We believed that clinical trial on PA by utilizing wearable device is feasible to further evaluate its role for CRC patients' health promotion as well as gut microbiome regulation.

5. Conclusions

In conclusion, higher physical activity level was associated with lower risk of death among Chinese mCRC patients. Such association might be related with its role on modulating gut microbiome, especially bacteria *Phascolarctobacterium* and *Ruminococcaceae*.

Declarations

**Author contribution statement**

Lingyun Sun: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Yunzi Yan: Performed the experiments; Contributed reagents, materials, analysis tools or data.
Shaohua Yan: Performed the experiments.
Yufei Yang: Conceived and designed the experiments.

**Funding statement**

Dr. Lingyun Sun and Yufei Yang were supported by National Natural Science Foundation of China [82004191 & 81573781].

**Data availability statement**

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

**Declaration of interest’s statement**

The authors declare no conflict of interest.

**Additional information**

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e11615.

**Acknowledgements**

We acknowledge all patients for their participation in this study, as well as our colleagues from the Oncology Department of Xiyuan Hospital for their support. We also thank Dr. Jun Mao from the Memorial Sloan Kettering Cancer Center in the U.S. for his guidance on the study design, as well as MS. Shiyao Li for her proofreading and editing of the English.

**References**

[1] F. Bray, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, Ca – Cancer J. Clin. 68 (6) (2018) 394–424.
[2] M. Araghi, et al., Global trends in colorectal cancer mortality: projections to the year 2035, Int. J. Cancer 144 (12) (2019) 2992–3000.
[3] M. Arnold, et al., Global patterns and trends in colorectal cancer incidence and mortality, Gut 66 (4) (2017) 683–691.
[4] The global, regional, and national burden of colorectal cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet Gastroenterol. Hepatol. 4 (12) (2019) 913–933.
[5] M.J. Gu, et al., Attributable causes of colorectal cancer in China, BMC Cancer 18 (1) (2018) 36.
[6] K. El-Shami, et al., American cancer society colorectal cancer survivorship care guidelines, Ca - Cancer J. Clin. 65 (6) (2015) 428–455.
[7] H. Jayasekara, et al., Associations of alcohol intake, smoking, physical activity and obesity with survival following colorectal cancer diagnosis by stage, anatomic site and tumor molecular subtype, Int. J. Cancer 142 (2) (2018) 238–250.
[8] Y. Le, et al., Acculturation and adherence to physical activity recommendations among Chinese American and non-Hispanic white breast cancer survivors, J. Immigr. Minority Health 21 (1) (2019) 80–88.
[9] Y.L. Eaglehouse, et al., Physical activity, sedentary time, and risk of colorectal cancer: the Singapore Chinese Health Study, Eur. J. Cancer Prev. 26 (6) (2017) 460–475.
[10] Z. Oruc, M.A. Kaplan, Effect of exercise on colorectal cancer prevention and treatment, World J. Gastrointest. Oncol. 11 (5) (2019) 348–366.
[11] A.T. Sax, et al., The insulin-like growth factor axis: a biological mechanism linking physical activity to colorectal cancer survival, Cancer Epidemiol. 38 (4) (2014) 455–459.
[12] M.N. Gunathilake, et al., Interaction between physical activity, PITX1 rs647161 genetic polymorphism and colorectal cancer risk in a Korean population: a case-control study, Oncotarget 9 (7) (2018) 7590–7603.
[13] J. Allen, C.L. Sears, Impact of the gut microbiome on the genome and epigenome of colon epithelial cells: contributions to colorectal cancer development, Genom Med. 11 (1) (2019) 11.
[14] S. Temraz, et al., Gut microbiome: a promising biomarker for immunotherapy in colorectal cancer, Int. J. Mol. Sci. 20 (17) (2019).
[15] L.J. Mailing, et al., Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health, Exerc. Sport Sci. Rev. 47 (2) (2019) 75–85.
[16] L. Sun, et al., Quxie capsule modulating gut microbiome and its association with T cell regulation in patients with metastatic colorectal cancer: result from a randomized controlled clinical trial, Int. J. Cancer. Ther. 19 (2020), 1534753420969820.
[17] P.C. Hallal, C.G. Victora, Reliability and validity of the international physical activity questionnaire (IPAQ), Med. Sci. Sports Exerc. 36 (3) (2004) 556.
[18] D. Schmid, M.F. Leitzmann, Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis, Ann. Oncol. 25 (7) (2014) 1293–1311.
[19] B.J. Guercio, et al., Associations of physical activity with survival and progression in metastatic colorectal cancer: results from cancer and leukemia group B (alliance)/SWOG 80405, J. Clin. Oncol. 37 (29) (2019) 2620–2631.
[20] D. Kucukvardar, et al., Factors influencing physical activity in patients with colorectal cancer, Ir. J. Med. Sci. 190 (2) (2021) 539–546.
[21] D.A. Muniz Pedrogo, et al., Gut microbial carbohydrate metabolism hinders weight loss in overweight Adult undergoing lifestyle intervention with a volumetric Diet, Mayo Clin. Proc. 95 (8) (2020) 1104–1116.
[22] W. Yang, et al., Moderate-intensity physical exercise affects the exercise performance and gut microbiota of mice, Front. Cell. Infect. Microbiol. 11 (2021), 712381.
[23] H. Nagao-Kitamoto, et al., Interleukin-22-mediated host glycoxylation prevents Clostridioides difficile infection by modulating the metabolic activity of the gut microbiota, Nat. Med. 26 (4) (2020) 608–617.
[24] Y. Zhang, et al., Gut microbiome analysis as a predictive marker for the gastric cancer patients, Appl. Microbiol. Biotechnol. 105 (2) (2021) 803–814.
[25] K. Vassbakk-Brovold, et al., Cancer patients participating in a lifestyle intervention during chemotherapy greatly over-report their physical activity level: a validation study, BMC Sports Med. Rehabil. 8 (2016) 10.