NEOPLASIA
www.neoplasia.com

Volume 29 Number xxx Month 2022 pp. 100800

Review

Diet-microbiome interactions in cancer treatment: Opportunities and challenges for precision nutrition in cancer

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Abstract

Dietary patterns contribute to cancer risk. Separately, microbial factors influence the development of several cancers. However, the interaction of diet and the microbiome and their joint contribution to cancer treatment response needs more research. The microbiome significantly impacts drug metabolism, immune activation, and response to immunotherapy. One of the critical factors affecting the microbiome structure and function is diet. Data demonstrate that the diet and microbiome composition affects the immune response. Moreover, malnutrition is a significant confounder to cancer therapy response. There is little understanding of the interaction of malnutrition with the microbiome in the context of cancer. This review aims to address the current knowledge of dietary intake patterns and malnutrition among cancer patients and the impact on treatment outcomes. Second, this review will provide evidence linking the microbiome to cancer treatment response and provide evidence of the potentially strong effect that diet could have on this interaction. This review will formulate critical questions that will need further research to understand the diet-microbiome relationship in cancer treatment response and directions for future research to guide us to precision nutrition therapy to improve cancer outcomes.

Neoplasia (2022) 29, 100800

Keywords: Oncology, Malnutrition, Dietary risk factors, Dietary intake, Quality of life, Cachexia

Recent evidence demonstrates that dietary intake directly impacts cancer treatment response to immunotherapy in patients with melanoma through a dietary fiber-gut microbiome mechanism.[1] However, the mechanisms by which the diet-microbiome relationship effects other cancers or treatment modalities remains unknown. In general, a prudent dietary pattern in cancer patients is associated with lower overall mortality in multiple cancer types.[2,3] This prudent diet includes higher consumption of vegetables, whole fruit, whole grains, nuts and legumes, omega-3 fatty acids, polyunsaturated fat, and lower consumption of sugar-sweetened beverages, red/processed meat, sodium, trans fat, and moderate alcohol consumption. Specifically, in colorectal cancer (CRC) higher intakes of fiber, calcium, omega-3 fatty acids, and milk are also associated with a lower risk of death, while whole-grain intake is associated with lower CRC-specific mortality.[4–6] In contrast, a diet high in processed meat is associated with decreased disease-free survival in CRC.[7] Critically, a variety of dietary patterns are also known

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Received 6 February 2022; received in revised form 13 April 2022; accepted 18 April 2022

https://doi.org/10.1016/j.neo.2022.100800

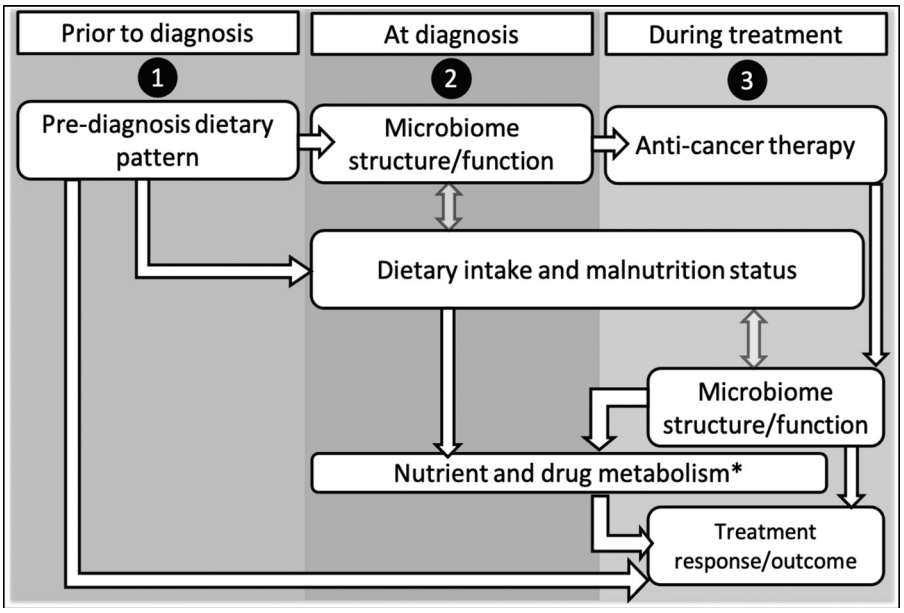

Fig. 1. Concept map of the diet-microbiome relationship in cancer treatment. (1) Prior to diagnosis, dietary patterns can affect both microbiome structure/function and malnutrition status at diagnosis, as well as treatment outcomes . (2) At diagnosis, microbiome structure/function affects anti-cancer therapy effectiveness, and possibly effects dietary intake and malnutrition status. Subsequently, dietary intake and malnutrition status can affect nutrient and drug metabolism, which itself can mediate* the relationship between dietary intake, malnutrition and treatment response. (3) During treatment, anti-cancer therapy affects dietary intake, malnutrition, and microbiome structure/function. The microbiome also impacts treatment response, which is likely mediated* by nutrient and drug metabolism. Other diseases states show a relationship between microbiome structure/function and malnutrition status, but this had not been demonstrated specifically for cancer. Note: While this model does not include the contribution of the immune system, it is understood to play a key role. (solid arrows = direct evidence; transparent arrows = indirect evidence).

to affect the composition and function of the microbiome (e.g. bacteria, viruses, fungi, archaea, and their genomic content). The impact of the diet on the microbiome is well-established, and comprehensive reviews on this relationship have been recently published.[4,5,8,9] Evidence for the importance of the relationship between diet and the microbiome in colon inflammation, a risk factor for CRC, was demonstrated by seminal work from O'Keefe et al.[10] They showed that a two-week dietary exchange, in which rural Africans consumed the typical low-fiber Western diet of African-Americans (AA) and African-Americans consumed the high-fiber plant-based diet of Africans, resulted in improvements in microbial structure and function, in particular increases in butyrate-producing bacteria and decreased secondary bile acids.[10] Furthermore, they saw reductions in inflammatory (bile acids) and proliferative markers (Ki-67) among the AA consuming the rural African diet in only two weeks. Together, these data suggest that long-term dietary patterns and acute dietary changes made before/during treatment may have favorable effects on the gut microbiome structure and function, which we propose could improve treatment response.

Before dietary patterns can be harnessed as adjuvants to improve cancer treatment response several areas need to be addressed. This review will focus on the following topics to explore diet and the microbiome in cancer treatment: A) the effect of diet and malnutrition on treatment response during cancer therapy, B) the effect of diet on the microbiome structure and function during cancer treatment, and C) the modifying effect of the microbiome on nutrient and drug metabolism during treatment, and overall treatment response (Fig. 1). We believe a precision nutrition approach to cancer treatment is achievable with a greater understanding of these critical relationships.

The current knowledge regarding medical nutrition therapy in cancer patients during treatment

Although data show prudent dietary patterns improve cancer treatment response, challenges from tumor burden and the effects of cancer treatment limit the ability to follow these dietary regimens. Patient-related factors complicating healthy dietary patterns or nutrition intervention include lack of appetite, altered taste, difficulty swallowing, nausea, vomiting, painful mouth, digestive issues, amongst others.[11] Studies show a strong association between inadequate nutritional status and severity of treatment-related symptoms.[12] The symptom burden, both physical and physiological, only increases upon initiation of chemotherapy.[13] Specifically, symptom burden among cancer patients is most severe one week after chemotherapy administration, leading to malnutrition.[14] As a result of the process of carcinogenesis and anti-cancer therapy, a vicious cycle of cancer-induced nutritional deficiencies and malnutrition-driven cancer complications ensue, further reducing beneficial patient treatment response. Addressing the issue of malnutrition among cancer patients is one of the most critical needs in cancer patient care.[15]

The incidence of malnutrition among hospitalized cancer patients is as high as 50%, which in itself is a strong predictor of overall survival.[16] Untreated malnutrition during therapy can significantly reduce chemotherapy or radiotherapy tolerance, increase toxicity, prolong hospital stay, complicate post-therapy patient care, and increase financial burden.[16–19] Malnutrition can also result from metabolic alterations due to tumor burden and treatment, precisely, an imbalance between patient nutritional

needs, tumor demands, and nutrient availability. In CRC, there is an association between low serum levels of glutamine, histidine, and alanine and poor cancer survival.[20] Specifically, protein-energy malnutrition or chronic protein restriction increases the risk of amino acid deficiency, influencing cancer response.[21] Since we know that the microbiome can itself confer metabolic alterations in the host (mediator), as demonstrated by fecal microbiome transplant studies in mice, the relationship between malnutrition and altered metabolism suggest a mediating effect of the microbiome on metabolic alterations.[22–25] The microbiome can also act as an effect modifier, in which the structure/function of the microbiome prior to dietary intervention or drug treatment (e.g. immunotherapy) modifies the effect of the intervention on host response.[26] Evidence in an animal models of protein restriction, supplemented with fiber (cellulose or inulin), demonstrates that the microbiome is critical in producing metabolic products that induce changes in metabolism; mainly through activation of fibroblast growth factor 21 (FGF21).[21] Specifically, supplementation with cellulose, but not inulin, was sufficient to mitigate the increased expression of FGF21 resulting from protein restriction, and to prevent weight loss in part through increased abundance of cellulose-responsive bacteria. Towards this idea of using diet and the microbiome to prevent or treat malnutrition, links have been identified between malnutrition in children and microbiome dysfunction. In general, protein energy malnutrition or undernutrition (PEU) in children (e.g. Kwashiorkor) is the result of prolonged food and nutrient deprivation related to starvation in the absence of disease.[27] In the context of cancer, malnutrition can result from several factors including tumor metabolism or burden and cancer treatment effects; while cancer cachexia is a complex syndrome that is represented mainly by skeletal muscle loss along with metabolic derangement.[28] Recently, significant strides have been made in reversing acute moderate malnutrition in children using microbiome-targeted therapeutic foods.[29,30] Given that PEU in children has components of fat and muscle wasting seen in cancer cachexia, this link between PEU and cancer cachexia provides proof-of-principle that a similar dietary approach may work by targeting the microbiome in cancer cachexia to prevent or treat metabolic dysfunction and wasting. However, much more research is needed in this area to address malnutrition in cancer, focusing on possible microbial mediating factors.

Studies indicate that the microbiome can be a factor affecting some of the negative anti-cancer treatment effects. Several animal model studies demonstrate that the gut microbiome is a contributing factor to inflammatory and neuropathic pain resulting from cancer therapy, and that modulation of the microbiome through fecal microbiome transplant (FMT), antibiotics, or probiotics can counter these effects.[31–37] A small number of studies using dietary prebiotics (e.g., pectin and inulin) and/or probiotics demonstrate improvements in side-effects from cancer treatment.[38–42] However, a more recent study indicates that for immunotherapy response probiotics may be couterproductive to efficiacy.[1] In general, probiotic interventions demonstrate moderate impacts on weight gain, BMI, and diarrhea but are still preliminary and not conclusive.[43–47] However, intervening during cancer treatment with dietary or supplementary adjuvants will be challenging given the physical and mental stress of cancer therapy. Although, several clinical trials are ongoing to address this lack of information regarding dietary intervention during cancer treatment.[48] Overall, tackling the issue of malnutrition and designing personalized nutrition therapy will require an in-depth understanding of the contribution of the gut microbiome to malnutrition, as well as genetics, nutrient and drug metabolism at diagnosis and during anti-cancer treatment.

One of the significant barriers to providing personalized nutrition therapy for cancer patients is the lack of standardized dietary capture tools, among several other factors (Table 1).[15] These tools would drastically improve the identification of at-risk patients early after diagnosis to manage and treat malnutrition and optimize treatment response. While there are several different malnutrition assessment tools available, including, Malnutrition Screening Tool (MST), NUTRISCORE, and Patient-Generated Subjective Global Assessment (PG-SGA), unfortunately, there is no current consensus on which screening tool to use for cancer patients specifically.[49,50] Furthermore, the dietary assessment tools such as Food Frequency Questionnaires (FFQs), Healthy Eating Index (HEI), Food Diaries, 24-hour recall, and short dietary screeners are designed for healthy populations and do not include questions specifically designed for cancer patients. Cancer patients represent a unique population with special nutritional needs, which may require specific evaluation tools on dietary intake assessment. Very little is known, however, about the dietary patterns or food intake fluctuations of cancer patients undergoing therapy, though numerous dietary interventions have been conducted.[51] Based on anecdotal clinical observations, cancer patients can experience dramatic shifts in dietary intake, which are dependent upon multiple factors, including the cycle of treatment and treatment type. Unfortunately, current dietary tools designed for healthy individuals do not adequately capture dietary collection from cancer patients. The most often used tools in dietary studies with cancer patients include 24 hour recalls and/or food FFQs (unpublished data). The advantage of the 24 hour recall is its ability to capture detailed short-term dietary intake, like dietary supplements or medical nutrition formulas often used by cancer patients (e.g. Two Cal HN), however, they rely on specific memory and trained interviewers, both of which are often limited in the cancer setting. Furthermore, multiple 24 hour recalls would be critical to capture fluctuations in dietary intake around treatment cycles and surgery. Similarly, the FFQs, which are limited to a finite set of foods, captures long-term diet (past month or year) based on the probability of consuming the food and amount on a given day. This estimate of usual intake assumes the person's diet does not fluctuate dramatically over the month or year, an assumption which may be violated during cancer treatment . These limitations are extensively reviewed in Shim et al.[52] and indicate the need to develop more appropriate cancer-specific dietary capture tools.

Table 1

Barriers and challenges in oncology nutrition care in cancer treatment centers.

Ninety percent of cancer patients receive outpatient care now, in place of inpatient care, drastically affecting treatment quality.[51]
Inconsistent or no nutritional screening despite evidence suggesting the importance of nutrition in treatment outcomes and screening mandates by The Joint Commission.[52]
InRDN to patient ratio insufficient.[15]
Lack of insurance reimbursements for nutrition consultation and rising out-of-pocket expenses, and[53] 76.8% centers do not bill for nutrition services.[54]
Half of the cancer centers screened for malnutrition; 64.9% used a validated screening tool (MST, PG-SGA, PG-SGA SF, MUST), remaining used non-validated tools.[54]
Lack of standardized protocols and methodologies for oncology nutrition care.[53]
Disparate operations of nutritional services and healthcare system, widening the gap between doctors and nutritionists.
An absence of a gold-standard malnutrition screening tool, especially designed for oncology patients considering varied symptom burden involved.
Call for more studies affirming the need for a successful nutrition intervention by an RDN as opposed to non-RDN interventions.[15]

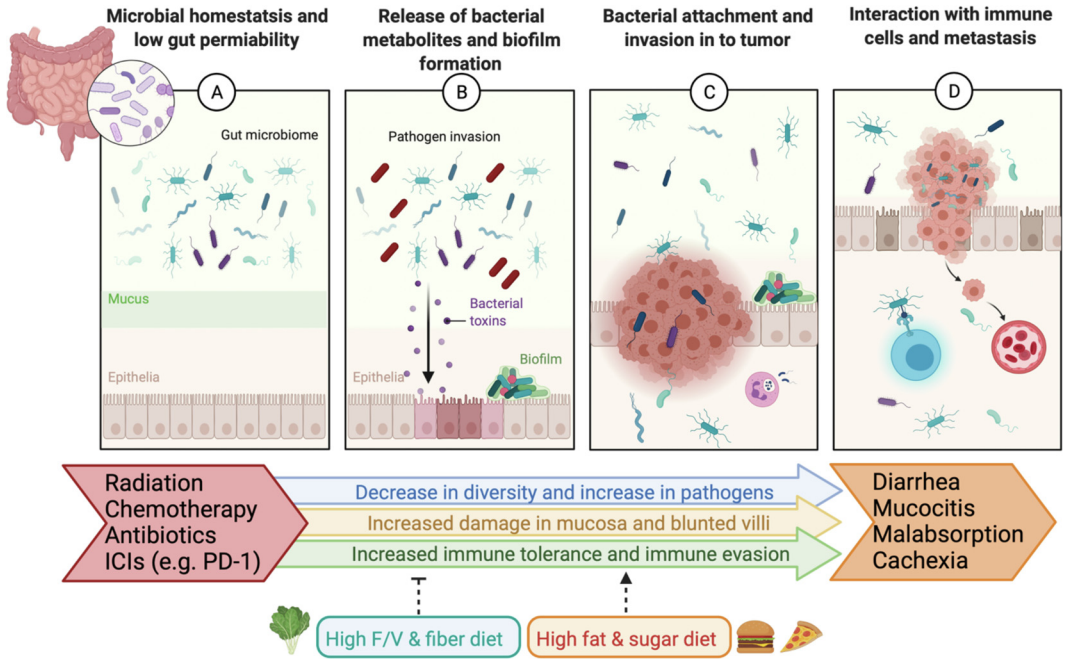

Fig. 2. Microbial interactions in the process of carcinogenesis and effects of diet and drug therapy on cancer treatment outcomes. *Top panel*: A) Microbial homeostasis is conferred by an immunocompetent immune system, microbial diversity, double mucus layer, epithelial tight junctions, and production of antimicrobial peptides, B) Disturbances in microbial homeostasis occur through gene mutations, loss of diversity, pathogen invasion, increased expression of virulence factors, development of biofilms, release of bacterial metabolites/toxins, and activation of inflammatory pathways, C) Neoplastic transformation of epithelial cells resulting from gene mutations and metabolic changes that alter bacterial attachment, reduce tight junctions, and allow microbes and microbial products intimate contact with the tumor cells, D) Additional tumor mutations and extravasation of tumor cells provide microbes with opportunities to invade the tumor microenvironment, tumor cells, and interact with immune cells to confer immune evasion. *Bottom panel:* Anti-cancer therapies induce changes in the microbiome, gut barrier function, epithelial structure leading to deleterious side effects. Dietary patterns are implicated in mediating some of these treatment effects. Note: While this example is focused on CRC, several mechanism and factors represented are also relevant to other solid tumors. Created with BioRender.com.

Diet-microbiome relationship in cancer treatment outcomes

Microbial interactions in carcinogenesis and cancer treatment

Both the diet and the microbiome independently impact cancer development and treatment outcomes. Complex interactions of the immune system, secretory antimicrobial peptides, two-layer mucus barrier, epithelial cell tight junctions, and the blood-brain barrier maintain the homeostasis between the microbiome and the body habitats (Fig. 2A).[56] When any of these control mechanisms fail, such as in the context of carcinogenesis, microbial homeostasis can be lost. Whether the loss of microbial homeostasis results from carcinogenesis or initiates the process is still the subject of intense research but likely results from a combination of both. During the process of carcinogenesis, bacterial diversity is often lost, as well as specific clades and species, due to multiple host factors, including metabolic and immune system changes.[57] Specifically, loss of diversity can occur through exogenous and endogenous factors. Exogenous factors include but are not limited to geolocation, hygiene, diet, drugs (e.g., antibiotics), and pathogen exposure.[57] Endogenous factors leading to diversity loss include metabolic changes in the epithelial cells (e.g., increased oxygen at the mucosal surface) resulting in loss of obligate anaerobes, DNA damage from bacterial toxins, loss of tight epithelial junctions, reduced mucin secretion, increased production of reactive oxygen species (ROS), loss of antimicrobial peptide secretion, changes in epithelial adherence proteins, and increased inflammation (Fig. 2B-C).[58–60] Induction of pro-inflammatory pathways can occur through multiple mechanisms, including the microbiome.[61] Enhanced pathogen invasions and bacterial toxin secretion can trigger pattern recognition receptors (PRRs) that activate toll-like receptors (TLR) on epithelial and immune cells resulting in the production of chemo- and cytokines that recruit neutrophils, macrophages, and other immune cells, which enhance the pro-inflammatory signaling (Fig. 1D).[62–65] Disruption of the microbiota by chronic inflammation, a risk factor for multiple cancer types, can also result in induction of pro-inflammatory pathways and select for pathogenic microbes, induce biofilm formation, or encourage the expression of virulence factors in commensal microbes.[66] The precise mechanisms of microbial homeostasis are unclear and likely heterogeneous between cancer types and between individuals.

Apart from exogenous and endogenous effects on the microbiome during carcinogenesis, microbes and microbial communities themselves can contribute to both initiation and promotion of several cancer types. Currently, ten microbes are classified as carcinogens by the International Agency for Research on Cancer.[67] Beyond these known carcinogens, four microbes (Salmonella enterica, Fusobacterium nucleatum, Enterotoxigenic Bacteroides fragilis (ETBF), Escherichia coli pks+) are possible cancer promoters based on current literature.[58] In general, they can produce toxins that damage DNA (e.g., pks+ E. coli and ETBF), initiate biofilm formation and inflammation, and contribute to immune evasion.[58] Specifically, F. nucleatum can bind T cell immunoreceptor with Ig and ITIM domains (TIGIT) receptors on NK- and T-cells, reducing the anti-tumor response.[68] Of importance to this review, is the ability of the microbiome to metabolize components of the Western diet (high in red meat, saturated fats, added sugars, and low in fiber) into metabolic products that can contribute to inflammation and cancer development. Hydrogen sulfide-producing bacteria

that metabolize sulfur compounds in red and processed meats and microbes that convert primary to secondary bile acids can induce DNA damage and reduce gut barrier function.[69] In contrast, a diet higher in whole grains, fruits, and vegetables contributes to increased microbial diversity, beneficial short-chain fatty acid production, and higher numbers of activated T-regulatory cells.[69] This latter beneficial effect of the microbiome could contribute to enhancing the immune response to anti-cancer therapy, notably immunotherapy.[1]

Beyond the effects of carcinogenesis, the microbiome can alter the effects of cancer treatment and is affected by cancer treatment. Cancer-directed therapies, chemotherapy, and radiation directly affect the microbiome, surrounding tissues, and immune response. These treatments can lead to damaged villi in the gut, loss of diversity, decreases in commensals, and subsequently chemotherapy-induced diarrhea, mucositis, and tissue atrophy (Fig. 2).[70] Specifically, chemotherapy-induced diarrhea occurs in as many as 50% of CRC patients and is associated with changes in the microbiome.[71] Similarly, radiation therapy has effects on the microbiome in reproductive tract cancers. In peri or postmenopausal females, radiation may permanently alter the vaginal mucosa making *Lactobacillus* spp. replenishment difficult despite vaginal estrogen replacement.[72,72] This loss of diversity results in a neutral pH, making the vagina more conducive to the growth of pathogenic bacteria.[73] Furthermore, pelvic radiotherapy can increase the abundance of *F. nucleatum*, a key species known to promote CRC and metastasis.[74] Among women undergoing chemoradiation for cervical cancer treatment, the gut microbiome diversity at treatment initiation was also predictive of survival.[75] Specifically, long-term survivors had enrichment of *Escherichia shigella, Enterobacteriaceae, and Enterobacteriales* and increases in CD4+ T cells, suggesting that these factors may be involved in positive treatment response to chemoradiation.[75,76] This evidence indicates that restoring microbial diversity and possibly gut barrier function would improve treatment response before or during cancer therapy.

Evidence supports that the microbiome also impacts the effectiveness of treatment through several different modes of action, including drug metabolism, immune modulation, and host diet/nutrient interaction.[1,77–79] Microbial taxa, like mammalian cells, possess enzymes capable of metabolizing drugs into various forms. In the case of the chemotherapeutic gemcitabine, the intertumoral Gammaproteobacteria can induce gemcitabine resistance,[78] while the species R. planticola, E. coli, and K. pneumonia can detoxify the chemotherapeutic doxorubicin, which also conferrs protection to the greater microbial community.[80] Likewise, microbial taxa carrying the enzyme β-glucuronidase can reactivate the anti-cancer drug irinotecan in the GI tract leading to severe diarrhea;[81] a significant complication in several types of anti-cancer therapies. Furthermore, studies demonstrate a causative effect of the chemotherapy-exposed microbiota on the development of side effects. Specifically, FMT from paclitaxel-treated mice induces inflammation, which is reversed through passive microbial transfer (coprophagia) when co-housed with unexposed mice.[82] Thus, the microbiota is a crucial player in therapeutic activity and toxicity for multiple anti-cancer therapies through pharmacodynamics and immunological pathways.

Likewise, the microbiome is critically essential to chemo- and immunotherapy effectiveness. Early work established that antibiotic treatment inhibits the efficacy of the chemotherapeutic oxaliplatin and immunotherapy through mechanisms that converge on the microbiome-immune axis.[83] Specifically, antibiotics decrease the LPS-producing bacteria, which are necessary to activate TLR4 on tumor-infiltrating myeloid cells to enhance tumor-killing ROS production upon oxaliplatin treatment.[84] Additional seminal work went on to identify specific microbial taxa that could either enhance (Bacteroides ovatus and Bacteroides xylanisolvens) or inhibit anti-cancer treatments.[85] Specifically, treatment with different consortia of probiotic bacteria (e.g., Roseburia intestinalis, Eubacterium hallii, Faecalibacterium prausnitzii, and Anaerostipes caccae) appears to promote a beneficial response to immunotherapy and, in some cases, work as well as chemo- and immunotherapy.[86–88] A recent key finding among individuals with melanoma treated with immunotherapy (i.e., anti-PD-1) showed that those who responded favorably also had the greatest fecal microbial diversity before treatment.[89] However, a more recent follow-up study could not replicate this finding.[1] Nonetheless, they later went on to show that those patients with melanoma who were responders to immunotherapy also had a higher intake of dietary fiber, which tends to increase overall microbial diversity and enhance gut barrier function.[1] To further interrogate this dietary fiber effect, they used an animal model of melanoma and found that supplementation of dietary pectin along with immunotherapy improved treatment response.[79] This beneficial effect of dietary pectin occurred through enhancing the microbial production of c-di-AMP, triggering the secretion of type I interferon by intertumoral monocytes creating an anti-tumorigenic environment. Following these studies, a more comprehensive study used both a previous cohort of patients with melanoma and a new cohort of melanoma patients treated with immunotherapy (e.g., anti-PD-1).[1] Both cohorts could recapitulate the increased abundance of Ruminococcaceae in responders vs. non-responders of immunotherapy. They also compared the survival time among those using or not using probiotics during treatment and found a lower but non-significant difference in survival among those using probiotics. However, in preclinical models of melanoma receiving FMT from responder patients, further treatment with either a Bifidobacterium or lactobacillus-based probiotic combined with anti-PD1 therapy significantly *increased* tumor size and decreased gut microbiome diversity. This effect of probiotics on response to immunotherapy had a similar deleterious effect by reducing IFN-γ producing CD8+ and CD4+ T-cells, indicating a harmful effect of these probiotics on response to immunotherapy. When they examined dietary fiber intake in patients using baseline intake at diagnosis, they found a significant increase in survival per 5g/day increase in dietary fiber (HR=0.71, P=0.04). Furthermore, when examining survival in those with both sufficient fiber intake (>20g/d) and no probiotic intake, the survival was significantly higher in those reporting adequate dietary fiber intake (HR=0.44, P=0.03) than those reporting insufficient fiber or probiotic use. In their preclinical melanoma models treated with anti-PD1, mice fed high fiber diets without probiotics had higher survival rates than the other treatments and a higher abundance of IFN-γ producing T-cells. These studies indicate that diet is likely a key contributing factor to the microbiome and its ability to modulate the immune system to affect a significant anti-cancer response. Furthermore, these data also suggest that diet may impact chemo- and radiotherapy response by modulating the microbiome, but much more work is needed in this area to understand the diet-microbiome effect.

Dietary patterns and impact on cancer treatment outcomes

To counter the effect of microbial alterations during anti-cancer therapy and the subsequent impact on treatment response, we propose using the diet to alter the microbial structure and function before or during treatment to improve cancer outcomes. As evidence, a significant body of work related to diet and the gut microbiome in healthy individuals demonstrates the beneficial impact of short-term dietary interventions on the composition and function of microbes in the gut mucosa and systemically in the following review.[90] However, it should be noted that the beneficial outcomes of dietary interventions can be small (e.g. 5%-16%) and heterogeneous due to the large variation in the gut microbiome between individuals.[91,92] There are only a small number of studies, however, that have attempted to use diet to modify the gut microbiome during cancer therapy. In particular, dietary prebiotics (e.g., fructo- and galactooligosaccharides) in animal models and human studies of cancer demonstrate the ability to modify the therapeutic response favorably through altering the microbial structure and immune function.[93–97] Additionally, the ketogenic diet (high fat, low carbohydrate diet) has shown favorable preliminary results in animal models of glioblastoma,[98] and early

case studies in humans are also supportive.[99] Likewise, different calorie restriction or intermittent fasting approaches have demonstrated effectiveness in modifying the gut microbiome and slowing cancer progression in animal models.[100] In terms of the ketogenic diet and calorie restriction, however, human studies in cancer are challenging due to treatment side effects and subsequent lack of adherence to the intervention. While we have data on the dietary impact on cancer treatment outcomes and promising results of specific nutritional and microbial factors on anti-cancer treatment response (e.g., fasting-mimicking diets, ketogenic diets, higher fiber diets),[79,98,101] we lack a clear understanding of diet-microbiome interactions, especially during the treatment phase of anti-cancer therapy. This lack of quality research is most likely the result of a lack of appropriate dietary capture tools, study design, sample size, and the challenge of working with patients undergoing cancer treatment.[26] However, without these key insights, precision nutrition therapy for cancer treatment will continue to be elusive.

Molecular pathological epidemiology: an approach to precision nutrition therapy

While precision nutrition therapy does not yet have an official definition, it can generally be defined as a nutrition intervention that improves treatment outcomes using an individual's unique characteristics, including genetics, gender, race/ethnicity, health history, lifestyle, and microbiome. An approach to precision nutrition that incorporates these factors is molecular pathological epidemiology (MPE). It is well understood that germline genetic variations impact tumorigenesis, the immune system, but more recently also the microbiome.[102] A study investigating the impact of genetics on the microbiome, using 113 mouse strains, demonstrated a 26-65% heritability of the most prevalent gut microbiota.[103] They further demonstrate a gene-environment interaction with the gut microbiome. In addition to finding a significant effect of genetic background differences on response to a high-fat/high-sucrose diet, they also demonstrated through cross-fostering a significant effect of the microbiome in altering metabolism. These data along with other studies indicate the gut microbiota can modify the effect of gene-environment interactions, especially dietary interactions.[104] In the context of cancer, MPE studies also demonstrate diet-immune interactions, where higher intake of omega-3 fatty acids in individuals with high FOXP3+ T regulatory cells (vs low FOX3P+ T regulatory cells) had lower risk of CRC.[105] Similarly, MPE studies of the microbiome show that prudent dietary patterns significantly impact development of *Fusobacterium nucleatum*-positive, but not *F. nucleatum*-negative, CRC. *F. nucleatum* also demonstrates interactions with genetic features of tumors (e.g. microsatellite instability-high), which is associated with lower immune infiltration.[106] Together these data indicate that precision nutrition therapy for cancer patients will require an understanding of both the genetic and environmental factors contributing to the pathology of their tumor in order to enhance the effectiveness of standard therapy.

Conclusions and future directions

Just as precision or personalized medicine has transformed cancer treatment from a one-size-fits-all to biomarker-guided drug therapy, we propose a similar approach to precision nutrition therapy in cancer treatment. By incorporating genetics, nutrition and the microbiome as factors in cancer therapy, we can dramatically improve treatment outcomes for cancer patients. To operationalize this concept will require several parallel approaches. First, we will need a more precise understanding of the critical genetic, dietary and microbial biomarkers predictive of treatment efficacy, toxicity, and drug resistance. To identify these factors, we will need large, well-designed studies to answer the following questions: a) which microbial factors mediate or modify the effects of diet on treatment response? and b) what biomarkers predict a favorable microbial response to nutrition intervention during cancer treatment? Expanding the research in this area will be an essential step toward precision nutrition in cancer.

Second, addressing malnutrition as part of the cancer treatment plan must become standard practice. While we work to collect more evidence towards precision nutrition therapy, several barriers must be overcome that are holding back improvements in nutrition therapy during cancer treatment. These include insufficient funding and reimbursement for nutrition support staff (e.g., oncology dietitians), lack of integration of nutrition services into the health care plan, lack of or inconsistent malnutrition screening, use of non-validated malnutrition screening tools, and in general, a lack of tools for dietary collection that meet the needs of cancer patients and their providers.[15,55] Cancer patients with weight loss, a significant sign of malnutrition, have the worst treatment outcome for chemotherapy.[107,108] Creating a robust tool for providers and patients to capture dietary data is a preventative approach to facilitate a personalized dietary plan for cancer patients. Capturing critical dietary and microbiome data in longitudinal cohorts will enhance our understanding of the diet-microbiome interactions along the treatment continuum and begin to inform our efforts toward precision nutrition therapy during cancer treatment.

Overall, by combining genetic, dietary and microbiome research efforts and addressing healthcare delivery, an enormous opportunity can be met in oncology using diet to improve microbial structure and function, reduce side effects and toxicity, and improve survival and quality of life for patients undergoing treatment for cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

K. Leigh Greathouse: Conceptualization, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Madhur Wyatt:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing. **Abigail J. Johnson:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Eugene P. Toy:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Joetta M. Khan:** Conceptualization, Writing – original draft, Writing – review & editing. **Kelly Dunn:** Conceptualization, Writing – original draft, Writing – review & editing. **Deborah J. Clegg:** Conceptualization, Writing – original draft, Writing – review & editing. **Sireesha Reddy:** Conceptualization, Writing – original draft, Writing – review & editing.

References

1. Spencer CN, McQuade JL, Gopalakrishnan V, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science* 2021;**374**(6575):1632–40. doi:10.1126/science.aaz7015.
2. Fung TT, Kashambwa R, Sato K, et al. Post diagnosis diet quality and colorectal cancer survival in women. *PLoS One* 2014;**9**(12):e115377. doi:10.1371/journal.pone.0115377.
3. Playdon MC, Nagle CM, Ibiebele TI, et al. Pre-diagnosis diet and survival after a diagnosis of ovarian cancer. *Br J Cancer* 2017;**116**(12):1627–37. doi:10.1038/bjc.2017.120.
4. Song M, Zhang X, Meyerhardt JA, et al. Marine omega-3 polyunsaturated fatty acid intake and survival after colorectal cancer diagnosis. *Gut* 2017;**66**(10):1790–1796. doi:10.1136/gutjnl-2016-311990.
5. Song M, Wu K, Meyerhardt JA, et al. Fiber intake and survival after colorectal cancer diagnosis. *JAMA Oncol* 2018;**4**(1):71–9. doi:10.1001/jamaoncol.2017.3684.

6. Yang W, Ma Y, Smith-Warner S, et al. Calcium intake and survival after colorectal cancer diagnosis. *Clin Cancer Res* 2019;**25**(6):1980–8. doi:10.1158/1078-0432.CCR-18-2965.
7. Zhu Y, Wu H, Wang PP, et al. Dietary patterns and colorectal cancer recurrence and survival: a cohort study. *BMJ Open* 2013;**3**(2):e002270. doi:10.1136/bmjopen-2012-002270.
8. Kolodziejczyk AA, Zheng D, Elinav E. Diet–microbiota interactions and personalized nutrition. *Nat Rev Microbiol* 2019;**17**(12):742–53. doi:10.1038/s41579-019-0256-8.
9. Riaz Rajoka MS, Shi J, Mehwish HM, et al. Interaction between diet composition and gut microbiota and its impact on gastrointestinal tract health. *Food Sci Hum Wellness* 2017;**6**(3):121–30. doi:10.1016/j.fshw.2017.07.003.
10. O'Keefe SJD, Li JV, Lahti L, et al. Fat, fibre and cancer risk in African Americans and rural Africans. *Nat Commun* 2015;**6**(1):6342. doi:10.1038/ncomms7342.
11. Lize N, Raijmakers N, van Lieshout R, et al. Psychosocial consequences of a reduced ability to eat for patients with cancer and their informal caregivers: a qualitative study. *Eur J Oncol Nurs* 2020;**49**:101838. doi:10.1016/j.ejon.2020.101838.
12. Hill A, Kiss N, Hodgson B, Crowe TC, Walsh AD. Associations between nutritional status, weight loss, radiotherapy treatment toxicity and treatment outcomes in gastrointestinal cancer patients. *Clin Nutr* 2011;**30**(1):92–8. doi:10.1016/j.clnu.2010.07.015.
13. Röhrl K, Guren MG, Småstuen MC, Rustøen T. Symptoms during chemotherapy in colorectal cancer patients. *Support Care Cancer* 2019;**27**(8):3007–17. doi:10.1007/s00520-018-4598-y.
14. Giesinger JM, Wintner LM, Zabernigg A, et al. Assessing quality of life on the day of chemotherapy administration underestimates patients' true symptom burden. *BMC Cancer* 2014;**14**:758. doi:10.1186/1471-2407-14-758.
15. Trujillo EB, Dixon SW, Claghorn K, Levin RM, Mills JB, Spees CK. Closing the gap in nutrition care at outpatient cancer centers: ongoing initiatives of the oncology nutrition dietetic practice group. *J Acad Nutr Dietetics* 2018;**118**(4):749–60. doi:10.1016/j.jand.2018.02.010.
16. Muscaritoli M, Lucia S, Farcomeni A, et al. Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. *Oncotarget* 2017;**8**(45):79884–96. doi:10.18632/oncotarget.20168.
17. Melchior JC, Jean-Claude M, Préaud E, et al. Clinical and economic impact of malnutrition per se on the postoperative course of colorectal cancer patients. *Clin Nutr* 2012;**31**(6):896–902. doi:10.1016/j.clnu.2012.03.011.
18. Pressoir M, Desné S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Br J Cancer* 2010;**102**(6):966–71. doi:10.1038/sj.bjc.6605578.
19. Planas M, Álvarez-Hernández J, León-Sanz M, et al. Prevalence of hospital malnutrition in cancer patients: a sub-analysis of the PREDyCES® study. *Support Care Cancer* 2016;**24**(1):429–35. doi:10.1007/s00520-015-2813-7.
20. Sirniö P, Väyrynen JP, Klintrup K, et al. Alterations in serum amino-acid profile in the progression of colorectal cancer: associations with systemic inflammation, tumour stage and patient survival. *Br J Cancer* 2019;**120**(2):238–46. doi:10.1038/s41416-018-0357-6.
21. Martin A, Ecklu-Mensah G, Ha CWY, et al. Gut microbiota mediate the FGF21 adaptive stress response to chronic dietary protein-restriction in mice. *Nat Commun* 2021;**12**(1):3838. doi:10.1038/s41467-021-24074-z.
22. Matam Vijay-Kumar, Aitken Jesse D, Carvalho Frederic A, et al. Metabolic syndrome and altered gut microbiota in mice lacking toll-like receptor 5. *Science* 2010;**328**(5975):228–31. doi:10.1126/science.1179721.
23. Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY. The gut microbiota mediates the anti-seizure effects of the ketogenic diet. *Cell* 2018;**173**(7):1728–41 e13. doi:10.1016/j.cell.2018.04.027.
24. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006;**444**(7122):1027–31. doi:10.1038/nature05414.
25. Argilés JM. Cancer-associated malnutrition. *Eur J Oncol Nurs* 2005;**9**:S39–50. doi:10.1016/j.ejon.2005.09.006.
26. Hughes RL, Marco ML, Hughes JP, Keim NL, Kable ME. The role of the gut microbiome in predicting response to diet and the development of precision nutrition models—part I: overview of current methods. *Adv Nutr* 2019;**10**(6):953–78. doi:10.1093/advances/nmz022.
27. Morley J. Protein-energy undernutrition (PEU). In: Merck Manual. 20th ed.
28. Meza-Valderrama D, Marco E, Dávalos-Yerovi V, et al. Sarcopenia, malnutrition, and cachexia: adapting definitions and terminology of nutritional disorders in older people with cancer. *Nutrients* 2021;**13**(3):761. doi:10.3390/nu13030761.
29. Chen RY, Mostafa I, Hibberd MC, et al. A microbiota-directed food intervention for undernourished children. *N Engl J Med* 2021;**384**(16):1517–28. doi:10.1056/NEJMoa2023294.
30. Gehrig JL, Venkatesh S, Chang HW, et al. Effects of microbiota-directed foods in gnotobiotic animals and undernourished children. *Science* 2019;**365**(6449):eaau4732. doi:10.1126/science.aau4732.
31. Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. *Curr Opin Neurol* 2015;**28**(5):500–7. doi:10.1097/WCO.0000000000000234.
32. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. *JCO* 2020;**38**(28):3325–48. doi:10.1200/JCO.20.01399.
33. Mukaida N. Intestinal microbiota: unexpected alliance with tumor therapy. *Immunotherapy* 2014;**6**(3):231–3. doi:10.2217/imt.13.170.
34. Shen S, Lim G, You Z, et al. Gut Microbiota is critical for the induction of chemotherapy-induced pain. *Nat Neurosci* 2017;**20**(9):1213–16. doi:10.1038/nn.4606.
35. Vázquez-Baeza Y, Callewaert C, Debelius J, et al. Impacts of the human gut microbiome on therapeutics. *Annu Rev Pharmacol Toxicol* 2018;**58**:253–70. doi:10.1146/annurev-pharmtox-042017-031849.
36. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science* 2013. Published online November 22Accessed September 4, 2021 https://www.science.org/doi/abs/10.1126/science.1240537 .
37. Wardill HR, Gibson RJ, Van Sebille YZA, et al. Irinotecan-induced gastrointestinal dysfunction and pain are mediated by common TLR4-dependent mechanisms. *Mol Cancer Ther* 2016;**15**(6):1376–86. doi:10.1158/1535-7163.MCT-15-0990.
38. Artene DV, Bordea CI, Blidaru A. Results of 1-year diet and exercise interventions for ER+/PR+-/HER2- breast cancer patients correlated with treatment type. *chr* 2017;**112**(4):457. doi:10.21614/chirurgia.112.4.457.
39. Bonner L. Synbiotics, a new alternative in bacteriotherapy, enter market. *Pharmacy Today* 2016;**22**(4):33. doi:10.1016/j.ptdy.2016.03.018.
40. De Loera Rodríguez LH, Ortiz GG, Rivero Moragrega P, et al. Effect of symbiotic supplementation on fecal calprotectin levels and lactic acid bacteria, Bifidobacteria, Escherichia coli and Salmonella DNA in patients with cervical cancer. *Nutr Hosp* 2018;**35**(6):1394–400. doi:10.20960/nh.1762.
41. Molan AL, Liu Z, Plimmer G. Evaluation of the effect of blackcurrant products on gut microbiota and on markers of risk for colon cancer in humans. *Phytother Res* 2014;**28**(3):416–22. doi:10.1002/ptr.5009.
42. Navaei M, Haghighat S, Janani L, et al. The effects of synbiotic supplementation on antioxidant capacity and arm volumes in survivors of breast cancer-related lymphedema. *Nutr Cancer* 2020;**72**(1):62–73. doi:10.1080/01635581.2019.1616781.
43. Raji Lahiji M, Zarrati M, Najafi S, et al. Effects of synbiotic supplementation on serum adiponectin and inflammation status of overweight and obese breast cancer survivors: a randomized, triple-blind, placebo-controlled trial. *Support Care Cancer* 2021;**29**(7):4147–57. doi:10.1007/s00520-020-05926-8.
44. Pellegrini M, Ippolito M, Monge T, et al. Gut microbiota composition after diet and probiotics in overweight breast cancer survivors: a randomized open-label pilot intervention trial. *Nutrition* 2020;**74**:110749. doi:10.1016/j.nut.2020.110749.
45. Lahiji MR, Najafi S, Janani L, Yazdani B, Razmpoosh E, Zarrati M. The effect of synbiotic on glycemic profile and sex hormones in overweight and obese breast cancer survivors following a weight-loss diet: A randomized, triple-blind, controlled trial. *Clin Nutr* 2021;**40**(2):394–403. doi:10.1016/j.clnu.2020.05.043.

46. Rosli D, Shahar S, Manaf ZA, et al. Randomized controlled trial on the effect of partially hydrolyzed guar gum supplementation on diarrhea frequency and gut microbiome count among pelvic radiation patients. *JPEN J Parenter Enteral Nutr* 2021;**45**(2):277–86. doi:10.1002/jpen.1987.
47. Weston N, Luscombe G, Duncanson K. Effects of a laxation and probiotic bowel preparation regimen: a randomized controlled trial in patients undergoing prostate radiation therapy. *Nutr Cancer* 2020;**72**(6):999–1003. doi:10.1080/01635581.2019.1669675.
48. Helmink BA, Khan MAW, Hermann A, Gopalakrishnan V, Wargo JA. The microbiome, cancer, and cancer therapy. *Nat Med* 2019;**25**(3):377–88. doi:10.1038/s41591-019-0377-7.
49. Jain R, Coss C, Whooley P, Phelps M, Owen DH. The role of malnutrition and muscle wasting in advanced lung cancer. *Curr Oncol Rep* 2020;**22**(6):54. doi:10.1007/s11912-020-00916-9.
50. Reber E, Schönenberger KA, Vasiloglou MF, Stanga Z. Nutritional risk screening in cancer patients: the first step toward better clinical outcome. *Front Nutr* 2021;**8**. doi:10.3389/fnut.2021.603936.
51. Conigliaro T, Boyce LM, Lopez CA, Tonorezos ES. Food intake during cancer therapy: a systematic review. *Am J Clin Oncol* 2020;**43**(11):813–19. doi:10.1097/COC.0000000000000749.
52. Shim JS, Oh K, Kim HC. Dietary assessment methods in epidemiologic studies. *Epidemiol Health* 2014;**36**:e2014009. doi:10.4178/epih/e2014009.
53. Halpern MT, Yabroff KR. Prevalence of outpatient cancer treatment in the united states: estimates from the medical panel expenditures survey (MEPS). *Cancer Invest* 2008;**26**(6):647–51. doi:10.1080/07357900801905519.
54. Patel V, Romano M, Corkins MR, et al. Nutrition screening and assessment in hospitalized patients. *Nutr Clin Pract* 2014;**29**(4):483–90. doi:10.1177/0884533614535446.
55. Trujillo EB, Claghorn K, Dixon SW, et al. Inadequate nutrition coverage in outpatient cancer centers: results of a national survey. *J Oncol* 2019:e7462940 2019. doi:10.1155/2019/7462940.
56. Hooper LV, Macpherson AJ. Immune adaptations that maintain homeostasis with the intestinal microbiota. *Nat Rev Immunol* 2010;**10**(3):159–69. doi:10.1038/nri2710.
57. Xavier JB, Young VB, Skufca J, et al. The cancer microbiome: distinguishing direct and indirect effects requires a systemic view. *Trends Cancer* 2020;**6**(3):192–204. doi:10.1016/j.trecan.2020.01.004.
58. Knippel RJ, Drewes JL, Sears CL. The cancer microbiome: recent highlights and knowledge gaps. *Cancer Discov* 2021;**11**(10):2378–95. doi:10.1158/2159-8290.CD-21-0324.
59. Dejea CM, Wick EC, Hechenbleikner EM, et al. Microbiota organization is a distinct feature of proximal colorectal cancers. *Proc Natl Acad Sci U S A* 2014;**111**(51):18321–6. doi:10.1073/pnas.1406199111.
60. Caruso R, Lo BC, Núñez G. Host–microbiota interactions in inflammatory bowel disease. *Nat Rev Immunol* 2020;**20**(7):411–26. doi:10.1038/s41577-019-0268-7.
61. Garrett WS. Cancer and the microbiota. *Science* 2015;**348**(6230):80–6. doi:10.1126/science.aaa4972.
62. Pushalkar S, Hundeyin M, Daley D, et al. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. *Cancer Discov* 2018;**8**(4):403. doi:10.1158/2159-8290.CD-17-1134.
63. Gagnaire A, Nadel B, Raoult D, Neefjes J, Gorvel JP. Collateral damage: insights into bacterial mechanisms that predispose host cells to cancer. *Nat Rev Microbiol* 2017;**15**(2):109–28. doi:10.1038/nrmicro.2016.171.
64. Bullman S, Pedamallu CS, Sicinska E, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. *Science* 2017;**358**(6369):1443–8. doi:10.1126/science.aal5240.
65. Sheikh A, Taube J, Greathouse KL. Contribution of the microbiota and their secretory products to inflammation and colorectal cancer pathogenesis: the role of toll-like receptors. *Carcinogenesis* 2021;**42**(9):1133–42. doi:10.1093/carcin/bgab060.
66. Stacy A, Fleming D, Lamont RJ, Rumbaugh KP, Whiteley M. A commensal bacterium promotes virulence of an opportunistic pathogen via cross-respiration. Gilmore MS. *mBio* 2016;**7**(3). doi:10.1128/mBio.00782-16.
67. de Martel C, J Ferlay, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;**13**(6):607–15. doi:10.1016/S1470-2045(12)70137-7.
68. Brennan CA, Garrett WS. Fusobacterium nucleatum - symbiont, opportunist and oncobacterium. *Nat Rev Microbiol* 2019;**17**(3):156–66. doi:10.1038/s41579-018-0129-6.
69. Song M, Chan AT, Sun J. Influence of the gut microbiome, diet, and environment on risk of colorectal cancer. *Gastroenterology* 2020;**158**(2):322–40. doi:10.1053/j.gastro.2019.06.048.
70. Muls A, Andreyev H, Lalondrelle S, Taylor A, Norton C, Hart A. Systematic review: the impact of cancer treatment on the gut and vaginal microbiome in women with a gynaecological malignancy. *Int J Gynecol Cancer* 2017;**27**(7):1550–1559. doi:10.1097/IGC.0000000000000999.
71. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *JCO* 2004;**22**(14):2918–26. doi:10.1200/JCO.2004.04.132.
72. Tsementzi D, Meador R, Eng T, et al. Changes in the vaginal microbiome and associated toxicities following radiation therapy for gynecologic cancers. *Front Cell Infect Microbiol* 2021;**11**:680038. doi:10.3389/fcimb.2021.680038.
73. Muhleisen AL, Herbst-Kralovetz MM. Menopause and the vaginal microbiome. *Maturitas* 2016;**91**:42–50. doi:10.1016/j.maturitas.2016.05.015.
74. Nam YD, Kim HJ, Seo JG, Kang SW, Bae JW. Impact of pelvic radiotherapy on gut microbiota of gynecological cancer patients revealed by massive pyrosequencing. *PLoS One* 2013;**8**(12):e82659. doi:10.1371/journal.pone.0082659.
75. Sims TT, El Alam MB, Karpinets TV, et al. Gut microbiome diversity is an independent predictor of survival in cervical cancer patients receiving chemoradiation. *Commun Biol* 2021;**4**(1):237. doi:10.1038/s42003-021-01741-x.
76. Tsakmaklis A, Vehreschild M, Farowski F, et al. Changes in the cervical microbiota of cervical cancer patients after primary radio-chemotherapy. *Int J Gynecol Cancer* 2020;**30**(9):1326–30. doi:10.1136/ijgc-2019-000801.
77. Bashiardes S, Tuganbaev T, Federici S, Elinav E. The microbiome in anti-cancer therapy. *Semin Immunol* 2017;**32**:74–81. doi:10.1016/j.smim.2017.04.001.
78. Geller LT, Barzily-Rokni M, Danino T, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. *Science* 2017;**357**(6356):1156–60. doi:10.1126/science.aah5043.
79. Lam KC, Araya RE, Huang A, et al. Microbiota triggers STING-type I IFN-dependent monocyte reprogramming of the tumor microenvironment. *Cell* 2021;**184**(21):5338–56 e21. doi:10.1016/j.cell.2021.09.019.
80. Blaustein RA, Seed PC, Hartmann EM. Biotransformation of doxorubicin promotes resilience in simplified intestinal microbial communities. McMahon K, ed. *mSphere* 2021;**6**(3). doi:10.1128/mSphere.00068-21.
81. Wallace BD, Wang H, Lane KT, et al. Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. *Science* 2010;**330**(6005):831–5. doi:10.1126/science.1191175.
82. Grant CV, Loman BR, Bailey MT, Pyter LM. Manipulations of the gut microbiome alter chemotherapy-induced inflammation and behavioral side effects in female mice. *Brain Behav Immun* 2021;**95**:401–12. doi:10.1016/j.bbi.2021.04.014.
83. Bailly C, Thuru X, Quesnel B. Combined cytotoxic chemotherapy and immunotherapy of cancer: modern times. *NAR Cancer* 2020;**2**(1):zcaa002. doi:10.1093/narcan/zcaa002.
84. Iida N, Dzutsev A, Stewart CA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* 2013;**342**(6161):967–70. doi:10.1126/science.1240527.
85. Heshiki Y, Vazquez-Uribe R, Li J, et al. Predictable modulation of cancer treatment outcomes by the gut microbiota. *Microbiome* 2020;**8**(1):28. doi:10.1186/s40168-020-00811-2.
86. Montalban-Arques A, Katkeviciute E, Busenhart P, et al. Commensal Clostridiales strains mediate effective anti-cancer immune response against solid tumors. *Cell Host Microbe* 2021;**29**(10):1573–88 e7. doi:10.1016/j.chom.2021.08.001.

87. Tanoue T, Morita S, Plichta DR, et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature* 2019;**565**(7741):600–5. doi:10.1038/s41586-019-0878-z.
88. Tomita Y, Ikeda T, Sakata S, et al. Association of probiotic *Clostridium butyricum* therapy with survival and response to immune checkpoint blockade in patients with lung cancer. *Cancer Immunol Res* 2020;**8**(10):1236–42. doi:10.1158/2326-6066.CIR-20-0051.
89. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 2018;**359**(6371):97–103. doi:10.1126/science.aan4236.
90. Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. *J Transl Med* 2017;**15**:73. doi:10.1186/s12967-017-1175-y.
91. Gwen Falony, Marie Joossens, Sara Vieira-Silva, et al. Population-level analysis of gut microbiome variation. *Science* 2016;**352**(6285):560–4. doi:10.1126/science.aad3503.
92. Vangay P, Johnson AJ, Ward TL, et al. US immigration westernizes the human gut microbiome. *Cell* 2018;**175**(4):962–72 e10. doi:10.1016/j.cell.2018.10.029.
93. Garcia-Peris P, Velasco C, Hernandez M, et al. Effect of inulin and fructo-oligosaccharide on the prevention of acute radiation enteritis in patients with gynecological cancer and impact on quality-of-life: a randomized, double-blind, placebo-controlled trial. *Eur J Clin Nutr* 2016;**70**(2):170–4. doi:10.1038/ejcn.2015.192.
94. Taper HS, Roberfroid MB. Nontoxic potentiation of cancer chemotherapy by dietary oligofructose or inulin. *Nutr Cancer* 2000;**38**(1):1–5. doi:10.1207/S15327914NC381_1.
95. Taper HS, Roberfroid MB. Inulin/oligofructose and anticancer therapy. *Br J Nutr* 2002;**87**(Suppl 2):S283–6. doi:10.1079/BJNBJN/2002549.
96. Taper HS, Roberfroid MB. Possible adjuvant cancer therapy by two prebiotics–inulin or oligofructose. *In Vivo* 2005;**19**(1):201–4.
97. Zhao R, Wang Y, Huang Y, et al. Effects of fiber and probiotics on diarrhea associated with enteral nutrition in gastric cancer patients. *Medicine (Baltimore)* 2017;**96**(43):e8418. doi:10.1097/MD.0000000000008418.
98. Maeyama M, Tanaka K, Nishihara M, et al. Metabolic changes and anti-tumor effects of a ketogenic diet combined with anti-angiogenic therapy in a glioblastoma mouse model. *Sci Rep* 2021;**11**(1):79. doi:10.1038/s41598-020-79465-x.
99. van der Louw EJTM, Olieman JF, van den Bemt PMLA, et al. Ketogenic diet treatment as adjuvant to standard treatment of glioblastoma multiforme: a feasibility and safety study. *Ther Adv Med Oncol* 2019;**11**:1758835919853958. doi:10.1177/1758835919853958.
100. Lien EC, Westermark AM, Zhang Y, et al. Low glycaemic diets alter lipid metabolism to influence tumour growth. *Nature* 2021;**599**(7884):302–7. doi:10.1038/s41586-021-04049-2.
101. Vernieri C, Fuca G, Ligorio F, et al. Fasting-mimicking diet is safe and reshapes metabolism and antitumor immunity in cancer patients. *Cancer Discov* 2021 Published online November 17:candisc.0030.2021. doi:10.1158/2159-8290.CD-21-0030.
102. Mima K, Kosumi K, Baba Y, Hamada T, Baba H, Ogino S. The microbiome, genetics, and gastrointestinal neoplasms: the evolving field of molecular pathological epidemiology to analyze the tumor–immune–microbiome interaction. *Hum Genet* 2021;**140**(5):725–46. doi:10.1007/s00439-020-02235-2.
103. Org E, Parks BW, Joo JWJ, et al. Genetic and environmental control of host-gut microbiota interactions. *Genome Res* 2015;**25**(10):1558–69. doi:10.1101/gr.194118.115.
104. Touré AM, Landry M, Souchkova O, Kembel SW, Pilon N. Gut microbiota-mediated gene-environment interaction in the TashT mouse model of hirschsprung disease. *Sci Rep* 2019;**9**(1):492. doi:10.1038/s41598-018-36967-z.
105. Song M, Nishihara R, Cao Y, et al. Marine ω-3 polyunsaturated fatty acid intake and risk of colorectal cancer according to tumor-infiltrating T cells. *JAMA Oncol* 2016;**2**(9):1197–206. doi:10.1001/jamaoncol.2016.0605.
106. Hamada T, Zhang X, Mima K, et al. *Fusobacterium nucleatum* in colorectal cancer relates to immune response differentially by tumor microsatellite instability status. *Cancer Immunol Res* 2018;**6**(11):1327–36. doi:10.1158/2326-6066.CIR-18-0174.
107. Andreyev HJN, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer* 1998;**34**(4):503–9. doi:10.1016/S0959-8049(97)10090-9.
108. Bakkal H, Dizdar OS, Erdem S, et al. The relationship between hand grip strength and nutritional status determined by malnutrition inflammation score and biochemical parameters in hemodialysis patients. *J Ren Nutr* 2020;**30**(6):548–55. doi:10.1053/j.jrn.2020.01.026.