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REVIEW

Exercise and the gut microbiome: implications for supportive care in cancer

Nicolas H. Hart[1,2,3,4,5] · Matthew P. Wallen[2,6] · Morgan J. Farley[1,7] · Darren Haywood[1,8,9] · Alexander N. Boytar[7] · Kate Secombe[10,11] · Ria Joseph[2] · Raymond J. Chan[2,3] · Marlou-Floor Kenkhuis[12] · Laurien M. Buffart[12] · Tina L. Skinner[1,7] · Hannah R. Wardill[13,14]

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Abstract

Purpose Growing recognition of the gut microbiome as an influential modulator of cancer treatment efficacy and toxicity has led to the emergence of clinical interventions targeting the microbiome to enhance cancer and health outcomes. The highly modifiable nature of microbiota to endogenous, exogenous, and environmental inputs enables interventions to promote resilience of the gut microbiome that have rapid effects on host health, or response to cancer treatment. While diet, probiotics, and faecal microbiota transplant are primary avenues of therapy focused on restoring or protecting gut function in people undergoing cancer treatment, the role of physical activity and exercise has scarcely been examined in this population.

Methods A narrative review was conducted to explore the nexus between cancer care and the gut microbiome in the context of physical activity and exercise as a widely available and clinically effective supportive care strategy used by cancer survivors.

Results Exercise can facilitate a more diverse gut microbiome and functional metabolome in humans; however, most physical activity and exercise studies have been conducted in healthy or athletic populations, primarily using aerobic exercise modalities. A scarcity of exercise and microbiome studies in cancer exists.

Conclusions Exercise remains an attractive avenue to promote microbiome health in cancer survivors. Future research should elucidate the various influences of exercise modalities, intensities, frequencies, durations, and volumes to explore dose-response relationships between exercise and the gut microbiome among cancer survivors, as well as multifaceted approaches (such as diet and probiotics), and examine the influences of exercise on the gut microbiome and associated symptom burden prior to, during, and following cancer treatment.

Keywords Physical activity · Aerobic · Resistance · Microbiota · Immune system · Supportive care

Introduction

Despite a continual increase in cancer incidence, the effective reduction of cancer mortality for most cancers has resulted in an ever-expanding group of cancer survivors [1, 2]. From the time of diagnosis through to the end of life, cancer survivors will experience a diverse range of cancer- and treatment-related health consequences (including side effects and symptoms) that have a profoundly negative impact on clinical outcomes and health-related quality of life [3]. Specifically, cancer survivors receive a variety of local, systemic, or targeted treatments across the disease trajectory, including surgery, radiotherapy, hormone therapy, chemotherapy, and immunotherapy, as mainstay options for curative-intent or cancer control outcomes [4]. While these therapies are effective at treating cancer, they also result in substantial damage to the immune system including the gut microbiome [5, 6] and to other bodily tissues near and distant to where tumours reside, subsequently producing negative sequelae of physical and psychological disturbances [7, 8]. Sustainable and innovative multidisciplinary solutions in supportive and cancer survivorship care models are therefore required.

Symptoms and side effects of cancer treatment, whether acute or chronic, are predominantly driven by the toxicity of cancer therapies in concert with dysregulated metabolic, immune, and behavioural factors which amplify tissue injury

Nicolas H. Hart and Matthew P. Wallen are co-first authors.

Extended author information available on the last page of the article

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or associated symptom burden. Increasingly, the gut microbiome (i.e., the collection of bacteria and other microorganisms that colonise the gastrointestinal tract) is implicated in almost all facets of cancer and its treatment [9]. In the context of symptoms and side effects of treatment, the gut microbiome can directly influence the metabolism of some cancer drugs (e.g., irinotecan) [10] resulting in different circulating levels of toxic metabolites. In parallel, it exerts profound control of the host's immune system [11], intestinal motility, cellular repair mechanisms, neuronal synapse function, blood-brain barrier integrity [12], endocrine function, and neurotransmitter production. As such, an individual's unique gut microbiome composition before therapy and the diverse changes it may undergo during therapy, each influence a patient's risk of developing symptoms and their subsequent persistence. For this reason, modulating the gut microbiome to a "desirable" composition prior to therapy, or supporting its resilience during and after therapy, is emerging as a promising supportive care avenue to promote optimal survivorship. This approach is especially compelling given the capacity of the gut microbiome to influence not only intestinal symptoms but also extra-intestinal symptoms, especially those related to cognition [12].

The highly malleable nature of the gut microbiome provides multiple opportunities for how it can be favourably modulated. To date, approaches targeting the gut microbiome have been largely constrained to traditional interventions such as diet, probiotics, and prebiotics [13, 14]. In contrast, few studies have explored how exercise can beneficially modulate the gut microbiome in the context of cancer care. Exercise medicine is a well-established, safe, feasible, and effective therapy in the management of treatment-related sequelae for most cancer types and stages of disease [15, 16], with strong evidence supporting its role to reduce, prevent, or reverse physical and psychosocial effects of cancer and its treatment [17, 18]. Further, the immune system is responsive to exercise, with innate and adaptive responses achievable following acute bouts and chronic programs of prescribed exercise [19–22]. However, the ability of exercise to exert favourable influence over the gut microbiome and, by extension, the immune system in cancer populations during and after cancer treatment has received little attention [23] despite preliminary evidence demonstrating the potential of exercise to enhance treatment efficacy and improve clinical outcomes for cancer survivors [24]. This review synthesises current evidence investigating the response of the gut microbiome to exercise and seeks to explore the potential interaction that contributes to, at least in part, the positive physical, psychosocial, and clinical outcomes observed with exercise prior to, during, and following cancer treatment across the entire cancer survivorship care domain (i.e., from diagnosis through to the end of life) [25].

Gut microbiome and cancer

The gut microbiome has been implicated in cancer outcomes from diagnosis and recurrence to prognosis as well as treatment outcomes [9]. Evidence is also growing for the involvement of some taxa in the development of colorectal cancers [26], and among other findings, interindividual differences in the gut microbiome have been shown to play a role in the efficacy of treatments [5, 27]. In this review, we focus on the latter, and their implications for supportive care in cancer. While the core taxa that make up an individual's microbiome tend to stabilise in early life, it is important to note that substantial intraindividual variation can occur due to diet, medication, comorbidities, stress, living conditions, and other environmental factors [28]. Collectively, these contribute to the dynamic nature of the gut microbiome and its ongoing development and adaptation throughout a person's lifetime.

At the point of diagnosis, numerous microbial traits have been shown to identify various cancer types and prognostic features. For example, specific gut bacteria including *Bacteroides fragilis* and *Fusobacterium nucleatum* have been shown to be enriched in colorectal adenomas and adenocarcinomas [29, 30]. A systematic review of these, and other related taxa, suggest tumour-associated bacteria could be used as a diagnostic or prognostic marker for these cancers, although this research remains in its infancy [31]. The gut microbiome constantly interacts with the host immune system, as well as producing a range of metabolites such as short-chain fatty acids (SCFAs), which exert local effects and, upon absorption in the colon, systemic effects [32]. The immense control and influence of the gut microbiome exerted on its host underlies the increasing recognition of the gut microbiome's contribution to cancer aetiology and treatment outcomes (Fig. 1).

Gut microbiome and cancer treatment

Emerging evidence suggests that an individual's unique pre-treatment (i.e., treatment naïve) gut microbiome composition plays a significant role in influencing the host's response to therapy. This phenomenon has been most prominently observed in the context of immunotherapy [33, 34], where specific microbial "fingerprints" have been found to accurately predict treatment efficacy, as indicated by both short-term tumour responses and long-term survival. Importantly, unlike other associations observed for the gut microbiome and treatment outcomes, these predictions have been causally confirmed through faecal transfer of responder and non-responder stool samples into

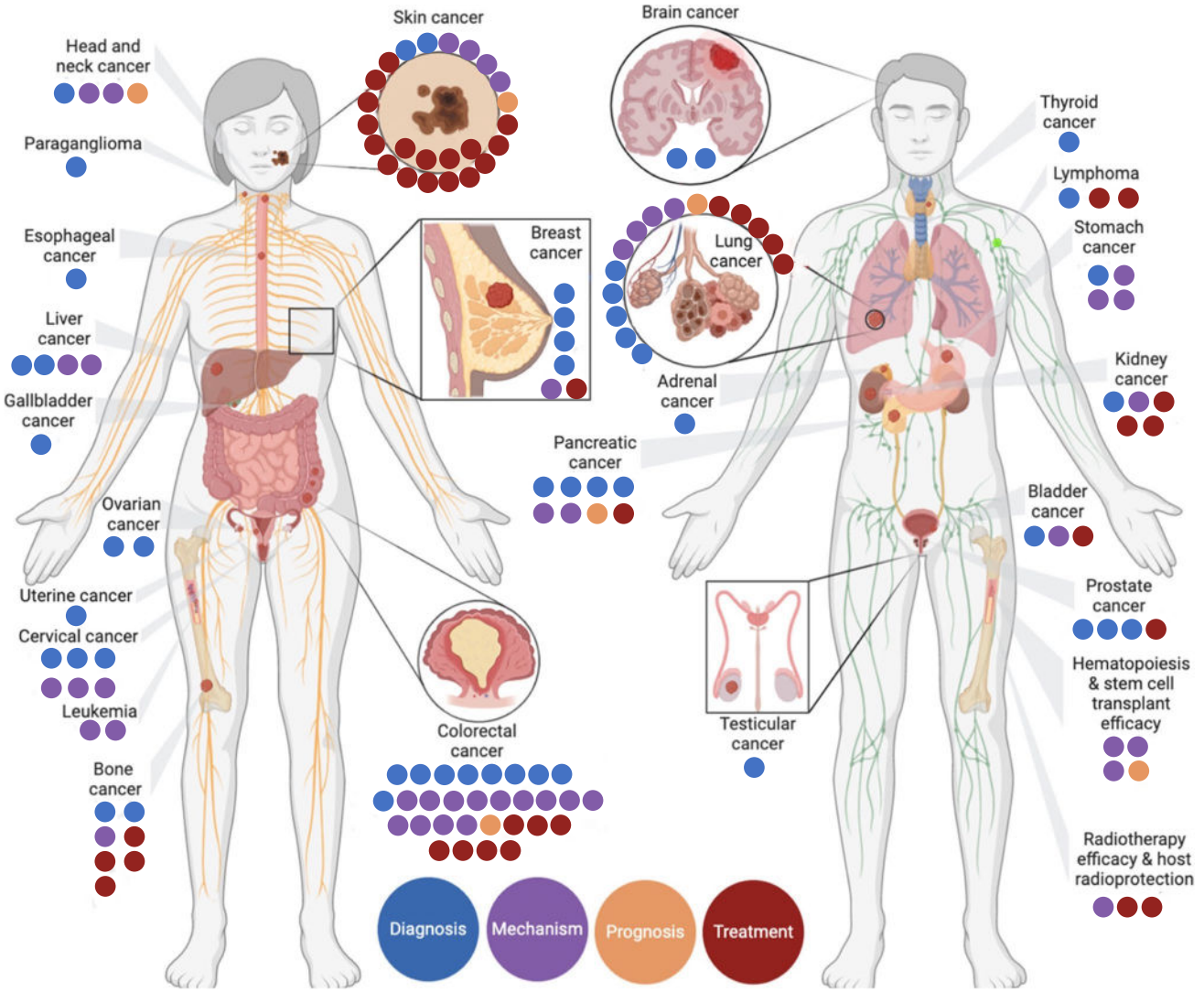

Fig. 1 Influence of the gut microbiome on cancer diagnosis (including recurrence monitoring (blue)), mechanisms (purple), prognosis (orange), and treatment (red), representing the number of studies in the literature implicating the gut microbiome across cancer management for particular cancers [9]. Adapted with permission from Sepich-Poore and colleagues (2022)

gnotobiotic (germ-free) mice who exhibited their donor response types. While unique microbial fingerprints have also been linked with other treatment responses (e.g., neuropathic pain and diarrhoea) [35–37], with some elegant machine-learning approaches predicting treatment responses [38], few studies have moved beyond associative findings. Despite the lack of causal clarity underpinning these observations, an individual's gut microbiome before therapy holds promise as an emerging strategy to predict the efficacy and toxicity of cancer drugs.

In addition to the influence of an individual's naïve microbiome on their acute response to therapy, treatment-induced changes in the gut microbiome are also recognised for their role in exacerbating acute and chronic toxicities [39, 40]. Almost all cancer agents cause a degree of microbial disruption, although current consensus implies these microbial changes are most likely secondary effects of treatment driven by mucosal inflammation ("mucositis") and dietary changes [6, 41]. Microbial characteristics and changes are commonly assessed using a variety of metrics that broadly fit into three categories: diversity, abundance, and function [42], though there can be nuance, exceptions, and modifications to these categories. Briefly, alpha diversity addresses overall species (or operational taxonomic unit) diversity of a sample, commonly assessed via measures of richness and evenness [43]. Beta diversity quantifies the similarity (or dissimilarity) between two or more samples, and these could be the same individual over time, different individuals, or different groups [44]. Abundance measures commonly refer to the change in relative

abundance of a microbe within a sample or between samples and are usually expressed as a percentage [45]. Diversity and abundance can be recorded at a variety of taxonomic levels (though generally kingdom through to species) [46]. These aforementioned components describe the gut microbiota, or the particular microbes, that are measurable. By contrast, the gut microbiome generally refers to how these microbes and their communities are behaving (i.e., their function) [47]. These functional aspects require in-depth techniques that assess gene activity of the microbes and may refer to metabolite producing capacity or other actions relating to interactions between microbes, their environment, and the host [48].

The specific changes in the gut microbiome that occur after cancer therapy are drug-specific, however are generally characterised by a decrease in alpha diversity, loss of commensal microbes, and the subsequent expansion of pathogens. These occur in parallel with functional deficits in the associated metabolome, with numerous studies showing a loss of beneficial SCFAs including butyrate, acetate, and propionate [49, 50]. SCFAs are a critical fuel source for the intestinal epithelium, while also acidifying the luminal environment to control pathogen expansion. As such, a loss of SCFAs leads to intestinal barrier dysfunction ("leakiness") and increases the risk of bacterial translocation and subsequent sepsis. A decrease in the richness and diversity of the gut microbiome has been associated with gastrointestinal toxicity [49]. For example, patients who experienced gastrointestinal toxicity after chemotherapy exhibited a notable decrease in the abundance of *actinobaceria* and *blautia* bacteria. Gastrointestinal toxicity represents a prevalent cause of treatment adjustments and hospitalisation [51], ultimately affecting treatment effectiveness and overall survival [52, 53].

While the gut microbiome has the capacity to recover after therapy, the rate of recovery is not well described and highly individualised, reflecting ongoing therapies (e.g., maintenance medication), persistent changes in diet, or ongoing stress among other factors. In fact, studies have reported microbial differences in childhood cancer survivors that persist into adulthood [54]. Of note, these data show that these microbial traits (or deficits) correlate with symptom burden and late effects, particularly those of metabolic origin. As such, this collective body of evidence suggests that promoting the composition and resilience of the gut microbiome before, during, and after therapy is critical for optimising treatment outcomes.

Given the rapidly growing body of evidence implicating the gut microbiome in the outcomes of cancer therapy and its highly modifiable nature, there is considerable potential to actively shift the gut microbiome to a more beneficial composition to improve cancer treatment efficacy while reducing cancer treatment toxicity [5]. Multiple methods have been trialled with varying levels of success. The effectiveness of probiotics in cancer survivor populations has yielded conflicting outcomes, likely due to a lack of specificity in strains employed for the particular group of cancer survivors studied [55, 56]. Faecal microbiota transplant (FMT), while met with understandable caution for use in people who are immunocompromised [57], has successfully been used in phase 1 clinical trials to improve treatment responsiveness to anti-PD-1 immunotherapy [58] and graft-versus-host disease in haematopoietic cell transplant recipients [59]. However, perceived inconsistencies in probiotic and FMT approaches have led to the emergence of nanotechnology methods that may target tumour-associated bacteria or modulate metabolites produced by the gut microbiome to potentiate the anti-tumour effects of traditional cancer therapies [60].

While approaches such as FMT, prebiotics and probiotics, and even nanotechnology hold promise, they may not be universally accessible and may not provide the most practical method for supporting the gut microbiome during cancer therapy. Hence, other approaches to modulating the gut microbiome are gaining traction [61], the most popular of which is diet [62]. Fermented foods, in particular, have shown a remarkable impact on the gut environment through their own microbiome and provision of beneficial nutrients for the indigenous microflora and microbiome [63]. The fermentation of dietary fibre in the gut microbiota produces beneficial microbial metabolites, such as SCFAs, which can influence the structure and diversity of the microbiome [64]. Additionally, high dietary fibre intake (>30 g/day) is associated with increased gut microbiota diversity during cancer therapy, especially in cancer survivors receiving immunotherapy [65–67]. This enables positive adaptation and regulation of the gut microbiota regardless of the inter-individual variation of the gut [68]. Next to diet, sleep and circadian rhythm are also established modulators of the gut microbiome [69, 70]. Another emerging area of research with great promise at positively influencing the entire human gut microbiome is exercise [71–73].

Modulation of gut microbiome by physical activity and exercise

Physical activity and exercise participation (or lack thereof) has the ability to effectively manipulate microbial communities [74–76]. To ensure future research is directed towards exploring therapeutic-driven strategies [77], it is critical to initially define and delineate the differences between physical activity and exercise. Physical activity is any bodily movement produced by skeletal muscle accompanied by energy expenditure [78], whereas exercise is the engagement of planned, purposeful, prescriptive, programmed, and progressive activities of a targeted and specific physical nature to influence human structure and function with the aim to

enhance physical health or fitness [79]. Exercise as medicine utilises the capacity for dose-response, load-adaptation outcomes between prescriptive exercise in its all forms [80, 81] and clinical management of acute injury or illness, or chronic disease or disorders, with the objective to improve one or more physical and psychosocial outcomes [80–82]. Participating in physical activity and exercise evokes positive changes across a myriad of health-related outcomes; however, these benefits are largely mediated by the appropriate dose of exercise reflected by exercise science principles, including FITT-VP (i.e., frequency, intensity, time, type, volume, progression), and exercise programming principles including periodisation and autoregulation [79–81, 83–86]. Herein, we explore the relationships between physical activity, exercise, and the gut microbiome.

Healthy individuals

Cross-sectional studies exploring the association between the levels of physical activity, exercise, or physical fitness (i.e., cardiorespiratory fitness or VO_2max) with the gut microbiome are derived from healthy, often athletic, populations [87–89]. Nevertheless, this research demonstrates that individuals reporting higher levels of physical activity or exercise, or possessing a greater degree of cardiorespiratory fitness, have a greater alpha or beta diversity [87, 90, 91]. These results are also reflected in athletic cohorts, where higher-level athletes (i.e., professional) from varying sports have a greater relative abundance of some microbial taxa compared to their lower-level counterparts (i.e., amateur) (e.g., 88). Although it is not clear to what extent this relates to performance compared to sport-specific demands, training, and dietary behaviours as it appears clustering of taxa does occur in athletes of similar sports [89]. Similarly, greater microbiota diversity has been found in athlete populations compared to controls; however, dietary differences, such as protein [87] and fibre [91] intake, are also often greater in athlete populations [87, 91]. Collectively, cross-sectional evidence to date suggests that participating in physical activity and exercise, or having a higher level of cardiorespiratory fitness, appears to be associated with a more favourable gut microbiome, independent to diet [92]. Further longitudinal research will be required to establish if and understand how exercise may influence the gut microbiota independently of diet, which is of interest when exploring mechanisms. However, it must also be acknowledged that pragmatically, exercise and diet are inextricably linked, with multidimensional interactive contributions to a favourable gut microbiome and the regulation of gut health [93, 94].

The number of longitudinal studies (i.e., sampling at multiple timepoints) exploring physical activity and exercise with the gut microbiome is growing; however, this literature is quite heterogenous, with distinct differences in temporal sampling (e.g., before and after a half or full marathon versus training blocks), observed cohorts (e.g., amateur versus professional athletes), and large variation between exercise prescriptions, making interpretation of the influence of FITT-VP difficult. Longitudinal studies [95, 96] consistently show favourable changes in gut microbiota composition (diversity and abundance). Emerging evidence also shows positive gut microbiome responses to exercise in clinical populations, such as those with diabetes [97], Crohn's disease and ulcerative colitis [98], and non-alcoholic fatty liver disease [99]. Various exercise prescriptions have been associated with a positive microbiota composition or function. To further optimise exercise prescription for this purpose, a better understanding of FITT-VP and its relationship to the human gut microbiota is needed.

Regarding exercise type, there is insufficient evidence to conclusively determine its influence on the gut microbiome. The only longitudinal study to investigate the impact of resistance training compared to aerobic training found no significant change with resistance training [100], suggesting that aerobic training is more effective in acutely changing the gut microbiome in the short term, whereas resistance training may require longer duration engagement to produce short-term or sustained modulatory outcomes. More evidence is clearly required to draw conclusions regarding exercise type. However, regarding change in exercise intensity or frequency, there is a range of emerging evidence examining the impact of detraining and tapering on the gut microbiome. Longitudinal intervention controlled trials examining exercise volume in previously sedentary populations found that positive changes in the gut microbiome through prior exercise were largely reversed after 3 to 12 weeks [92, 100, 101]. However, similar reversal does not seem to occur for athletes or highly active participants following a particularly physically demanding event. For example, rowers who participated in a competition over almost 34 days experienced no or only slight reductions 3 months post-event in the improved alpha diversity that they obtained during the event [102]. Moreover, following planned tapers (i.e., programmed reduction in training load), competitive runners did not appear to have a change in their microbiome profile [103]. However, for competitive swimmers [104], alpha and beta diversity was significantly reduced following reductions in training load over a 6-week period (2 weeks of peak training, 2 weeks start of taper, 2 weeks end of taper). This suggests that the gut microbiome is flexible in response to exercise, and sedentary individuals can make rapid changes to their gut microbiome with exercise; however, long-term engagement (as highlighted by studies recruiting athletes or highly active participants) may be required to establish a new and stable community that is largely resistant to the withdrawal of exercise stimulus.

These studies using multiple samples throughout exercise provide insight into microbial flexibility, suggesting that reductions in exercise volume, whether intentional (e.g., tapering) or non-intentional (e.g., illness or injury) [95, 102, 105], could reverse positive exercise-induced changes. However, there is a notable lack of research exploring these effects in resistance training. Further, whether the restoration of the microbiome is sensitive to the re-commencement of exercise following reduced exercise volume also remains unknown.

Body composition and exercise-induced gut microbiome changes

Body composition may influence how the gut microbiome changes with exercise. For example, Allen and colleagues [92] demonstrated that 6 weeks of aerobic exercise performed three times per week at a moderate intensity significantly modified a wide range of taxonomy for men and women with and without obesity, from relative phyla abundance through to genera abundance and SCFA production. Crucially, the authors found the way in which these genera, especially the functional changes of SCFA production, were dependent on participant body composition. Participants who were not classified as overweight or obese (BMI < 25 kg/m^2) noted significant increases in *Faecalibacterium* spp. and *Lachnospira* spp., reductions in Bacteroides, and positive changes in butyrate production, whereas within those who were obese (BMI > 30 kg/m^2), reductions in *Faecalibacterium* spp. and increases in *Bacteroides* and *Colinsella* were seen with no significant change in SCFA production. This study presents speculative evidence that exercise-induced changes in the gut microbiome may vary depending on other physiological factors, notably body habitus. There also seems to be interplay between exercise intensity and the gut microbiome. Kern and colleagues [96] investigated the impact of aerobic exercise on the gut microbiome among 88 participants who were overweight or obese. These participants were randomised to one of four groups including (a) no intervention (i.e., control), (b) cycling as active transport, (c) moderate intensity aerobic exercise (50% VO_2R), or (d) vigorous intensity (70% VO_2R) aerobic exercise for 6 months. There was a statistically significant improvement in alpha diversity for the vigorous intensity group at 3 months, a trend towards significant improvements for the moderate intensity group at 3 months, and the vigorous intensity group at 6 months. It is important to note that there were changes in macronutrient ratios in some groups, with overall daily energy intake remaining stable. This suggests that aerobic exercise performed at a moderate or vigorous intensity may be necessary to produce improvements in alpha diversity in the gut microbiome for overweight or obese people. However, it is important to recognise that all intervention groups demonstrated significant changes in microbial community structures (assessed by Bray-Curtis dissimilarity) compared to the control group, suggesting that aerobic exercise can influence the microbiome in this population. The authors also suggested that exercise upregulated inferred functional potential of the gut microbiome compared to the control group, primarily observed within central metabolism, amino acid degradation, and carbohydrate degradation. Future research is warranted to investigate how changes to the gut microbiome may be optimised through FITT-VP and how other physiological factors and behaviours may interact with the taxonomic and functional changes observed [106]. These findings considered that further research investigating FITT-VP manipulation in varying groups is warranted to understand how to improve the microbiome with exercise when accounting for possible factors that may attenuate any significant changes (Fig. 2).

Cancer survivorship

Epidemiological evidence consistently demonstrates that performing regular exercise is associated with a better prognosis, tolerance to, and recovery from cancer and its treatment, as well as to lower the incidence of treatment-related comorbidities, compared to those who are sedentary [108]. Emerging evidence highlights the potential application of exercise to induce positive changes to the gut microbiome for people with colorectal cancer [107], prostate cancer [109], and breast cancer [110] to date. The following sections outline the current preclinical and clinical evidence regarding exercise and the gut microbiome in cancer survivorship.

Preclinical evidence

Preclinical evidence from healthy rodent models suggests that short-term (15 days), low-intensity treadmill walking (1 m/min) performed after local abdominal irradiation was associated with significant improvements in microbiota structure when compared to a control group, noting reductions in alpha diversity and a significant increase in beta diversity [111]. Moreover, mice allocated to the walking group noted remodelling in radiation-shifted intestinal bacterial profile, showing a predominance of *Dubosiella*, *Bacteroides*, *Akkermansia*, and *Lactobacillus*. Synonymous improvements in metabolite profile were also seen within those who participated in exercise. Interestingly, exercise-induced microbiome changes, and reductions in inflammatory factors and oxidative stress, may have attenuated intestinal radiation toxicity. Specifically, the female mice who underwent irradiation and completed the walking protocol had more goblet cells, intestinal villi that were denser, and colons that were longer when compared to the mice who underwent radiation but did not complete

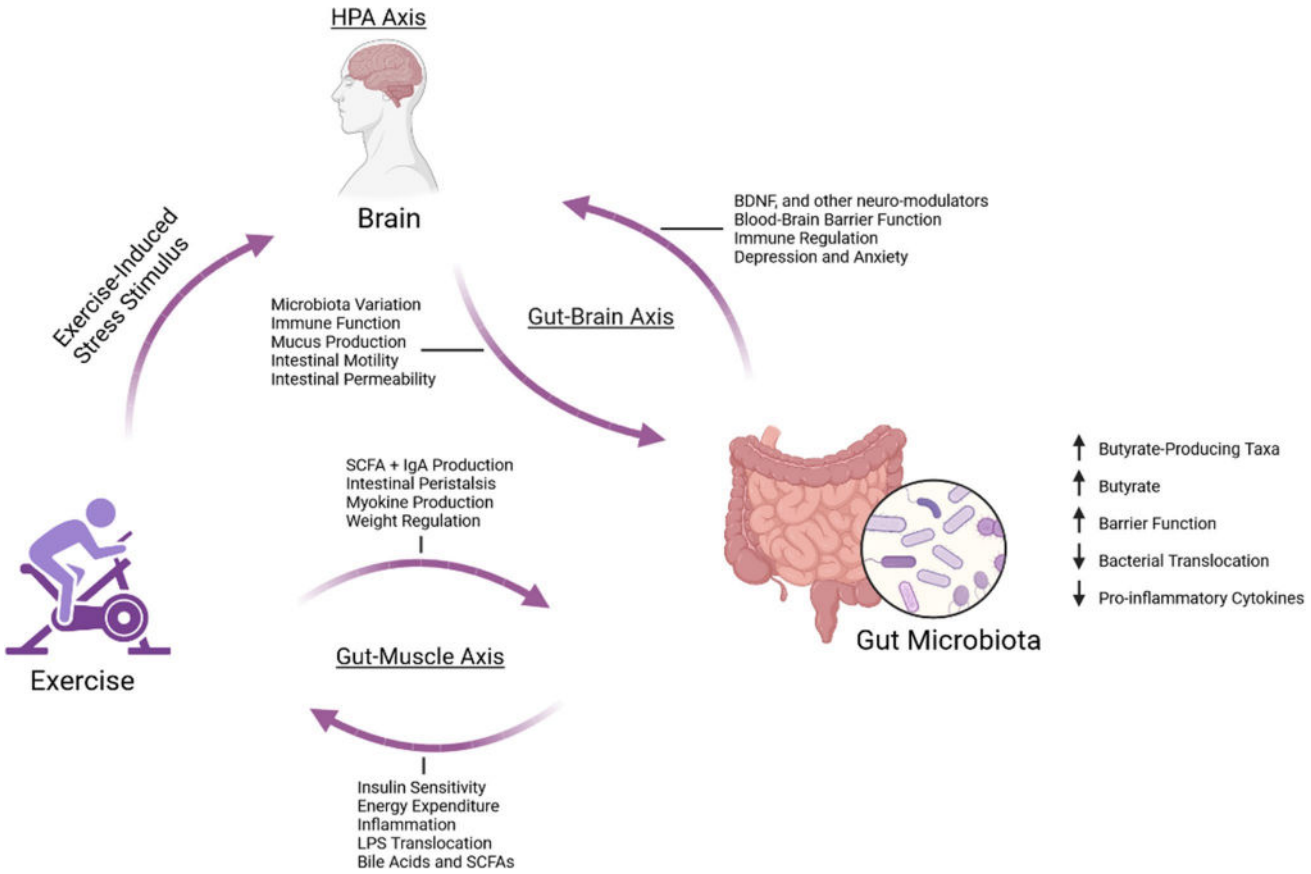

Fig. 2 Interplay of exercise and gut microbiota through the hypothalamic pituitary adrenal (HPA) axis, gut-brain axis, and muscle-brain axis. Exercise frequency, intensity, time, type, volume, and progression may adjust intestinal bacteria composition and activity. Paracrine-endocrine effects of exercise on the gut microbiome may contribute to modulating immune function (i.e., butyrate production), reducing intestinal inflammation (i.e., myokine production and salivary cortisol reduction), and improving psychophysiological issues such as anxiety and stress-induced depression; all of which have clear implications in cancer survivors. BDNF, brain-derived neurotrophic factor; SCFA, short-chain fatty acid; LPS, lipopolysaccharides; IgA, immunoglobulin A [72, 107]

any of the walking protocol. Another preclinical study found that germ-free mice with a faecal transplant from donor mice who participated in voluntary exercise (i.e., wheel running) for 6 weeks had favourable responses to chemically induced colitis (a risk factor for colorectal cancer), compared to mice with sedentary faecal donors [112]. These improvements were linked to different beta diversity, metabolite profiles, and inflammation, as a result of a donor, as well as an attenuated response to insult with exercise-mice presenting attenuated mucus depletion and altered cytokine expression [112].

Clinical evidence

While preliminary evidence suggests there may be potential protective or rehabilitative benefits of exercise on the gut microbiome in preclinical models, the translation of these findings to humans is currently limited. Only two clinical trials are in progress, including men with prostate cancer receiving androgen deprivation therapy [109] and adolescents (12–19 years) with cancer [113]. However, a single centre, cross-sectional study in small cohort ($n = 15$) of lung cancer survivors 1 year after lung resection [114] noted significant correlations between metrics of exercise tolerance and butyrate-producing species abundance, a key mechanism suggested to positively modulate immunity, inflammation, and risk of cancer-specific mechanisms. For example, *Parabacteroides merdae* was significantly associated with residual volume percentage ($r = .75–1$, $p > .01$), *Parabacteroides distasonis* was significantly associated to the ratio of minute ventilation to oxygen uptake ($r = .75–1$, $p > .01$), and *Alistipes onderdonkii* was significantly associated with specific airway conductance ($r = .75–1$, $p > .05$) and ratio of minute ventilation to carbon dioxide production ($r = .50–.75$, $p > .05$). However, there were also negative associations between some metrics and butyrate-producing species. For example, *Parabacteroides distasonis* and *Alistipes onderdonkii* were significantly negatively associated with forced expiratory volume in 1-s workload ($r = -.50$ to

−.75, $p > .05$). Further research is required to better understand the intricacies of these associations. Additionally, the authors found a significant relationship between peakVO_2 and the ratio between *Proteobacteri*a and *Euroyarchaeota* and *Actinobacteria* ($r = 0.56$, $p = 0.032$). A cross-sectional investigation in survivors of breast cancer ($n = 37$) supported these findings, where it was found that alpha diversity metrics (Chao 1, observed species, PD whole tree, and Shannon index) were positively associated with VO_2peak ($r = 0.34–0.51$, $p < 0.05$) [115]. It was reported that greater aerobic capacity was associated with higher relative abundance of *Bacteroides* and *Prevotella*, and lower *Escherichia*. This study further supported the relevance of cardiorespiratory fitness to gut microbiota interactions rather than physical activity as no association was found between any microbiota metric and total energy expenditure or active energy expenditure. Following this, the authors conducted a multiple linear regression and found that VO_2peak accounted for 22 and 26% of the variance in observed species and phylogenetic diversity, respectively. Collectively, these studies support findings from healthy populations where peakVO_2 accounted for more than 20% of the variability in taxonomic richness [90]. Together, these findings suggest elevated levels of cardiorespiratory fitness may be related to some bacterial species, and particularly metabolite production, of which have been implicated in reduced tumorigenesis; however, definitive trials are necessary to provide certainty [61, 116]. Additionally, in a recent study among colorectal cancer survivors, greater gut microbiome diversity and differential abundances were found between physically active and inactive patients [117]. Preliminary evidence suggests the dose of physical activity is likely relevant. A recent retrospectively study considered physical activity in a cohort of colorectal cancer survivors ($n = 40$) where the authors found that participants who reported high physical activity had significantly greater alpha diversity compared to those reporting moderate physical activity levels ($p = 0.04$) [118]. Using regression analysis, it was found that over a median follow-up time of 28.6 months, high physical activity was associated with a lower risk of mortality (relative risk 0.13, $p = 0.014$). The authors proposed the gut microbiota as a potential intermediary between physical activity and mortality; however, further research is required.

One single-group longitudinal pilot study investigated the change in gut microbiomes associated with participation in physical activity for breast cancer survivors [110]. Twelve, physically inactive (< 30 min vigorous or < 60 min moderate intensity exercise/week) breast cancer survivors (DCIS, stages I–IIIA) were enrolled. Participants were provided with basic exercise information (e.g., written materials and basic behaviour change to increase weekly PA), and five of these participants also received a behavioural change intervention aimed to increase PA to at least 150 min per week. Faecal samples and submaximal exercise test data to estimate maximal VO_2 were collected at baseline and at 3 months following enrolment. Interestingly, this study found a difference in beta diversity metrics and changes in fatigue interference ($p = 0.01$) and anxiety ($p = 0.022$) at 3 months. No significant relationship was found between change in estimated maximal VO_2 and Shannon index. However, a significant relationship was found between beta diversity and maximal VO_2 obtained at follow-up, and that the improvement in cardiorespiratory fitness was linked to the genera frequency, notably *Roseburia*, a known butyrate producer, and *SMB53*. Despite these findings, this study did not quantify nor observe the exercise of the participants. As within the literature, there is often changes seen in the gut microbiome of healthy populations, and other clinical populations with deliberate and structured exercise intervention, there is a potential benefit for cancer survivors. The established link between cancer and the gut microbiome paired with the emerging capacity of exercise to positively modify the microbiome suggests that the exercise-microbiome interaction may be a key missing link in explaining the inverse relationship between exercise and cancer risk. However additional, higher powered and more tightly controlled, research is required to better understand this potential explanatory power. The published evidence regarding microbiota-exercise interactions in people living with and beyond cancer is currently scarce; however, numerous ongoing registered trials provide further insight into the research landscape at present. Table 1 summarises identified published research investigating longitudinal changes in exercise and the gut microbiome across the cancer continuum. Studies were identified through a repeated search consistent with search strategy used in a recent systematic review [126], as well as keyword search in study protocol journals (JMIR Research Protocols, BMC Trials, BMC Cancer, BMJ Open, Contemporary Clinical Trials) and clinical trial registries (ANZCTR.org.au and ClinicalTrials.gov). The keyword search was conducted by DH and ANB (with NHH as arbiter) using Boolean operators (cancer AND microbiome OR microbiota AND exercise OR physical activity). Although this is a narrative review, due to this rapidly evolving field of interest in exercise oncology, an environmental scan of completed, ongoing, and planned (but registered) exercise and gut microbiome trials has been provided to benefit the design and development of future research in this field and has thus been included here.

Exercise, gut microbiome, cancer, and future challenges

It appears that the capacity for exercise to impact the gut microbiome has utility at all stages across the cancer continuum. The changes seen in the microbiome with exercise

Table 1 Summary of published studies, and registered completed, ongoing, or planned clinical trials within clinical trial registries, that examines the role of exercise with the human gut microbiome in people with cancer

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
Published studies							
Paulsen et al. (2017) [110]	Observational single arm	12 (55 ± 13)	Breast cancer (54 ± 56 months)	3 months Encouraged to increase PA; 5 participants received supervised 150 min exercise week^{-1}	Observe 3-day diet diary	16S rRNA	BMI, aerobic fitness (submaximal VO_{2max}), hospital anxiety and depression (HADS), fatigue symptom inventory, sleep quality (PSQI)
Bielik et al. (2023) [119]	Single-arm, healthy controls	16 CS (8.9 ± 3.3) 16 HC (9.0 ± 3.3)	Acute lymphoblastic leukaemia (1–3 years)	8 weeks 2 × week^{-1} 25–45 min, mod-to-vig, AT and RT	Provided with commercial probiotic (Danone, Belgium) 1 × day^{-1}	16S rRNA	NA
Donati Zeppa et al. (2023) [120]	Single arm	20 (51.8 ± 7.8)	Breast cancer (10.2 ± 3.1 months)	12 weeks 3 × week^{-1}, 20–60 min, 40–70% HRR, AT Note: 10 participants did not receive exercise	Advice based on Mediterranean diet (MD)	16S rRNA	BMI, VO_{2max}, fasting glucose, hormone profile, cholesterol and triglyceride, CRP, MD adherence
Registered studies							
ClinicalTrials.gov, NCT05939791	Single arm	16 (6–12) CS Healthy controls (n = NR)	Acute lymphoblastic leukaemia (1–3 years)	8 weeks 2 × week^{-1} 25–45 min, mod-to-vig, AT and RT	Provided with probiotic (*Lactobacillus casei*)	NR	NR
ClinicalTrials.gov, NCT05686213	RCT	39 (≥18)	Rectal or oesophageal cancer (ongoing)	5 weeks AT + RT group: 2 × week^{-1}, 60 min supervised AT and RT, 1 × week^{-1} unsupervised, 30 min AT moderate intensity AT group: 5 × week^{-1}, 30 min, moderate intensity	NR	16S rRNA	Body composition (BIA), aerobic fitness (submaximal), muscle strength, physical activity, health-related quality of life, treatment toxicity, satisfaction, immune cell function, immune cell mobilisation, immune cell infiltration, cytokines, tumour vascularisation

Table 1 (continued)

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
ClinicalTrials.gov, NCT05539794	RCT	136 (12–19)	Malignant extracranial tumour (ongoing)	Timeframe NR/duration of treatment 3 × week^{-1}, AT and RT, 5 × week^{-1}, respiratory muscle training	Twice monthly nutritional counselling, 3-day diet recalls	NR	Change in left ventricular function, arterial blood pressure, lipid profile, adiposity index, body composition (DEXA), physical activity, TEE, cardiorespiratory fitness, muscle strength, inspiratory muscle strength, psychological status (QoL, fatigue, stress, anxiety, depression), clinical variables (survival, treatment tolerability, days of hospitalisation), metabolic markers, inflammation, immune phenotype, immune function
ClinicalTrials.gov, NCT05000502	RCT	40 (18–70)	Breast cancer (≥1 year)	10 weeks 1 × week^{-1} video conference, home-based exercise	Participants asked to maintain usual diet	NR	Feasibility (recruitment, adherence, attrition, AEs, participant satisfaction), physical activity, body composition (BIA), physical performance, fatigue, anxiety, depression, sleep, pain, post-traumatic stress
ClinicalTrials.gov, NCT04866810	RCT	80 (18–120)	Melanoma (30 days post-systemic therapy, before immunotherapy)	4 months Prescribed 150 min of moderate, or 75 min of high intensity × week^{-1}	Plant-based high-fibre diet. Food recorded via MyFitnessPal	NR	Feasibility, physical activity, diet adherence, progression-free survival, QoL, objective response rate

Table 1 (continued)

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
ClinicalTrials.gov, NCT05307367	Single arm	144 (18–100)	Lung cancer (ongoing)	8 weeks 2–5 × week^{-1}, single-leg kicking training intervention	NR	NR	Disease outcome, muscle mass, insulin sensitivity, proteomic skeletal muscle, QoL
Gnagnarella et al. (2022) [121] ClinicalTrials.gov, NCT05155618	RCT (crossover)	300 (≥18)	Prostate cancer (ongoing)	6 months Unspecified day week^{-1}, counselling on physical activity	Counselling on diet	NR	Adherence to healthy lifestyle score, serum biomarkers (PSA), body composition (BIA), QoL, dietary intake, physical activity, acute and late toxicity (to radiation therapy)
ClinicalTrials.gov, NCT04706676	RCT	127 (6–18)	All malign and benign disorders treated with chemotherapy and/or radiation (ongoing)	6 months 2 × week^{-1} for 7 weeks, 3 × week^{-1} for weeks 8–24	3–5 days self-reporting	16S	Knee extension strength, markers of metabolic syndrome (triglycerides, HDL, BGL, BP), isometric bench press, GS, 6MWT, 30s sit-to-stand, TUG, hospitalised days, body composition (DEXA), QoL, metabolic syndrome prevalence

Table 1 (continued)

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
ClinicalTrials.gov, NCT05238376	Single arm	70 (18–80)	Hematologic malignancy (90 ± 30 days post-allogenic haematopoietic stem cell transplant and caregivers)	12 weeks Unspecified days week^{-1}, HIIT (AT) and RT	Observation of diet by clinicians and questionnaires	16S rRNA	HIIT attendance and adherence, physical function/activity (SPPB, 6MWT, 30 s sit-to-stand, grip strength), frailty questionnaires, muscle mass (BIA), CPET, intramuscular adipose tissue, intramuscular glycogen content, muscle thickness and area, subcutaneous fat, cognitive assessments, mental health, depression, anxiety, emotional support, isolation, self-efficacy, resilience, caregiver strain, support, and preparedness, skin and stool microbiota, inflammatory biomarkers, survival, disease-free survival, infection and hospitalisation rates, QoL
ClinicalTrials.gov, NCT04088708	RCT, aerobic training and attention control	126 (18–74)	Breast cancer (≥1 year)	10 weeks Alternate days, 20–60 min, AT, continuous progressing to HIIT	Controlled-feeding diet	NR, will address diversity and taxa	Systemic inflammation, ECG (autonomic nervous system, heart rate variability), cortisol, fatigue, VO_{2peak}, 6MWT, accelerometry-based PA, body composition (DEXA), QoL, self-efficacy, mood and stress, memory

Table 1 (continued)

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
ClinicalTrials.gov, NCT05349227	RCT (waitlist)	660 (≥80)	Any (≤1 year completion of primary treatment)	6 months 1 × consult week^{-1} to encourage PA	Consultation regarding diet as part of intervention, 24-h dietary assessment	16S rRNA	Acceptability and feasibility of coaching (regarding diet, exercise, fatigue, financial toxicity and associated symptoms), disease-related self-efficacy, physical function, QoL, anxiety, depression, cognitive function, sleep impairment, sexual function and satisfaction, financial toxicity of cancer treatment, symptom burden, PA, diet, health care utilisation
ClinicalTrials.gov, NCT05312255	3-arm, non-randomised	150 (≥18)	Multiple myeloma (ongoing)	6 months 2 × week^{-1}, resistance training and physical activity reminders (first arm)	NR Separate arm with time restricted eating intervention (second arm)	NR	Changes in immune cells, adherence to drug intervention (third arm), serum bone markers, body composition (DEXA), anxiety, fatigue, functional status, stress-related biomarkers
Newton et al. (2019) [109] ANZCTR.org.au ACTRN12618000280202	RCT	60 (NA)	Prostate cancer (ongoing)	12 weeks 3 × week^{-1}, AT and RT	Observation of diet via questionnaire	16S rRNA Targeted SCFA and metabolite, calprotectin	Dietary behaviour, biomarkers, clinical data, QoL, bowel function, body composition, muscle strength, aerobic fitness

Table 1 (continued)

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
ANZCTR.org.au ACTRN12621000256875	RCT, exercise and control	60 (18–80)	Breast cancer (3–12 months)	12 weeks Unspecified session duration, AT of 150 min week^{-1}, 2–3 RT week^{-1}	NR	16S rRNA	Inflammation, QoL, fitness, body composition (DEXA), barriers to exercise, daily PA, self-reported PA, algometry, general health questionnaire (SF-36)
ANZCTR.org.au ACTRN12621000698875	Single arm	15 (≥18)	Breast, prostate, and colorectal cancer (≥1 month)	6 months 3 × week^{-1}, 4 × 4 HIIT, 85–95% HRmax	3-day diet diary	16S rRNA	VO_{2peak}, body composition (DEXA), inflammation, adherence to exercise, MVPA, QoL, general health (SF-36), cancer-related fatigue, grip strength, depression, anxiety and stress, self-reported insomnia
Ryu et al. (2023) [122] Korean Clinical Trials Registry, KCT0007853	RCT	80 (19–70)	Breast cancer (ongoing)	12 months Unspecified days week^{-1}, ≥150 min week^{-1}, AT and RT periodised, low intensity to high intensity	Food frequency questionnaires	16S	Fasting insulin, shoulder ROM and strength, QoL, shoulder pain, PA, inflammatory markers
Demark-Wahnefried et al. (2016) [123], ClinicalTrials.gov, NCT01886677	RCT (waitlist)	40 (≥19)	Prostate cancer (ongoing)	3.5–24 weeks 2 × week^{-1} supervised and/or 5 × week^{-1} at home. Not all participants received supervised exercise	Diet counselling, with recommendations for caloric deficit of 1000 kcal/day	16S	Tumour proliferation rate, BMI, energy intake, PA

Table 1 (continued)

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
Ueland et al. (2022) [124], ClinicalTrials.gov, NCT04200482	RCT	90 (≥18)	Breast cancer (<10 years)	6 months Low-dose arm: 1 "PA class" High-dose arm: 12 "PA class"	Diet counselling delivered during PA class	16S	Accrual rate, adherence, retention, acceptability, biospecimen collection rate, change in dietary intake, MVPA, systemic inflammation, gut barrier permeability (LPS)
Kenfield et al. (2022) [125], ClinicalTrials.gov, NCT05056077	RCT	800 (≥18)	Colorectal cancer (>4 weeks)	48 weeks 16 conditions: all Pts receive booklet describing PA guidelines, 15 groups one, or a combination of: health encouragement text messages and/or direct health consults and/or coaching (4–15 sessions for each component depending on condition allocation)	Self-reported food intake	NR	Change in American Cancer Society guideline score (mean and individual component)
ClinicalTrials.gov, NCT05930496	RCT	30 (18–70)	Colorectal cancer (60 days–3 years)	8 weeks Unspecified exercise intervention	24-h dietary recall	NR Faecal SCFA concentrations	Recruitment, adherence, retention, acceptability
ClinicalTrials.gov, NCT05588700	RCT	236 (≥18)	Testicular cancer (ongoing)	1 year While on chemotherapy: 2–4 × week^{-1}, supervised exercise, moderate intensity After chemotherapy: 2–3 × week^{-1}, PA encouraged	NR	16S	Cancer-related fatigue, general fatigue, QoL, cognition, anxiety, depression, BMI, muscular strength, PA, sleep, motivation, pain, cancer relapse, return to work, inflammation and liver function biomarkers

Table 1 (continued)

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
ClinicalTrials.gov, NCT05113485	RCT	30 (50–75)	Breast cancer (>6 months)	6 months 2 virtual home visits, 2 virtual group education sessions, 7 individual telephone coaching session	Diet intervention for both groups: (1) Caloric restriction diabetes prevention program (2) High microbiota accessible foods	16S	CRP, visceral fat (DEXA), insulin resistance, BMI, waist circumference, SBP, QoL, HDL, VO_{2max}, triglycerides
ClinicalTrials.gov, NCT04499950	Sequentially assigned CT	55 (≥18)	Breast cancer (≥3 months)	6 months Behaviour coach telephone consults weekly (1–3 months) and monthly (4–6 months)	Diet conversations included in behaviour coach consult	NR	≥5% weight loss occurrence, HbA1c, IGF-1, BGL, blood lipids, insulin, adiponectin, leptin, Godin leisure time exercise, sleep quality, physical function, pain interference, fatigue, emotional distress, sexual function, MVPA, daily steps
ClinicalTrials.gov, NCT04818359	RCT	172 (30–70)	Breast cancer (<12 months following surgery, <6 months following chemotherapy)	3 months 2 × $week^{-1}$, supervised AT, 1 × $week^{-1}$ unsupervised, progressive intensity and duration (40–70% HRR and 20–60 min, respectively)	Diet habits questionnaire	16S	QoL, fatigue, BMI, body composition (BIA), cardiac function, HRV, VO_{2max}, flexibility, GS, proprioception, posture balance, upper limb viscoelastic characteristics, psychological well-being, insulin resistance, IGF-1, CRP, osteoporosis, cancer recurrence

Table 1 (continued)

Authors (year)	Study design	Participants (mean age ± SD)	Cancer type (time since treatment)	Exercise intervention	Diet consideration	Microbial assessment	Cancer-related outcomes
ClinicalTrials.gov, NCT05390398	RCT	184 (≥18)	Colorectal cancer (6 months–5 years)	6 months Behaviour change lifestyle coach per World Cancer Research Fund cancer prevention guidelines	Unspecified, implied to be included guidance in lifestyle coaching. Food frequency questionnaire	16S	Cancer-related fatigue, skeletal muscle fat infiltration and muscle circumference, QoL, 3-min step test, 5 × sit-to-stand, physical performance, GS, sleep, depression, anxiety, behavioural determinants, PA, waist circumference, cost-effectiveness

All included studies provided an exercise intervention and reported microbiota change as an outcome. If a study was ongoing, registered, and had a published protocol, data was extracted from the trial registry. Abbreviations: *AE* adverse event, *AEE* active energy expenditure, *ANZCTR* Australia and New Zealand Clinical Trials Registry, *AT* aerobic training, *BIA* bioelectrical impedance analysis, *BGL* blood glucose level, *BMI* body mass index, *BP* blood pressure, *CPET* cardiopulmonary exercise test, *CRF* cardiorespiratory fitness, *CRP* C-reactive protein, *GS* grip strength, *CT* controlled trial, *HDL* high-density lipoprotein, *HIIT* high-intensity interval training, *HRR* heart rate reserve, *HRV* heart rate variability, *IGF-1* insulin-like growth factor 1, *LPS* lipopolysaccharide, *MD* Mediterranean diet, *MVPA* moderate-to-vigorous physical activity, *NA* not applicable, *NR* not recorded, *PA* physical activity, *PSA* prostate-specific antigen, *Pts* participants, *QoL* quality of life, *RCT* randomised controlled trial, *REE* resting energy expenditure, *ROM* range of motion, *RT* resistance training, *SCFA* short-chain fatty acid, *SPB* systolic blood pressure, *SPPB* short physical performance battery, *TUG* timed up and go, $VO_{2max/peak}$ max/peak oxygen uptake, *6MWT* six-minute walk test, *16S* 16S ribosomal RNA sequencing; ↑, increase/positive; ↓ decrease/inverse

have potential crossover with factors thought to play a role in improved tolerance and response to treatment, improved recovery from treatment, and potentially quality of life following treatment [108]. Due to the diverse interactions of the gut microbiome with the host, it is feasible that optimising the gut microbiome in cancer settings is likely to not only benefit risk and recovery from cancer but also assist in positively modulating mental health, systemic immunity and lower comorbidity risk, and improve muscle quality and function with potential implications for sarcopenia and aging [105, 127–129]. With such promise, a greater understanding of these interactions is needed. For clinical utility, exercise-microbiome studies in cancer observing different stages of cancer progression, to diagnosis, treatment, and survivorship will be needed.

There are numerous challenges seen with microbiome literature, especially in humans, and even more so with the intention to draw clinical outcomes. Recent articles by Shanahan and colleagues [130] and Lloyd and colleagues [131] draw warranted attention to how previous models of research and conceptualising the microbiome struggle to address the translatable desire of this research, namely, what defines a healthy microbiome and subsequently, how do we evaluate, measure, and develop the gut microbiome in such a way that can reliably address how unique our gut microbiome profiles are? A key limitation of current research in humans is that interindividual variation in microbiome profiles are enormous, with factors at play from birth through to adulthood that influence this profile uniquely that randomised controlled trials with separate intervention and control groups cannot address [130, 131]. To navigate this in the context of exercise interventions in humans with the goal of measuring its impact on the gut microbiome, it is suggested here that changes are assessed via a waitlist or crossover control group compared to a traditional randomised controlled trial, such that we can compare the intraindividual response when on a control period compared to the intervention.

Previous studies have also focused on taxonomic identification of microbes in the gut to assess change with the most common techniques being variations of 16S rRNA gene sequencing that alone can often only identify to the level of genus reliably. This presents two challenges: (1) the variability between individuals means that when subjected to exercise, some may experience changes consistently in a certain type of bacteria while others see no change or change in a different microbe with no way to compare these changes, and (2) that the changes at the degree of species, and even further, strain of microbe are missed with these sequencing techniques, meaning the specific impact and interaction these microbes are having with the host are not assessable or somewhat an estimate. As sequencing techniques develop and become more affordable, the solution to both issues is to employ metagenomic techniques where possible. These techniques allow the identification and quantification of not only species and strain of microbe but also gene activity, so that functional understanding can be achieved, solving the second challenge highlighted by previous studies. This solution in recent research has also had the benefit of demonstrating that while microbiome profiles (identified by taxonomy) can vary dramatically between individuals, the functional tasks or "housekeeping" that the microbiome conducts is similar and can be compared when using techniques that allow for comprehensive functional assessment of the gut microbiome. This requires specialist knowledge and equipment to conduct; however, the findings from studies designed with a waitlist or crossover control paired with metagenomic sequencing to assess microbiome function provide a practical step towards gaining clinical insight in research regarding exercise and the human gut microbiome. If metagenomic analysis of the gut microbiome is not feasible, it is vital to interrogate the functional capacity of the gut microbiome by targeted metabolomic analyses (e.g., plasma SCFAs) in parallel to 16S rRNA gene sequencing.

Physiological response to exercise is highly varied depending on aspects of exercise prescription (frequency, intensity, time, and type) and therefore can be harnessed in a clinical setting to modify risk factors and optimise health in the context of disease management. What is not yet clear is how the nuances of exercise prescription may impact the gut microbiome. Some evidence is present that vigorous intensity activity is best to promote positive changes in commensal bacteria. However, it is important to acknowledge that this speculation deviates from findings of a recent systematic review which highlighted that exercise performed at a moderate intensity may be optimal for gut microbiome health [132]. Theoretical aspects of gut disruption that encourage adaptation and changes in the microbiome such as intestinal barrier dysfunction have been shown to be similar between 20 min of high intensity exercise (≥80% HRmax) [133] and 60 min of moderate intensity exercise (~60% HRmax) [134], suggesting that different prescriptions of intensity and duration may satisfy this mechanism of adaptation when used appropriately [135]. What remains to be seen is whether manipulation of other factors of exercise prescription can modify this response. Identification of further mechanisms linking exercise to the gut microbiome will also be crucial for this. The greatest and most rapid changes in the gut microbiome with exercise in humans are reported in athletic settings that are beyond what would be expected in a clinical setting. Hence, there is potential capacity for the development of exercise prescriptions to encourage microbial responses in those who are not accustomed to structured exercise, including developing our understanding of how exercise impacts the microbiome of cancer survivors as an emerging area of research.

Baseline microbiome characteristics may also be linked to an individual's microbial response to exercise or dietary interventions. Identification of the underlying mechanisms that are responsible for microbiome change observed with exercise will be important to inform and review exercise prescriptions seeking to target the gut microbiome. Future research is also required to understand how exercise may be incorporated with multidisciplinary approaches (such as diet) to improve the human gut microbiota in clinical settings. This will provide actionable tools that can be implemented to reliably provide positive change to the microbiome and reduce the risk of dysbiosis and potentially improve outcomes for cancer survivors. However, future research is required in those with cancer to describe the utility of exercise to modify the gut microbiome in such populations. Murine and human research including measures of systemic inflammation and immune factors to help describe how the gut-exercise interaction may modulate immune response would be of relevance from a clinical population perspective. Finally, as an understanding of exercise-microbiome interactions develops in those with cancer, understanding how diet and exercise may be utilised together to provide a more holistic approach is warranted. Together, these are likely more effective than either in isolation to gut microbiome modification, and a combination is likely necessary to optimise the direct nutrients the gut has access to (diet) as well as promote an environment for commensal bacteria and beneficial metabolite production (through exercise and diet in tandem).

Future directions and translational research

Numerous intestinal and extra-intestinal cancer treatment side effects are associated, and some causally implicated, with unique gut microbiome signatures or traits. Exercise appears to facilitate a more diverse gut microbiome and functional metabolome; however, most physical activity and exercise studies have been conducted in healthy or athletic populations, primarily using aerobic-based activities or exercise modalities. Accordingly, there are many future research directions to pursue in this field to address important questions, such as: (1) How does exercise prescription (FITT-VP) influence changes in the human gut microbiota?; (2) Does baseline microbial composition or do participant characteristics influence changes seen with exercise (i.e., influence of interindividual microbiome variation)?; (3) How does a combined approach to microbial manipulation compare to isolated (e.g., exercise and diet versus exercise or diet alone) interventions?; (4) How effective is exercise to influence the gut microbiome within an individual relative to their normal levels of variation, and how does this change over an intervention (i.e., influence of intraindividual microbiome variation)?; and (5) Does exercise promote beneficial gut microbiome abundance and diversity, and protect gut microbiome abundance and diversity, prior to, during, and following cancer treatment known to induce toxicities such as gut dysbiosis (e.g., chemotherapy, radiotherapy, immunotherapy, and hormone therapy).

These questions, and others, remain to be answered and would help progress this field forward. As such, we have provided some recommendations for future research that are key for translation of evidence to clinical utility, including:

1. Elucidating the various influences of exercise modalities (aerobic exercise, resistance exercise, combined exercise), types, intensities, frequencies, durations, and volumes to explore dose-response relationships when investigating interaction with the gut microbiome in cancer survivors.
2. Examining the influence of exercise on the gut microbiome, associated symptom burden, and potential treatment efficacy paradox, prior to, during, and following various forms of cancer treatment, including immunotherapy, chemotherapy, hormone therapy, and radiation therapy.
3. Exploring various methodological design features, such as: (a) metagenomic approaches to analysis of gut microbiome profiles around exercise, (b) obtaining multiple faecal samples during study windows, and (c) utilising crossover or waitlist controls in randomised controlled trials, to provide information and adequate temporal data and capacity to explore sensitivity of microbial changes during prescribed interventions or observed cancer treatment, specific to time course of change, and to account for inter- and intraindividual variation in the gut microbiome.
4. Inclusion of diet observation in exercise studies to allow for consideration of the moderating effects diet may have on the exercise and gut microbiome interactions. Similarly, this would support covariate analysis to provide more understanding of the independent interactions of exercise and the human gut microbiome and inform clinical translation of these methods.

Conclusion

The human gut microbiome is largely modifiable and highly sensitive; and therefore, responsive to endogenous, exogenous, and environmental inputs. Cancer treatment efficacy and toxicity outcomes are influenced by the gut microbiome. Thus, activities or therapies that modulate the gut microbiome may therefore improve the treatment efficacy-toxicity paradox. The well-established link between cancer and the gut microbiome paired with the emerging capacity of exercise to positively modify the human gut microbiome

suggests that the exercise-microbiome interaction may be an emerging, albeit promising factor towards explaining the inverse relationship between exercise and cancer risk. Studies in mostly healthy and athletic populations have demonstrated that exercise stimuli may positively modulate the gut microbiome and support an environment that facilitates diverse microbial profile and function. However, limited research in cancer and the gut microbiome exists and this requires urgent attention. It is recommended that future research is designed as waitlist or crossover trials with high sensitivity analysis such that function and microbial interactions with the host may be considered while accounting for inter- and intraindividual variation. Capturing all aspects of exercise prescription (FITT-VP) in these studies is also crucial to enable comparison and understanding of how exercise prescription may be relevant, and how it can be optimised. Multifaceted (i.e., diet and probiotics) studies investigating modulators of the microbiome are required. However, in clinical populations such as cancer, the exercise-microbiome interaction must be assessed in isolation before meaningful understanding can be achieved in a layered, multidisciplinary approach that may follow and be used in practice.

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Declarations

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Nicolas H. Hart Ph.D. AES CSCS FESSA is an NHMRC Emerging Leadership Fellow in Cancer Survivorship and the Program Director of Clinical Exercise Physiology at the University of Technology Sydney (UTS) in Australia. He is a MASCC 'Terry Langbaum' Survivorship Fellow and has developed MASCC-ASCO Standards and Practice Recommendations promoting survivorship care for people affected by advanced or metastatic cancer.

Authors and Affiliations

Nicolas H. Hart[1,2,3,4,5] · Matthew P. Wallen[2,6] · Morgan J. Farley[1,7] · Darren Haywood[1,8,9] · Alexander N. Boytar[7] · Kate Secombe[10,11] · Ria Joseph[2] · Raymond J. Chan[2,3] · Marlou-Floor Kenkhuis[12] · Laurien M. Buffart[12] · Tina L. Skinner[1,7] · Hannah R. Wardill[13,14]

✉ Nicolas H. Hart
nicolas.hart@uts.edu.au

1 Human Performance Research Centre, INSIGHT Research Institute, University of Technology Sydney (UTS), Moore Park, NSW 2030, Australia

2 Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Adelaide, SA, Australia

3 Cancer and Palliative Care Outcomes Centre, Faculty of Health, Queensland University of Technology (QUT), Brisbane, QLD, Australia

4 Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, Australia

5 Institute for Health Research, University of Notre Dame Australia, Fremantle, WA, Australia

6 Institute for Health and Wellbeing, Federation University, Ballarat, VIC, Australia

7 School of Human Movement and Nutrition Sciences, The University of Queensland, St. Lucia, QLD, Australia

8 Mental Health Division, St Vincent's Hospital Melbourne, Melbourne, VIC, Australia

9 Department of Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC, Australia

10 The University of Queensland Diamantina Institute, Faculty of Medicine, The University of Queensland, St. Lucia, QLD, Australia

11 Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia

12 Department of Medical BioSciences, Radboud University Medical Center, Nijmegen, The Netherlands

13 School of Biomedicine, University of Adelaide, Adelaide, SA, Australia

14 Supportive Oncology Research Group, Precision Cancer Medicine, South Australian Health and Medical Research Institute, Adelaide, SA, Australia

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