Review

The Multifaceted Roles of Diet, Microbes and Metabolites in Cancer

Heather Armstrong 1,2,*, Michael Bording-Jorgensen 1,2 and Eytan Wine 1,2,3,*

1 CEGIIR, University of Alberta, Edmonton, AB T6G 2X8, Canada; bordingj@ualberta.ca
2 Department of Pediatrics, University of Alberta, Edmonton, AB T6G 1C9, Canada
3 Department of Physiology, University of Alberta, Edmonton, AB T6G 1C9, Canada
* Correspondence: harmstro@ualberta.ca (H.A.); wine@ualberta.ca (E.W.)

Simple Summary: The involvement of microbes (virus, fungi, bacteria) and diet in different cancers is slowly being uncovered, yet the complexity of the relationship between these factors has reduced the impact of potential interventions in the clinic. In this review we have highlighted the results of the most recent studies published and have related what the evidence suggests and how we can utilize this knowledge best in directing patients’ diets and future research at this time.

Abstract: Many studies performed to date have implicated select microbes and dietary factors in a variety of cancers, yet the complexity of both these diseases and the relationship between these factors has limited the ability to translate findings into therapies and preventative guidelines. Here we begin by discussing recently published studies relating to dietary factors, such as vitamins and chemical compounds used as ingredients, and their contribution to cancer development. We further review recent studies, which display evidence of the microbial-diet interaction in the context of cancer. The field continues to advance our understanding of the development of select cancers and how dietary factors are related to the development, prevention, and treatment of these cancers. Finally, we highlight the science available in the discussion of common misconceptions with regards to cancer and diet. We conclude this review with thoughts on where we believe future research should focus in order to provide the greatest impact towards human health and preventative medicine.

Keywords: cancer; diet; nutrition; microbes; misconceptions; risk factors; prevention

1. Introduction

Although cancer development is known to be complex and related, in many cases, to a diverse array of factors (genetic and environmental), with well-described impacts of longitudinal exposures, there are still critical gaps in the knowledge of what some of these exposures are and how they impact cancer biology. Diet has long been considered a critical and, importantly, modifiable factor in many different biological processes, including cancer. Recent advances in measuring dietary intake and its effect on biological processes (e.g., using metabolomics), and especially the interaction between diet and gut microbes, have opened the way to a myriad of papers implicating diet, the gut microbiome, and related metabolites in the pathogenesis, course, and response to therapy of major cancers. A better definition of how diet is related to cancer biology is especially attractive, as diet is rarely utilized in cancer therapy or prevention and it can provide a safe alternative for intervention in a variety of other chronic conditions [1–5]. However, the potential for diet to affect cancer development and progression remains to be fully elucidated. We focus on diet–microbiome interactions in this setting, as not only do dietary factors and nutrition have profound effects on the health of host cells, but they also affect the human microbiome [6], which in turn is closely linked to cancer.
These observations are especially relevant to the gut: emerging evidence continues to demonstrate that nutritional states directly drive intestinal adaptation, resulting in altered signalling mechanisms within adult intestinal stem cells relevant to intestinal tumour formation [7–10]. Some correlations to chronic conditions, such as inflammatory diseases, may help inspire future research. The link between inflammation and concomitant tumour development in cancers was first suggested by Virchow in 1863 [11,12], and today roughly 20% of cancers are thought to directly result from chronic inflammation [13]. Likely one of the most well studied examples to date is the link between inflammatory bowel diseases (IBD) and colorectal cancer (CRC) [14–17]. Notably, select dietary factors including saturated fats, red meat, and refined carbohydrates have been suggested to display pro-inflammatory properties and diet has been shown to play a key role in up to 40% of all cancers [18–21]. These dietary factors are further involved in modulating the gut microbiome, which in turn is involved in regulating both gut physiology and immune response [22–24]. This model of IBD–CRC has further demonstrated the critical role of microbes in inflammatory pathways due to their ability to modulate inflammatory cytokines (e.g., tumour necrosis factor (TNF), interleukin (IL)-1, IL-6), which are similarly dysregulated in both IBD and CRC [25–28]. While dietary factors have clear effects on organs of the intestinal tract, absorption of these factors results in systemic effects on a number of organ systems, which have been implicated in the progression of a variety of cancers, as detailed in later sections (Figure 1).

Figure 1. Cancer promoting and preventative interactions of dietary factors and organ systems. Intake of dietary factors, as demonstrated only by more recent research studies, can affect cancer progression through positive (green) or negative (red) effects on organ systems, as indicated. Details are further highlighted in Table 1.
In this review we describe some of the key findings supported by peer-reviewed research studies to date regarding cancer and diet, including the impact of dietary factors such as macronutrients, micronutrients, preservatives/additives, and vitamins, and analyse the more recently recognized contribution of the microbiome. We use some examples to elucidate how diet can impact cancer, through the microbiome, and discuss common misconceptions regarding diet and cancer. The review first presents current knowledge on dietary components that have defined (or at least well-supported) action on cancer biology. We then describe some key cancers with strong data on the involvement of dietary factors in the development of malignancy and provide a few examples of how this knowledge could be used to prevent or reduce risk for these cancers. Finally, we highlight the role of microbes in these pathways and suggest potential novel ideas on how dietary or microbe-altering treatments may be used in the future to prevent or even treat cancer, mostly as an adjuvant therapy. While the field of diet and microbes in cancer is not yet supported by a large number of empirical studies, we expect that it will grow over the next few years and will offer new facets to the world of cancer research and patient care. However, given the breadth of this topic, the long list of dietary factors known to impact cancer, and the recent explosion in the field, this review cannot provide a comprehensive list of all relevant dietary components and studies, but rather provides a flavour of how this field has developed (especially over the last couple of years) and what implications this may have.

2. Impact of Select Dietary Factors on Cancer Biology

While diet is considered an environmental exposure, it is difficult to measure accurately in humans for several reasons. In contrast to cigarette smoking, for example, which can be expressed as pack-years, food contains thousands of molecules, is not easily quantified, varies geographically, and humans are notoriously inaccurate in reporting consumption [29]. Although it would probably be best to define dietary exposures using food patterns [30], most current research has focused on specific nutrients. A series of recent review articles highlighting the studies examining cancer in relation to specific dietary patterns labelled Mediterranean [31], Western, Ketogenic [32], or other such common dietary patterns [33], demonstrate that the nutrients or food groups that are specific to these diets appear to underscore potential mechanisms behind the positive or negative effects correlated with these diets. This section will present some examples of links between these specific nutrients and cancer (Figure 1).

2.1. Protective Effects of Vitamins

Vitamins A, C, and D have been demonstrated to play an anticarcinogenic role in a range of studies [34]. A recent meta-analysis of random controlled trials concluded that Vitamin D significantly reduced mortality (13%) but did not have an impact on cancer incidence, with the exception of colorectal and ovarian cancers [35]. Furthermore, vitamin A has been shown to play a significant role in cell proliferation and differentiation [36] and studies demonstrate an inverse relationship between vitamin A and bladder, colorectal, and liver cancers [37–39]. These studies suggest that the effects of vitamins may occur through enhanced DNA repair, antioxidant effects, or immunomodulation of host cells [40,41]. The in-depth role of vitamins has previously been well reported in relation to cancer [42,43].

2.2. Sodium and Potassium

Sodium and potassium have long been thought to play a role in the development of cancer as, for example, patients with decreased potassium levels, or hypokalemia (<3.5 mmol/L), associated with cell aging, obesity, alcoholism, and stress, display increased rates of cancer; in contrast patients with hyperkalemia (>5.3 mmol/L) and diseases associated with increased potassium levels, such as Parkinson and Addison disease, display
reduced cancer rates [34]. The concentrations of sodium and potassium also interestingly play a role in regulating the effects of calcium, resulting in a series of varied results in studies investigating the tumorigenicity of calcium [34]. Furthermore, almost 50% of cancer patients have been shown to display hyponatremia (<135 mmol/L sodium), although this may also be secondary to the cancer itself [44].

2.3. Food Preservatives Linked to Cancer

The sodium salt of propionic acid, sodium propionate, is often used as a food preservative in bakery products and has been shown to exert an antitumour effect through the mitogen-associated protein kinase (MAPK) signalling pathway in breast cancer xenograft models. [45] This example illustrates the complexity between food preservatives, microbes, and cancer, as most are observed to be negatively associated. Nitrates have also been well-described to be associated with colorectal cancer [46], while sorbate and benzoate correlate with the occurrence of breast cancer [47]. Processed foods and the use of food preservatives have dramatically increased over the last few decades and many have attempted to link this with increases in cancer [48]. Food preservatives are a diverse group of ingredients and therefore we have decided to only highlight a few in this review. Most studies focus on negative associations between preservatives and cancer, but to balance the literature, we choose to describe here some studies that display protective effects.

2.4. Not All Additives Are Bad: Potentially Beneficial Chemical Food Components

Capsaicin has long been thought to display anti-inflammatory, antioxidant, anti-proliferative, metabolic, and cardioprotective effects and, interestingly, has been shown to affect microbes within the gut too [49]. Decursin, an extract from the Angelica gigas root, has been shown to display potent anticancer activity in cell line models of lung and colon cancer, along with Lewis lung carcinoma allograft mouse models of tumour growth [50]. A recent study has shown the capacity of decursin to promote HIF-1α degradation within the proteasome, therefore improving T cell activation and antitumour effects within the tumour microenvironment [50].

A subset of dietary fibres, collectively known as β-glucans, are found in a variety of food groups, from mushrooms and other fungi, to wheat, oats, and barley. Interestingly, raw and roasted barley rich in β-glucan has been shown to provide chemoprotective effects via inhibition of growth and promotion of apoptotic pathways [51]. Similar studies examining the effects of raw and roasted oat flakes, following fermentation with human fecal microbes, demonstrated that the fermentation supernatants, with reduce pH and increased butyrate, significantly decreased growth and increased apoptosis of colon adenoma cells [52]. These findings suggest that food products, mostly made of specific grain β-glucans, harbour chemoprotective potential.

The flower buds of adaptogenic plants, typically found in Chinese traditional medicines, including Gardenia jasminoides, Sophora japonica, and Lonicerae japonicae, demonstrated a significant effect on reducing polyp burden, along with lowering expression of oncogenic signaling molecules in mice [53]. These changes were associated with a reduction in pathobiont microbes including Helicobacter pylori, along with an increase in beneficial microbes, including the key short chain fatty acid (SCFA) producers, Akkermansia, Barnesiella, Coprococcus, Lachnoclostridium, and Ruminococcus [53]. A diet high in seaweed has been linked with promotion of Bacteroides plebeius, which is involved in the breakdown of the seaweed Sargassum wightii to polysaccharides (SWP1 and SWP2); this significantly reduces cell proliferation and induces apoptosis in human breast cancer cell lines [54,55]. Seaweeds’ health benefits have been associated with the polyphenols, polysaccharides, sterols, and bioactive molecules that have been shown to play a role in anti-inflammatory and anticancer effects [56].
3. Microbes as Key Mediators in Diet–Cancer Interactions

The gut microbiome is known to have significant consequences on human health and disease, including cancer, as demonstrated by studies where direct modification of gut microbes, through fecal microbial transplantation, for example, impacts cancer outcomes and response to therapy [57]. We focus in this section on an indirect role of microbes, which likely provide a link between diet and cancer, and have highlighted some key recent examples in Table 1. However, there is still a knowledge gap between changes in the microbiome due to diet and long-term consequences, such as cancer development. A recent study looking at the effects of ketogenic diet on the microbiome found a reduction in Bifidobacterium sp., which are known to increase gut Th17 cells, together with increases in Fusobacterium and Escherichia coli through the production of ketone bodies [58]. While evidence supports the fact that a ketogenic diet decreases long term health due to high consumption of dietary fats, limited studies have demonstrated that specifically when combined with select cancer therapies, a ketogenic diet may improve outcomes for those suffering from cancers involving the protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway [59]. Fusobacterium and Th17 cells are also associated with an increased risk of colorectal cancer, suggesting that ketogenic diets may be detrimental when used long-term [60]. A diet high in fats or meats has also been shown to increase the abundance of select opportunistic microbe species responsible for the production of enzymes such as B-glucuronidase, which plays a key role in xenobiotic-induced toxicity within the intestine [61,62]. B-glucuronidase has been previously associated with increased risk of select breast cancers [63], pancreatic cancer [64], and colorectal cancer [65], and recent evidence supports the use of inhibitor compounds targeting B-glucuronidase for improved anticancer efficacy [66].

There are few studies looking at the effects of food preservatives on the microbiota, typically limited to using animal models [67]. A recent study showed that a combination of antimicrobial food preservatives (sodium benzoate, sodium nitrite, and potassium sorbate) induced a decrease in the abundance of Firmicutes (Clostridiales order) while increasing Proteobacteria (Burkholderiales order) in human-microbiota associated mice, suggesting a possible link to dysbiosis [68]. A recent literature review illustrated evidence suggesting that food additives can drive dysbiosis through the reduction of anti-inflammatory bacteria such as Clostridium tyrobutyricum and Lactobacillus paracasei with a link to irritable bowel syndrome [69].

Interestingly, studies have demonstrated variable effects of the Na/K ratio on microbe diversity, based on geographical location (environment), suggesting that sodium and potassium consumption play a variable role in regulating the abundance of pathogenic microbes, such as Staphylococcus and Moraxellaceae, along with SCFA-producing microbes, such as Phascolarctobacterium and Lachnospiraceae [70]. Specifically, studies suggest that increased sodium consumption results in decreases in key microbial metabolites, including butyrate and isobutyrate, along with anti-inflammatory phenols [70,71].

A recent review article clearly outlined the diet–microbe interaction with regards to prostate and colon cancers [72]. This review summarized studies demonstrating that an increase in dietary fibre may provide the necessary nutrients for the establishment of the microbiota involved in butyrate production, leading to improved colorectal cancer outcomes. The authors suggest a link between linoleic acid (found in high fat diets) and prostate cancer, explained by cancer cells having a higher concentration of arachidonic acid and prostaglandin E2. Linoleic acid metabolic pathway has also been linked to colorectal cancer progression in individuals with ulcerative colitis combined with enrichment of Enterobacteriaceae and Proteobacteria [73].

Although the intestinal microbiota has profound effects on our overall health, it is important to also consider the oral microbiota, which is clearly impacted by diet. Periodontitis is a microbial-induced chronic inflammatory disease associated with dysbiosis of the oral microbiota that can lead to systemic health issues, such as type 2 diabetes [74,75]. The oral microbe Fusobacterium nucleatum is increased in patients with periodontitis,
which is also associated with an increased risk of colorectal cancer [75,76]. In addition, a recent study showed that individuals with pancreatic cancer have higher circulating and salivary antibodies against *F. nucleatum*, suggesting a link between oral microbiota and pancreatic cancer [77]. Polyphenols are first metabolized in the oral cavity, modulating inflammatory responses as well as eliciting antimicrobial activity, inhibiting the growth of *F. nucleatum* [76]. Although the metabolism of polyphenols in the oral cavity is largely unknown, data suggest that diet also modulates the oral microbiota and therefore impacting our overall health. In addition, polyphenols from foods such as red grape wine, cocoa, and blueberries have anti-inflammatory and antioxidant properties that have potential for prevention of other cancers, such as colorectal cancer [76]. A recent review discussing the in-depth role of polyphenols in cancer has brought new light to this topic [78].

More recent research has highlighted the role of the local microbiome of the tumour microenvironments outside of the gut; for example, a Mediterranean diet has been shown to alter the microbiome of the breast by increasing the abundance of microbes, such as *Lactobacillus*, when compared to a western diet [79]. Further, studies have begun to identify a series of distinct tumour-specific microbiomes associated with select cancers [80–82], which can be associated with therapeutic response [83,84]. Understanding these distinct microbe profiles may allow for early detection in the future, or allow for preventative measures through microbe-altering therapies or dietary interventions.

3.1. Microbe-Altering Approaches to Cancer

Although changes in the microbiota can be detrimental, there may be some microbe-altering approaches that may be used in the treatment or prevention of cancer. Studies on the effects of probiotic use have largely focused on colon cancer. There is evidence that the probiotic *Clostridium butyricum* may inhibit intestinal tumour development through suppression of the Wnt/β-Catenin pathway as well as modulation of the gut microbiota [85]. The Wnt signalling pathway has a central role in stimulating and promoting cell proliferation; mutations in the Wnt pathways are frequently found in carcinomas, specifically CRC [86]. Probiotics have the potential to influence cell signalling pathways in the intestinal tract, however more studies are needed to determine if they indeed have a role in CRC and whether they are beneficial for other cancers.

3.2. SCFA from Microbial Metabolism

Fermentation of nondigestible carbohydrates (starch and fiber) and proteins by select microbes results in the production of SCFAs [87,88]. A variety of dietary components associated with SCFA production have been shown to further improve response to cancer therapies, including immune checkpoint blockers, as highlighted in a recent review by Russo *et al.* [89]. A number of SCFAs have been shown to significantly inhibit proliferation of cancer cells *in vitro*. This has been demonstrated by modulating multiple signalling pathways, including the inhibition of histone deacetylase (HDAC), inducing apoptosis, and upregulating select G protein-coupled receptors (GPCRs/GPR) associated with cancers [90]. Interestingly, omega-3 polyunsaturated fatty acids (PUFAs), commonly found in fish oils, have also been demonstrated to play a role as agonists of these GPRs, namely GPR40 and GPR120, as documented in a recent review by Freitas and Campos [91]. Furthermore, n-3 PUFAs have also been shown to modulate the intestinal microbiome, leading to improved intestinal barrier integrity and reduced inflammation [92–94].

Of the SCFAs, propionate has been shown to upregulate the immune stimulatory and antitumorigenic NKG2D ligand, MICA/B, through pathways not directly associated with the traditional SCFA receptors GPR41/43 [95,96]. Propionate further participates as a precursor molecule for acyl-CoAs that are involved in the acetylation of histones, which reduces cancer phenotype and improves clinical outcomes [97]. The SCFAs acetate, butyrate, and propionate have been further shown to promote IL-22 production, specifically in CD4+ T cells and innate lymphoid cells, through elevation of hypoxia-inducible factor (HIF)1α, interaction with GPR41, and inhibition of HDAC [98].
The microbe *Butyricoccus pullicaecorum* produces the SCFA butyrate, which activates select SCFA transporter (SLC5A8) and receptor (GPR43) pairs, improving the clinical outcome of a colorectal cancer model in mice [99]. Butyrate specifically decreases intercellular adhesion molecule (ICAM)-1, which plays a key role in leukocyte migration in the oral epithelium; this decrease results in reduced inflammation and may play a protective role in progression to oral squamous cell carcinoma [100]. A recent review by Hajjar et al. nicely highlights the evidence to date which demonstrates that butyrate’s natural anticancer activity is in part modulated by its effects as a HDAC inhibitor [101], suggesting supplementation of butyrate in patients as a potential antitumour therapy. Sodium butyrate has further been shown to induce growth arrest and inhibit DNA synthesis in breast, prostate, and colorectal cancer [102–106]. Sodium phenylbutyrate, which is rapidly metabolized to the metabolically-active phenylacetate, has been examined in both clinical and preclinical settings, demonstrating positive effects when combined with chemotherapeutics, cisplatin, gefitinib, or erlotinib, to promote apoptosis in pancreatic, cervical, colon, and central nervous system cancers [107–110]. Increased systemic butyrate and propionate, thought to be due to increased intestinal permeability, have typically been associated with immune modulation via induction of Treg cells, and recently have been shown to limit antitumour activity of anticytotoxic T-lymphocyte-associated protein 4 in multiple tumour mouse models [111].

Interestingly, studies have demonstrated key microbial changes in premenopausal patients at time of breast cancer diagnosis, suggesting that specifically SCFA-producing microbes are significantly lower in abundance in premenopausal breast cancer patients [112]. Furthermore, the SCFAs propionate and butyrate have been shown to inhibit breast cancer cell growth in vitro [112]. Valproic acid, a histone deacetylase inhibitor, has recently been demonstrated to inhibit growth of glioma cells in models of high-grade gliomas [113]. In contrast to the highlighted positive effects of SCFAs, the bacterial metabolite butyric acid plays a role in exacerbating ameloblastoma, a benign tumour of the jawbone, through interactions with epidermal growth factor and transforming growth factor β1 secreted by the tumour cells [114].

### 4. Examples of Cancer Impacted by Diet, Linked to Microbiome

Diet clearly has an impact on every aspect of human health and disease. One of the biggest challenges is that diet is difficult to measure, dietary interventions are hard to enforce, and documenting adherence is known to be biased. Still, there are some examples of cancers with quite strong support for a role for diet. Some of these key conditions are detailed in the text below and in Table 1, while the potential mechanism of interaction between dietary factors and select organ systems will be highlighted below (Figure 2).

| Cancer Type               | Possible Microbes Involved                     | Dietary Risk Factors                                      | Preventative Dietary Factor         |
|--------------------------|-----------------------------------------------|-----------------------------------------------------------|-------------------------------------|
| CNS, Neuroblastoma and Glioma | *Bifidobacterium adolescentis* [58]           | Alcohol consumption and high temperature beverages [119] | Valproic acid [113]                |
|                          |                                               |                                                           | Ketogenic diet [115–117]            |
|                          |                                               |                                                           | Sodium phenylbutyrate [107,108,110] |
| Esophageal               | *Pasteurellales* [118]                        |                                                           | Valproic acid [123,124]             |
|                          |                                               |                                                           | Seaweed [54,55]                    |
|                          |                                               |                                                           | Sodium propionate [45]             |
|                          |                                               |                                                           | Sodium butyrate [102–106]           |
|                          |                                               |                                                           | Mediterranean diet [112,123,124]     |
|                          |                                               |                                                           | Sorbate [47]                       |
|                          |                                               |                                                           | Benzoate [47]                      |
| Breast                   | *Bacteroides plebeius* [54,55]                | Acid-producing diets [121,122]                            | Valproic acid [90]                 |
|                          |                                               | B-glucuronidase [63]                                      | Vitamin D [35]                     |
| Ovarian                  | *Clostridia* [125]                            |                                                           | SCFA [72,126]                      |
| Prostate                 | Possibly *Enterobacteriaceae* and *Proteobacteria* [73] | High-fat (keto) diet [72]                              | Sodium phenylbutyrate [107,108,110] |
**Figure 2.** Potential effects of dietary factors on organs effected by cancer. Intake of dietary factors potentially affect bodily organs through direct filtration of blood or absorptive processes, or indirectly through regulation of metabolites absorbed by the gut, glycemic control (glucose, insulin, cholesterol), regulation of metabolic pathways, inflammatory response to systemic cytokine production, altered sex hormone activity, neurotransmitter metabolism, and response to chronic obesity, as indicated.
4.1. Neuroblastoma and Gliomas

Cancers of the brain such as neuroblastoma, which develops during nervous system expansion in the embryo, or glioma, developing in the adult postmitotic brain, represent rare, yet highly lethal forms of cancer [134,135]. Limited evidence has supported a role for diets such as the ketogenic diet in reducing tumour burden in neuroblastoma xenograft models [115]. Ketogenic diets have recently been shown to reduce proliferation and stemness in glioma cells through metabolic changes that result in a disproportional increase in reactive oxygen species (ROS) production associated with cell arrest and apoptosis [116,117]. Intake of dietary factors potentially results in effects on the brain through regulation of metabolites from the gut-driving glycemic control (glucose, insulin, cholesterol, SCFA), systemic cytokines altering inflammatory activity, and neurotransmitter metabolism [136,137].

4.2. Esophageal Cancer

A number of risk factors have been associated with esophageal cancers, especially the more prevalent esophageal squamous cell carcinoma, including smoking, alcohol consumption, consumption of high temperature beverages, genetics, and diet [119]. Specifically, diet appears to have both direct and indirect effects on the esophagus through cytokine signalling pathways and obesity [138–140].

4.3. Breast Cancer

Breast cancer remains the most common malignancy among women, at times treated using the antimetabolite capecitabine, which, in combination with SCFA, has been shown to provide even greater antitumour effects [90]. SCFAs, namely valproic acid, provide proapoptotic and anti-proliferative effects in breast cancer cells [123,124]. Foods that would promote production of these microbial metabolites could be of benefit in this setting, while others have been shown to function through altering androgenic activity, regulating metabolism, and through cytokine signalling [141].

4.4. Ovarian Cancer

The effects of diet in ovarian cancer are thought to operate through similar pathways to breast cancer, via altered sex hormones and regulation of metabolism [141]. Most interestingly, SCFA have been demonstrated to play a role in inhibiting HDAC in ovarian cancer cells lines and it has been suggested that combining valproic acid with chemotherapeutics such as paclitaxel or doxorubicin could result in increased apoptosis, decreased poly (ADP-ribose) polymerase enzymes, and inhibition of DNA repair in ovarian cancer cells, although yet to be tested clinically [90].

4.5. Prostate Cancer

Similarly, SCFAs have been shown to target histone acetylation processes resulting in the re-expression of cyclin D2, which results in the inhibition of prostate cancer cell growth, migration, and invasion [126]. Dietary factors are thought to affect the prostate via altered androgenic activity, cytokine signalling pathways, and through metabolic effects [142–144].

4.6. Hepatocellular Carcinoma (HCC)

HCC progression has been directly associated with increased Notch signalling, which is downregulated by microbe fermentation processes and in response to SCFAs [129,130]. The specific interactions between the liver and dietary factors are thought to occur through blood filtration of absorbed nutrients, toxins, and metabolites, as well as thorough systemic metabolic regulation [128,145].
4.7. Pancreatic Cancer

Some of the most exciting evidence on the use of diet and microbial strategies in cancer relates to pancreatic cancers. Phase I and phase II clinical trials have been performed based on the positive effects of SCFAs as antitumour aids in pancreatic cancer [132,133]. These studies demonstrated 91.7% tumour control in patients with advanced stage pancreatic cancer [132]. The pancreas plays a well-known role in the regulation of metabolic pathways and therefore it is not surprising that its interactions with dietary factors occur through glucose and enzyme regulation, cytokine signalling, and indirectly through the effects of chronic obesity [146].

4.8. Colorectal Cancer

Colorectal cancer represents one of the leading causes of cancer-related death, which is thought to be due to dietary changes, increased incidence of chronic IBD, and increasing life expectancies globally. Diet has been suggested to play a leading role in up to 50% of colorectal cancer cases and probiotics have shown some benefit in the treatment of IBD, diarrhea, irritable bowel syndrome, gastroenteritis, and cancer, suggesting that altering diet and microbes could be an effective therapeutic option for colorectal cancers [147]. However, clinical data on the utility of diet and microbe-related treatments for CRC are still in the early stages. The gut is the primary site of dietary interactions within the body as it is responsible for the majority of the digestive and absorptive processes resulting in direct effects within the epithelial lining, alterations of the host microbiome, metabolic regulation, immune response, systemic hormone alterations, and indirect responses related to chronic obesity [148,149].

5. Common Misconceptions Regarding Diet and Cancer

As research continues to demonstrate the powerful links between diet, microbes, and progression to cancer, it is important to distinguish what facts are supported by science, on the one hand, and the myths that continue to plague popular belief, on the other. We recently reviewed a number of common misconceptions in relation to diet, microbiome, and cancer [6] and will update and expand on these ideas here, relevant to this review.

One common misconception involves the idea that consumption of organic foods reduces risk of cancer. In a decade-long study of 623,080 middle-aged women in the UK, researchers demonstrated that there was little to no decrease in risk of cancer associated with an organic diet [150]. Interestingly, one French study of 68,946 participants followed over seven years, suggested that heightened frequency of organic food consumption was in fact associated with reduced risk of cancer; however, one major drawback of this study that is commonly overlooked, pertains to the fact that the occurrence of cancer also correlated with the overall consumption of fiber, fruits, and vegetables, and their findings were not adjusted to these residual cofactors [151]. A number of studies have demonstrated the protective correlation between a diet high in fruits and vegetables [120,152–157] resulting in a lack of substantiated reason to suggest that organic food consumption holds any protective benefits.

Although not well supported at this time, one possibility that may explain the connection between select organic foods and cancer risk includes the consumption of pesticides [151,158–160]; however, a recent publication highlighted the serious limitations within the studies of dietary pesticide consumption and the connection to cancer risk resulting again, in a lack of substantiated reason to suggest that organic food consumption holds any protective benefits [161]. Once more, the likely reason behind the results of this particular study relates to lifestyle and demographic covariates as this was not an interventional study but rather observational. On this topic, it is also important to note the large geographical and regulatory differences in pesticide use globally, leading to variability in how we may relate study findings to outcomes [162].
Alkaline diets are often misconstrued to be protective of development of cancer, although there currently remains little research to support or disprove this concept [163]. Recent evidence from two observational studies suggests that diets categorized as acid-producing are associated with greater risk of inflammation in estrogen receptor-negative and triple-negative breast cancers [121,122]; these studies support the need for ongoing research on this topic.

One interesting highly popularized misconception that crosses multiple fields of health research is that of cleansing or detoxes for use in “removing toxins”, harmful substances, or cancer cells from the body. The body has a series of organs (liver and kidneys) and natural processes in place to complete these tasks and there remains no evidence to date for any magic potion to replace these processes; in fact, the harmful effects on fluid balance and loss of nutrients need to be considered [164–169]. At this time, we would promote general recommendations that individuals avoid heavy consumption of alcohol and eat a healthy, well balanced diet, to ensure proper organ function continues.

In contrast to those common misconceptions that involve dietary factors that are not in fact associated with cancer risk, the subject of sugar consumption in relation to cancer is a difficult topic to summarize and is commonly misconceptualised as “unassociated” with cancer. There are a number of reasons for this, namely that all of the cells in the human body utilise sugars as an energy source and therefore require sugars for proper organ function [170]. That being said, many studies have correlated the outcomes of a poor diet, high in sugars, with health conditions (e.g., obesity) that are positively correlated with increased risk of cancer [171,172]. Within recent years a number of published studies have demonstrated that high glucose both in vitro and in clinical settings not only drives promotion of cancer, but also represses the anti-proliferative and pro-apoptotic effects of cancer therapies, including Metformin [171,173,174]. While avoiding consumption of sugar altogether is not necessarily beneficial, it should be recommended that a high-sugar diet be avoided to reduce risk of cancer, and to prevent interference with select anticancer therapies.

Misconception and myths continue to plague the field of medicine surrounding the concepts of diet and cancer; however, it is important to recognize the pros and cons, and potential risks involved. Ongoing research will continue to uncover new beneficial and detrimental factors associated with cancer; until then, researchers will need to ensure that fact-based evidence is promoted over misconception and myth.

6. Future Perspectives and Opportunities

Cancer remains one of the most prevalent diseases in the western world, and a leading cause of death, yet our comprehension of the role of diet and microbes in promoting inflammation and malignancy remains limited. As research continues to demonstrate, providing clinical advice related to nutrition and microbiome can be difficult for a number of reasons, including the limited understanding of these topics to date, in part due to the complexity of these studies. Here we discussed some key recently published studies, which have accelerated our understanding of dietary factors and microbes in a number of cancers.

We recognize that there are a number of complex systemic factors related to cancer development, progression, and prevention that were not thoroughly covered in this review and would like to highlight selective recent papers and reviews related to some of these aspects. For example, hormones appear to impact the interaction between diet, the microbiome, and cancer, as demonstrated by comparing the gut metagenome in pre-menopausal and post-menopausal women, with and without breast cancer [175], and reviewed elsewhere [176]. Ketogenic diets have been discussed here in the context of glioblastoma, prostate, pancreatic, and colorectal cancers, but are likely relevant in a broader sense to other settings, as the tumour microenvironment created with this diet has the potential to suppress or promote cancer cells, and regulate the effect of antitumour therapies [131,177], dependent on the individual’s microbiome [178]. Another important aspect
connecting the diet-microbiome axis to cancer is epigenetics, as DNA methylation and histone modification, including HDACs, as highlighted in this review, are impacted by dietary and microbial compounds, with a potential to mediate additional mechanisms leading to cancer [179]. With improving technologies (high-throughput sequencing and omics [180,181]) and evolving methodologies for tracking dietary intake (openly available rapid and accurate reporting tools [182,183]), we may continue to improve the significance of ongoing research associating microbes and diet with cancer.

By combining the data published to date, one begins to notice patterns associated with the benefits of consumption of fruits, vegetables, and grains made up of fermentable dietary factors that are utilised by beneficial microbes, ultimately resulting in the production of key SCFAs and reduced risk of malignancy. Similar findings have been established in studies of a broad range of diseases, suggesting that consumption of greater amounts of these foods, in combination with the appropriate microbes, imparts beneficial health effects. These studies do not necessarily promote a vegetarian diet, so much as a diverse diet high in fruits and vegetables, yet the studies to date do support limiting the consumption of red meats [21] in particular. It is imperative that we consider that it is in part the gut microbes that require the correct nutrients, sourced from dietary intake, in order to survive, thrive, and aid in promoting host health; dysbiosis, or loss of key microbes, is associated with a number of chronic illnesses that are associated with increased cancer burden.

One of the biggest challenges in determining the involvement of microbes and diet in health is the need for long term studies, performed over decades, which examine precise metabolites (metabolomics), microbiome (sequencing), epidemiology, dietary intakes, and clinical outcomes. By ensuring only the most precise and up-to-date techniques are utilised in future studies, using thorough planning and preparation, we can ensure the combination of basic, translational, and clinical research outcomes are able to direct precision medicine involving microbe-altering approaches and dietary interventions reducing cancer burden. A number of fantastic reviews [181,183] have recently highlighted the best techniques in use at this time, and further review should be performed during any planning phase in order to ensure the appropriate techniques are being utilised to ensure translation of results for clinical use.

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**References**

1. Grammatikopoulou, M.G.; Goulis, D.G.; Gkiouras, K.; Nigdelis, M.P.; Papageorgiou, S.T.; Papamitsou, T.; Forbes, A.; Bogdanos, D.P. Low FODMAP Diet for Functional Gastrointestinal Symptoms in Quiescent Inflammatory Bowel Disease: A Systematic Review of Randomized Controlled Trials. *Nutrients* **2020**, *12*, 3648.

2. Anupama, P.H.; Prasad, N.; Nzana, V.B.; Tiwari, J.P.; Mathew, M.; Abraham, G. Dietary Management in Slowing Down the Progression of CKDu. *Indian J. Nephrol.* **2020**, *30*, 256–260.

3. Rubio, C.; Luna, R.; Rosiles, A.; Rubio-Osornio, M. Caloric Restriction and Ketogenic Diet Therapy for Epilepsy: A Molecular Approach Involving Wnt Pathway and KATP Channels. *Front. Neurol.* **2020**, *11*, 584298.

4. McAuliffe, S.; Ray, S.; Fallon, E.; Bradfield, J.; Eden, T.; Kohlmeier, M. Dietary micronutrients in the wake of COVID-19: An appraisal of evidence with a focus on high-risk groups and preventative healthcare. *BMJ Nutr. Prev. Health* **2020**, *3*, 93–99.
5. Lombardi, R.; Iuculano, F.; Pallini, G.; Fargion, S.; Fracanzani, A.L. Nutrients, Genetic Factors, and Their Interaction in Non-Alcoholic Fatty Liver Disease and Cardiovascular Disease. *Int. J. Mol. Sci.* 2020, 21, 8761.

6. Armstrong, H.; Bording-Jorgensen, M.; Dijk, S.; Wine, E. The Complex Interplay between Chronic Inflammation, the Microbiome, and Cancer: Understanding Disease Progression and What We Can Do to Prevent It. *Cancers (Basel)* 2018, 10, 83.

7. Alonso, S.; Yilmaz, O.H. Nutritional Regulation of Intestinal Stem Cells. *Annu. Rev. Nutr.* 2018, 38, 273–301.

8. Cangelosi, A.L.; Yilmaz, O.H. High fat diet and stem cells: Linking diet to intestinal tumor formation. *Cell Cycle* 2016, 15, 1657–1658.

9. Calibasi-Kocal, G.; Mashinchan, O.; Basbinar, Y.; Ellidokuz, E.; Cheng, C.-W.; Yilmaz, O.H. Nutritional Control of Intestinal Stem Cells in Homeostasis and Tumorigenesis. *Trends Endocrinol. Metab.* 2020, 32, 30221–30226.

10. Hou, Y.; Wei, W.; Guan, X.; Liu, Y.; Bian, G.; He, D.; Fan, Q.; Cai, X.; Zhang, Y.; Wang, G.; et al. A diet-microbial metabolism feedbackloop modulestestinal stem cell renewal in the stressed gut. *Nat. Commun.* 2021, 12, 271.

11. Balkwill, F.; Mantovani, A. Inflammation and cancer: Back to Virchow? *Lancet* 2001, 357, 539–545.

12. Schmidt, A.; Weber, O.F. In memoriam of Rudolf virchow: A historical retrospective including aspects of inflammation, infection and neoplasia. *Contrib. Microbiol.* 2006, 13, 1–15.

13. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2016. *CA Cancer J. Clin.* 2016, 66, 7–30.

14. Yi, M.; Xu, J.; Liu, P.; Chang, G.J.; Du, X.L.; Hu, C.Y.; Song, Y.; He, J.; Ren, Y.; Wei, Y.; et al. Comparative analysis of lifestyle factors, screening test use, and clinicopathologic features in association with survival among Asian Americans with colorectal cancer. *Br. J. Cancer* 2013, 108, 1508–1514.

15. Tung, J.; Politis, C.E.; Chadder, J.; Han, J.; Niu, J.; Fung, S.; Rahal, R.; Earle, C.C. The north-south and east-west gradient in colorectal cancer risk: A look at the distribution of modifiable risk factors and incidence across Canada. *Curr. Oncol.* 2018, 25, 231–235.

16. Patel, P.; De, P. Trends in colorectal cancer incidence and related lifestyle risk factors in 15–49-year-olds in Canada, 1969–2010. *Cancer Epidemiol.* 2016, 42, 90–100.

17. Wang, X.; Chan, A.T.; Slattery, M.L.; Chang-Claude, J.; Potter, J.D.; Gallinger, S.; Cana, B.; Lampe, J.W.; Newcomb, P.A.; Zubair, N.; et al. Influence of Smoking, Body Mass Index, and Other Factors on the Preventive Effect of Nonsteroidal Anti-Inflammatory Drugs on Colorectal Cancer Risk. *Cancer Res.* 2018, 78, 4790–4799.

18. Hardman, W.E. Diet components can suppress inflammation and reduce cancer risk. *Nutr. Res. Pract.* 2014, 8, 233–240.

19. Dumas, J.A.; Bunn, J.Y.; Nickerson, J.; Crain, K.J.; Ebenstein, D.B.; Tarleton, E.K.; Makarewicz, J.; Poynter, M.E.; Kien, C.L. Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women. *Metabolism* 2016, 65, 1582–1588.

20. Lopez-Alarcon, M.; Perichart-Perera, O.; Flores-Huerta, S.; Inda-Icaza, P.; Rodriguez-Cruz, M.; Armenta-Alvarez, A.; Bram-Falcon, M.T.; Mayorga-Ochoa, M. Excessive refined carbohydrates and scarce micronutrients intakes increase inflammatory mediators and insulin resistance in prepubertal and pubertal obese children independently of obesity. *Mediat. Inflamm.* 2014, 2014, 849031.

21. Samraj, A.N.; Pearce, O.M.; Laubli, H.; Crittenden, A.N.; Bergfeld, A.K.; Banda, K.; Gregg, C.J.; Bingman, A.E.; Secrest, P.; Diaz, S.L.; et al. A red meat-derived glycan promotes inflammation and cancer progression. *Proc. Natl. Acad. Sci. USA* 2015, 112, 542–547.

22. De Filippo, C.; Cavalieri, D.; Di Paola, M.; Ramazzotti, M.; Poullet, J.B.; Massart, S.; Collini, S.; Pieraccini, G.; Lionetti, P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc. Natl. Acad. Sci. USA* 2010, 107, 14691–14696.

23. Li, W.; Dowd, S.E.; Scurluck, B.; Acosta-Martinez, V.; Lyte, M. Memory and learning behavior in mice is temporally associated with diet-induced alterations in gut bacteria. *Physiol. Behav.* 2009, 96, 557–567.

24. Armstrong, H.; Alipour, M.; Valcheka, R.; Bording-Jorgensen, M.; Jovel, J.; Zaidi, D.; Shah, P.; Lou, Y.; Ebeling, C.; Mason, A.L.; et al. Host immunoglobulin G selectively identifies pathobionts in pediatric inflammatory bowel diseases. *Microbiome* 2019, 7, 1–17.

25. Karlsen, T.H.; Folseraas, T.; Thorburn, D.; Vesterhus, M. Primary sclerosing cholangitis—A comprehensive review. *J. Hepatol.* 2017, 67, 1298–1323.

26. Ong, H.S.; Yim, H.C.H. Microbial Factors in Inflammatory Bowel Diseases and Cancers. *Adv. Exp. Med. Biol.* 2017, 1024, 153–174.

27. Maeda, Y.; Takeda, K. Role of Gut Microbiota in Rheumatoid Arthritis. *J. Clin. Med.* 2017, 6, 60.

28. Møllemkjaer, L.; Linet, M.S.; Gridley, G.; Frisch, M.; Moller, H.; Olsen, J.H. Rheumatoid arthritis and cancer risk. *Eur. J. Cancer* 1996, 32, 1753–1757.

29. Weaver, C.M.; Miller, J.W. Challenges in conducting clinical nutrition research. *Nutr. Rev.* 2017, 75, 491–499.

30. Lichtenstein, A.H.; Petersen, K.; Barger, K.; Hansen, K.E.; Anderson, C.A.M.; Baer, D.J.; Lampe, J.W.; Rasmussen, H.; Matthan, N.R. Perspective: Design and Conduct of Human Nutrition Randomized Controlled Trials. *Adv. Nutr.* 2021, 12, 4–20, doi:10.1093/advances/nmaa109.

31. Mentella, M.C.; Scaldaferri, F.; Ricci, C.; Gasbarrini, A.; Miggiano, G.A.D. Cancer and Mediterranean Diet: A Review. *Nutrients* 2019, 11, 2059.

32. Weber, D.D.; Aminazdeh-Gohari, S.; Kolf, B. Ketogenic diet in cancer therapy. *Aging (Albany NY)* 2018, 10, 164–165.

33. Steck, S.E.; Murphy, E.A. Dietary patterns and cancer risk. *Nat. Rev. Cancer* 2020, 20, 125–138.

34. Jansson, B. Potassium, sodium, and cancer: A review. *J. Environ. Pathol. Toxicol. Oncol.* 1996, 15, 65–73.
35. Keum, N.; Lee, D.H.; Greenwood, D.C.; Manson, J.E.; Giovannucci, E. Vitamin D supplementation and total cancer incidence and mortality: A meta-analysis of randomized controlled trials. Ann. Oncol. 2019, 30, 733–743.

36. Nutting, C.M.; Huddart, R.A. Retinoids in the prevention of bladder cancer. Expert Rev. Anticancer. Ther. 2001, 1, 541–545.

37. Tang, J.E.; Wang, R.J.; Zhong, H.; Yu, B.; Chen, Y. Vitamin A and risk of bladder cancer: A meta-analysis of epidemiological studies. World J. Surg. Oncol. 2014, 12, 130.

38. Okayasu, I.; Hana, K.; Nemoto, N.; Yoshida, T.; Saegusa, M.; Yokota-Nakatsuma, A.; Song, S.Y.; Iwata, M. Vitamin A Inhibits Development of Dextran Sulfate Sodium-Induced Colitis and Colon Cancer in a Mouse Model. Biomed. Res. Int. 2016, 2016, 4874809.

39. Lan, Q.Y.; Zhang, Y.J.; Liao, G.C.; Zhou, R.F.; Zhou, Z.G.; Chen, Y.M.; Zhu, H.L. The Association between Dietary Vitamin A and Carotenoids and the Risk of Primary Liver Cancer: A Case-Control Study. Nutrients 2016, 8, 624.

40. Fleet, J.C.; DeSmet, M.; Johnson, R.; Li, Y. Vitamin D and cancer: A review of molecular mechanisms. Biochim. J. 2012, 441, 61–76.

41. Vissers, M.C.M.; Das, A.B. Potential Mechanisms of Action for Vitamin C in Cancer: Reviewing the Evidence. Front. Physiol. 2018, 9, 809.

42. Carlgberg, C.; Munoz, A. An update on vitamin D signaling and cancer. Semin. Cancer Biol. 2020, doi:10.1016/j.semcancer.2020.05.018.

43. Mamede, A.C.; Tavares, S.D.; Abrantes, A.M.; Trindade, J.; Maia, J.M.; Botelho, M.F. The role of vitamins in cancer: A review. Nutr. Cancer 2011, 63, 479–494.

44. Holland-Bill, L.; Christiansen, C.F.; Farkas, D.K.; Donskov, F.; Jorgensen, J.O.L.; Sorensen, H.T. Diagnosis of hyponatremia and increased risk of a subsequent cancer diagnosis: Results from a nationwide population-based cohort study. Acta Oncol. 2018, 57, 522–527.

45. Park, H.S.; Han, J.H.; Park, J.W.; Lee, D.H.; Jang, K.W.; Lee, M.; Heo, K.S.; Myung, C.S. Sodium propionate exerts anticancer effect in mice bearing breast cancer cell xenograft by regulating JAK2/STAT3/ROS/p38 MAPK signaling. Acta Pharmacol. Sin. 2020, 1–13, doi:10.1038/s41401-020-00522-0.

46. Crowe, W.; Elliott, C.T.; Green, B.D. A Review of the In Vivo Evidence Investigating the Role of Nitrite Exposure from Processed Meat Consumption in the Development of Colorectal Cancer. Nutrients 2019, 11, 2673.

47. Javanmardi, F.; Rahmani, J.; Ghiasi, F.; Gahrue, H.H.; Khaneghab, A.M. The Association between the Preservative Agents in Foods and the Risk of Breast Cancer. Nutr. Cancer 2019, 71, 1229–1240.

48. Fiolet, T.; Srour, B.; Sellem, L.; Kesse-Guyot, E.; Alles, B.; Mejean, C.; Deschasaux, M.; Fassier, P.; Latino-Martel, P.; Beslay, M.; et al. Consumption of ultra-processed foods and cancer risk: Results from NutriNet-Sante prospective cohort. BMJ 2018, 360, k322.

49. Rosca, A.; Lesanu, M.L.; Zahiu, C.D.M.; Voiculescu, S.E.; Pasiaru, A.C.; Zagrean, A.-M. Capsaicin and Gut Microbiota in Health and Disease. Molecules 2020, 25, 5681.

50. Ge, Y.; Yoon, S.H.; Jang, H.; Jeong, J.H.; Lee, Y.M. Decursin promotes HIF-1alpha proteasomal degradation and immune responses in hypoxic tumour microenvironment. Phytomedicine 2020, 78, 153318.

51. Schlormann, W.; Atanasov, S.; Lorkowski, S.; Dzwczynski, C.; Glei, M. Study on chemopreventive effects of raw and roasted beta-glucan-rich rye winter barley using an in vitro human colon digestion model. Food Funct. 2020, 11, 2626–2638.

52. Glei, M.; Zetzmann, S.; Lorkowski, S.; Dzwczynski, C.; Schlormann, W. Chemopreventive effects of raw and roasted oat flakes after in vitro fermentation with human faecal microbiota. Int. J. Food Sci. Nutr. 2020, 1–13, doi:10.1080/09637486.2020.1772205.

53. Xia, W.; Khan, I.; Li, X.A.; Huang, G.; Yu, Z.; Leong, W.K.; Han, R.; Ho, L.T.; Wendy Hsiao, W.L. Adaptogenic flower buds exert cancer preventive effects by enhancing the SCFA-producers, strengthening the epithelial tight junction complex and immune responses. Pharmcol. Res. 2020, 159, 108492.

54. Hehemann, J.H.; Correc, G.; Barbyron, T.; Helbert, W.; Czpek, M.; Michel, G. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. Nature 2010, 464, 908–912.

55. Vaikundamoorthy, R.; Krishnamoorthy, V.; Vilwanathan, R.; Rajendran, R. Structural characterization and anticancer activity (MC7 and MDA-MB-231) of polysaccharides fractionated from brown seaweed Sargassum wightii. Int. J. Biol. Macromol. 2018, 111, 1229–1237.

56. Penalver, R.; Lorenzo, J.M.; Ros, G.; Amarowicz, R.; Pateiro, M.; Nieto, G. Seaweeds as a Functional Ingredient for a Healthy Diet. Mar. Drugs 2020, 18, 18.

57. Baruch, E.N.; Youngster, I.; Ben-Betzalel, G.; Ortenberg, R.; Lahat, A.; Katz, L.; Adler, K.; Dick-Necula, D.; Raskin, S.; Bloch, N.; et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science 2020, eabb5920, doi:10.1126/science.abb5920.

58. Ang, Q.Y.; Alexander, M.; Newman, J.C.; Tian, Y.; Cai, J.; Upadhyay, V.; Turnbaugh, J.A.; Verdin, E.; Hall, K.D.; Leibel, R.L.; et al. Ketogenic Diets Alter the Gut Microbiome Resulting in Decreased Intestinal Th17 Cells. Cell 2020, 181, 1263–1275.e1216.

59. Hopkins, B.D.; Pauli, C.; Du, X.; Wang, D.G.; Li, X.; Wu, D.; Amadiumie, S.C.; Goncalves, M.D.; Hodakoski, C.; Lundquist, M.R.; et al. Publisher Correction: Suppression of insulin feedback enhances the efficacy of PDK inhibitors. Nature 2018, 563, E24.

60. Zhou, Z.; Chen, J.; Yao, H.; Hu, H. Fusobacterium and Colorectal Cancer. Front. Oncol. 2018, 8, 371.

61. Reddy, B.S.; Weisburger, J.H.; Wynder, E.L. Fecal bacterial beta-glucuronidase: Control by diet. Science 1974, 183, 416–417.
62. Creekmore, B.C.; Gray, J.H.; Walton, W.G.; Biernat, K.A.; Little, M.S.; Xu, Y.; Liu, J.; Gharaibeh, R.Z.; Redinbo, M.R. Mouse Gut Microbiome-Encoded beta-Glucuronidases Identified Using Metagenome Analysis Guided by Protein Structure. *mSystems* 2019, 4, doi:10.1128/mSystems.00452-19.

63. Kwa, M.; Plotel, C.S.; Blaser, M.J.; Adams, S. The Intestinal Microbiome and Estrogen Receptor-Positive Female Breast Cancer. *J. Natl Cancer Inst.* 2016, 108, 108.

64. Sperker, B.; Werner, U.; Murdter, T.E.; Tekkaya, C.; Fritz, P.; Wacke, R.; Adam, U.; Gerken, M.; Drewelow, B.; Kroemer, H.K. Expression and function of beta-glucuronidase in pancreatic cancer: Potential role in drug targeting. *Naunyn Schmiedebergs Arch. Pharmacol.* 2000, 362, 110–115.

65. Kim, D.H.; Jin, Y.H. Intestinal bacterial beta-glucuronidase activity of patients with colon cancer. *Arch. Pharm. Res.* 2001, 24, 564–567.

66. Bhatt, A.P.; Pellock, S.J.; Biernat, K.A.; Walton, W.G.; Wallace, B.D.; Creekmore, B.C.; Letertre, M.M.; Swann, J.R.; Wilson, I.D.; Roques, J.R.; et al. Targeted inhibition of gut bacterial beta-glucuronidase activity enhances anticancer drug efficacy. *Proc. Natl. Acad. Sci. USA* 2020, 117, 7374–7381.

67. Gultekin, F.; Oner, M.E.; Savas, H.B.; Dogan, B. Food additives and microbiota. *North. Clin. Istanb.* 2020, 7, 192–200.

68. Hmrinella, E.; Cintoni, M.; Rofail, P.; Gasbarrini, A.; Mele, M.C. Food Additives, Gut Microbiota, and Irritable Bowel Syndrome: A Hidden Track. *Int. J. Environ. Res. Public Health* 2017, 14, 8816.

69. Wang, Y.; Wang, H.; Howard, A.G.; Tsilimigras, M.C.B.; Avery, C.L.; Meyer, K.A.; Sha, W.; Sun, S.; Zhang, J.; Su, C.; et al. Associations of sodium and potassium consumption with the gut microbiota and host metabolites in a population-based study in Chinese adults. *Am. J. Clin. Nutr.* 2020, 112, 1599–1612, doi:10.1093/ajcn/nqaa263.

70. Larrosa, M.; Luceri, C.; Vivoli, E.; Pagliuca, C.; Lodovici, M.; Moneti, G.; Dolara, P. Polyphenol metabolites from colonic microbiota exert anti-inflammatory activity on different inflammation models. *Mol. Nutr. Food Res.* 2009, 53, 1044–1054.

71. Mann, S.D.; Sidhu, M.D.; Gowin, K.D. Understanding the Mechanisms of Diet and Outcomes in Colon, Prostate, and Breast Cancer; Malignant Gliomas; and Cancer Patients on Immunotherapy. *Nutrients* 2020, 12, 2226.

72. Tang, Q.; Cang, S.; Jiao, J.; Rong, W.; Xu, H.; Bi, K.; Li, Q.; Liu, R. Integrated study of metabolomics and gut metabolic activity from ulcerative colitis to colorectal cancer: The combined action of disordered gut microbiota and linoleic acid metabolic pathway might fuel cancer. *J. Chromatogr. A* 2020, 1629, 461503.

73. Belstrom, D. The salivary microbiome in health and disease. *J. Oral Microbiol.* 2012, 12, 1723975.

74. Lundmark, A.; Hu, Y.O.O.; Huss, M.; Johannsen, G.; Andersson, A.F.; Yucel-Lindberg, T. Identification of Salivary Microbiota and Its Association With Host Inflammatory Mediators in Periodontitis. *Front. Cell Infect. Microbiol.* 2019, 9, 216.

75. Cueva, C.; Silva, M.; Pinillos, I.; Bartolome, B.; Moreno-Arribas, M.V. Interplay between Dietary Polyphenols and Oral and Gut Microbiota in the Development of Colorectal Cancer. *Nutrients* 2020, 12, 625.

76. Alkhaarana, H.; Lu, L.; Gabbarrini, G.; Halimi, A.; Ateeb, Z.; Sobkowiak, M.J.; Davanian, H.; Fernandez Moro, C.; Jansson, L.; Del Chiaro, M.; et al. Circulating and Salivary Antibodies to Fusobacterium nucleatum Are Associated With Cystic Pancreatic Neoplasm Malignancy. *Front. Immunol.* 2020, 11, 2003.

77. Briguglio, G.; Costa, C.; Pollicino, M.; Giambò, F.; Catania, S.; Fenga, C. Polyphenols in cancer prevention: New insights (Review). *Int. J. Funct. Nutr.* 2020, 1, doi:10.3892/ijfn.2020.9.

78. Shively, C.A.; Register, T.C.; Appt, S.E.; Clarkson, T.B.; Überseder, B.; Clear, K.Y.J.; Wilson, A.S.; Chiba, A.; Tooze, J.A.; Cook, K.L. Consumption of Mediterranean versus Western Diet Leads to Distinct Mammary Gland Microbiome Populations. *Cell Rep.* 2018, 25, 47–56.e43.

79. Nejman, D.; Livyatan, I.; Fuks, G.; Gavert, N.; Zwang, Y.; Geller, L.T.; Rotter-Maskowitz, A.; Weiser, R.; Mallel, G.; Gigi, E.; et al. Human tumour microbiome is composed of tumour-type-specific intracellular bacteria. *Science* 2020, 368, 973–980.

80. Jarman, R.; Ribeiro-Milhograna, S.; Kalle, W. Potential of the Microbiome as a Biomarker for Early Diagnosis and Prognosis of Breast Cancer. *J. Breast Cancer* 2020, 23, 579–587.

81. Parida, S.; Sharma, D. The microbiome and cancer: Creating friendly neighborhoods and removing the foes within. *Cancer Res.* 2020, 80, doi:10.1158/0008-5472.CAN-20-2629.

82. Geller, L.T.; Barzily-Rokni, M.; Danino, T.; Jonas, O.H.; Shental, N.; Nejman, D.; Gavert, N.; Zwang, Y.; Cooper, Z.A.; Shee, K.; et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemicatibine. *Science* 2017, 357, 1156–1160.

83. Chiba, A.; Bawaneh, A.; Velazquez, C.; Clear, K.Y.J.; Wilson, A.S.; Howard-McNatt, M.; Levine, E.A.; Levi-Polyachenko, N.; Yates-Alston, S.A.; Diggle, S.P.; et al. Neoadjuvant Chemotherapy Shifts Breast Tumor Microbiota Populations to Regulate Drug Responsiveness and the Development of Metastasis. *Mol. Cancer Res.* 2020, 18, 130–139.

84. Chen, D.; Jin, D.; Huang, S.; Wu, J.; Xu, M.; Liu, T.; Dong, W.; Liu, X.; Wang, S.; Zhong, W.; et al. Clostridium butyricum, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota. *Cancer Lett.* 2020, 469, 456–467.

85. Nusse, R.; Clevers, H. Wnt/beta-Catenin Signaling, Disease, and Emerging Therapeutic Modalities. *Cell* 2017, 169, 985–999.

86. Chen, C.; Li, H. The Inhibitory Effect of Gut Microbiota and Its Metabolites on Colorectal Cancer. *J. Microbiol. Biotechnol.* 2020, 30, 1607–1613.
88. Armstrong, H.; Mander, I.; Zhang, Z.; Armstrong, D.; Wine, E. Not all fibres are born equal; variable response to dietary fibre subtypes in IBD. *Front. Pediatr.* 2020, 8, 620189, doi:10.3389/fped.2020.620189.

89. Russo, E.; Nannini, G.; Dinu, M.; Pagliai, G.; Sofi, F.; Amedei, A. Exploring the food-gut axis in immunotherapy response of cancer patients. *World J. Gastroenterol.* 2020, 26, 4919–4932.

90. Lipska, K.; Gumieniczek, A.; Filip, A.A. Anticonvulsant valproic acid and other short-chain fatty acids as novel anticancer therapeutics: Possibilities and challenges. *Acta Pharm.* 2020, 70, 291–301.

91. Freitas, R.D.S.; Campos, M.M. Protective Effects of Omega-3 Fatty Acids in Cancer-Related Complications. *Nutrients* 2019, 11, 945.

92. Parolini, C. Effects of Fish n-3 PUFAs on Intestinal Microbiota and Immune System. *Mar. Drugs* 2019, 17, 374.

93. Watson, H.; Mitra, S.; Croden, F.C.; Taylor, M.; Wood, H.M.; Perry, S.L.; Spencer, J.A.; Quirke, P.; Tooood, G.J.; Lawton, C.L.; et al. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. *Gut* 2018, 67, 1974–1983.

94. Menni, C.; Zierer, J.; Pallister, T.; Jackson, M.A.; Long, T.; Mohney, R.P.; Steves, C.J.; Spector, T.D.; Valdes, A.M. Omega-3 fatty acids correlate with gut microbiome diversity and production of N-carbamylglutamate in middle aged and elderly women. *Sci. Rep.* 2017, 7, 11079.

95. Sheppard, S.; Ferry, A.; Guedes, J.; Guerra, N. The Paradoxical Role of NKG2D in Cancer Immunity. *Front. Immunol.* 2018, 9, 1808.

96. Hogh, R.I.; Moller, S.H.; Jepsen, S.D.; Mellergaard, M.; Lund, A.; Pejtersen, M.; Fitzner, E.; Andresen, L.; Skov, S. Metabolism of short-chain fatty acid propionate induces surface expression of NKG2D ligands on cancer cells. *FASEB J.* 2020, 34, 15531–15546.

97. Dai, Z.; Ramesh, V.; Locasale, J.W. The evolving metabolic landscape of chromatin biology and epigenetics. *Nat. Rev. Genet.* 2020, 21, 737–753.

98. Yang, W.; Yu, T.; Huang, X.; Bilotta, A.J.; Xu, L.; Lu, Y.; Sun, J.; Pan, F.; Zhou, J.; Zhang, W.; et al. Intestinal microbiota-derived short-chain fatty acids regulation of immune IL-22 production and gut immunity. *Nat. Commun.* 2020, 11, 4457.

99. Chang, S.C.; Shen, M.H.; Liu, C.Y.; Pu, C.M.; Hu, J.M.; Huang, C.J. A gut butyrate-producing bacterium Butyrivibrio succinogenes regulates short-chain fatty acid transporter and receptor to reduce the progression of 1,2-dimethylyhydracine-associated colorectal cancer. *OncoLett.* 2020, 20, 327.

100. Magrin, G.L.; Di Summa, F.; Strauss, F.J.; Panahipour, L.; Mildner, M.; Magalhaes Benfati, C.A.; Gruber, R. Butyrate Decreases ICAM-1 Expression in Human Oral Squamous Cell Carcinoma Cells. *Int. J. Mol. Sci.* 2020, 21, 1679.

101. Hajjar, R.; Richard, C.S.; Santos, M.M. The role of butyrate in surgical and oncological outcomes in colorectal cancer. *Am. J. Physiol. Liver Physiol.* 2021, doi:10.1152/ajpgi.00316.2020.

102. Steliou, K.; Boosalis, M.S.; Perrine, S.P.; Sangerman, J.; Faller, D.V. Butyrate histone deacetylase inhibitors. *Biores. Open Access* 2012, 1, 192–198.

103. Damaskos, C.; Garmips, N.; Valsami, S.; Kontos, M.; Spartalis, E.; Kalampokas, T.; Kalampokas, E.; Athanasiou, A.; Moris, D.; Daskalogiorgouli, A.; et al. Histone Deacetylase Inhibitors: An Attractive Therapeutic Strategy Against Breast Cancer. *Anticancer Res.* 2017, 37, 35–46.

104. Abazam, M.S.; Afzal, A.; Afzal, M. Short-chain fatty acids are antineoplastic agents. *Fatty Acids* 2017, 57–70, doi:10.5772/intechopen.68441.

105. Matthews, G.M.; Howarth, G.S.; Butler, R.N. Short-chain fatty acids induce apoptosis in colon cancer cells associated with changes to intracellular redox state and metabolic. *Chemotherapy* 2012, 58, 102–109.

106. Cho, J.H.; Dimri, M.; Dimri, G.P. MicroRNA-31 is a transcriptional target of histone deacetylase inhibitors and a regulator of cellular senescence. *J. Biol. Chem.* 2015, 290, 10569–10576.

107. Mottamal, M.; Zheng, S.; Huang, T.L.; Wang, G. Histone deacetylase inhibitors in clinical studies as templates for new anticancer agents. *Molecules* 2015, 20, 3898–3941.

108. Vishwakarma, P.; Kumar, A.; Sharma, M.; Garg, M.; Saxena, K. Histone deacetylase inhibitors: Pharmacotherapeutic implications as epigenetic modifier. *Int. J. Clin. Pharmacol.* 2014, 3, 27–36.

109. Ali-Keilani, M.S.; Alzoubi, K.H.; Jaradat, S.A. The effect of combined treatment with sodium phenylbutyrate and cisplatin, erlotinib, or gefitinib on resistant NSCLC cells. *Clin. Pharmacol.* 2018, 10, 135–140.

110. Almotairy, A.R.Z.; Gandin, V.; Morrison, L.; Marzano, C.; Montagner, D.; Erxleben, A. Antitumor platinum(IV) derivatives of carboxplatin and the histone deacetylase inhibitor 4-phenylbutyric acid. *J. Inorg. Biochem.* 2017, 177, 1–7.

111. Coutzac, C.; Jouniaux, J.M.; Paiz, A.; Schmidt, J.; Mallard, D.; Seck, A.; Asvatourian, V.; Cassard, L.; Saulnier, P.; Lacroix, L.; et al. Systemic short chain fatty acids limit antitumor effect of CTLA-4 blockade in hosts with cancer. *Nat. Commun.* 2020, 11, 2168.

112. He, C.; Liu, Y.; Ye, S.; Yin, S.; Gu, J. Changes of intestinal microflora of breast cancer in premenopausal women. *Eur. J. Clin. Microbiol. Infect. Dis.* 2020, 1–11, doi:10.1007/s10096-020-04036-x.

113. Kuo, Y.J.; Yang, Y.H.; Lee, I.Y.; Chen, P.C.; Yang, J.T.; Wang, T.C.; Lin, M.H.; Yang, W.H.; Cheng, C.Y.; Chen, K.T.; et al. Effect of valproic acid on overall survival in patients with high-grade gliomas undergoing temozolomide: A nationwide population-based cohort study in Taiwan. *Medicine (Baltimore)* 2020, 99, e21147.

114. Ishikawa, T.; Terashima, J.; Shimoyama, Y.; Ohashi, Y.; Mikami, T.; Takeda, Y.; Sasaki, M. Effects of butyric acid, a bacterial metabolite, on the migration of ameloblastoma mediated by laminin 332. *J. Oral Sci.* 2020, 62, 435–438.

115. He, J.; Lu, L.; Peng, J.; Li, C.; Kong, X.; Zhang, J.; Peng, L. Inhibitory effect of ketogenic diet on neuroblastoma in BALB/c-nu mouse models. *Nan Fang Yi Ke Da Xue Xue Bao* 2020, 40, 1155–1164.
116. Liou, G.Y.; Storz, P. Reactive oxygen species in cancer. Free Radic. Res. 2010, 44, 479–496.
117. Ji, C.C.; Hu, Y.Y.; Cheng, G.; Liang, L.; Gao, B.; Ren, Y.P.; Liu, J.T.; Cao, X.L.; Zheng, M.H.; Li, S.Z.; et al. A ketogenic diet attenuates proliferation and stemness of glioma stemlike cells by altering metabolism resulting in increased ROS production. Int. J. Oncol. 2020, 56, 606–617.
118. Cheung, M.K.; Yue, G.G.L.; Tsui, K.Y.; Gomes, A.J.; Kwan, H.S.; Chiu, P.W.Y.; Lau, C.B.S. Discovery of an interplay between the gut microbiota and esophageal squamous cell carcinoma in mice. Am. J. Cancer Res. 2020, 10, 2409–2427.
119. Yang, C.S.; Chen, X.L. Research on esophageal cancer: With personal perspectives from studies in China and Kenya. Int. J. Cancer 2020, 10, doi:10.1002/ijc.33421.
120. Liu, J.; Wang, J.; Leng, Y.; Lv, C. Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: A meta-analysis of observational studies. Int. J. Cancer 2013, 133, 473–485.
121. Park, Y.M.; Steck, S.E.; Fung, T.T.; Merchant, A.T.; Elizabeth Hodgson, M.; Keller, J.A.; Sandler, D.P. Higher diet-dependent acid load is associated with risk of breast cancer: Findings from the sister study. Int. J. Cancer 2019, 144, 1834–1843.
122. Wu, T.; Seaver, P.; Lemus, H.; Hol lenbach, K.; Wang, E.; Pierce, J.P. Associations between Dietary Acid Load and Biomarkers of Inflammation and Hyperglycemia in Breast Cancer Survivors. Nutrients 2019, 11, 1913.
123. Terranova-Barberio, M.; Roca, M.S.; Zotti, A.L; Leone, A.; Bruzzese, F.; Vitagliano, C.; Scogliamiglio, G.; Russo, D.; D’Angelo, G.; Franco, R.; et al. Valproic acid potentiates the anticancer activity of capcitabine in vitro and in vivo in breast cancer models via induction of thymidine phosphorylase expression. Oncotarget 2016, 7, 7715–7731.
124. Jawed, S.; Kim, B.; Ottenhof, T.; Brown, G.M.; Werstücker, E.S.; Niles, L.P. Human melatonin MT1 receptor induction by valproic acid and its effects in combination with melatonin on MCF-7 breast cancer cell proliferation. Eur. J. Pharmacol. 2007, 560, 17–22.
125. Alizadehmohajer, N.; Shojaeifar, S.; Neda einia, R.; Esparvarinha, M.; Mohammadi, F.; Ferns, G.A.; Ghayour-Mobarhan, M.; Manian, M.; Balouchi, A. Association between the microbiota and women’s cancers—Cause or consequences? Biomed. Pharmacother. 2020, 127, 110203.
126. Witt, D.; Burfeind, P.; von Hardenberg, S.; Opitz, L.; Salinas-Riester, G.; Bremmer, F.; Schweworthy, S.; Thelen, P.; Neesen, J.; Kaulfuss, S. Valproic acid inhibits the proliferation of cancer cells by re-expressing cyclin D2. Carcinogenesis 2013, 34, 1115–1124.
127. Gupta, H.; Youn, G.S.; Shin, M.J.; Suk, K.T. Role of Gut Microbiota in Hepatocarcinogenesis. Microorganisms 2019, 7, 121.
128. Kombi, L. Dietary factors can protect against liver cancer development. World J. Hepatol. 2017, 9, 119–125.
129. Sun, G.; Mackey, L.V.; Coy, D.H.; Yu, C.Y.; Sun, L. The Histone Deacetylase Inhibitor Vaproic Acid Induces Cell Growth Arrest in Hepatocellular Carcinoma Cells via Suppressing Notch Signaling. J. Cancer 2015, 6, 996–1004.
130. Sun, L.; Qian, Q.; Sun, G.; Mackey, L.V.; Fuselier, J.A.; Coy, D.H.; Yu, C.Y. Valproic acid induces NET cell growth arrest and enhances tumor suppression of the receptor-targeted peptid drug conjugate via activating somatostatin receptor type II. J. Drug Target. 2016, 24, 169–177.
131. Klement, R.J.; Pazienza, V. Impact of Different Types of Diet on Gut Microbiota Profiles and Cancer Prevention and Treatment. Medicina (Kaunas) 2019, 55, 84.
132. Iwahashi, S.; Utsunomiya, T.; Imura, S.; Morine, Y.; Ikemoto, T.; Arakawa, Y.; Saito, Y.; Ishikawa, D.; Shimada, M. Effects of valproic acid in combination with S-1 on advanced pancreatobiliary tract cancers: Clinical study phases I/II. Anticancer Res. 2014, 34, 5187–5191.
133. Kobyakawaw, M.; Kojima, Y. Tegafur/gimeracil/oteracil (S-1) approved for the treatment of advanced gastric cancer in adults when given in combination with cisplatin: A review comparing it with other fluoropyrimidine-based therapies. Onco Targets Ther. 2011, 4, 193–201.
134. De Weille, J. On the Genesis of Neuroblastoma and Glioma. Int. J. Brain Sci. 2014, 2014, doi:10.1155/2014/217503.
135. Jovecevška, I. Genetic secrets of long-term glioblastoma survivors. Bosn. J. Basic Med. Sci. 2019, 19, 116–124.
136. Medawar, E.; Huhn, S.; Villringer, A.; Witte, A.V. The effects of plant-based diets on the body and the brain: A systematic review. Transl. Psychiatry 2019, 9, 226.
137. Gomez-Pinilla, F.; Gomez, A.G. The influence of dietary factors in central nervous system plasticity and injury recovery. PMR 2011, 3, S111–S116.
138. Newberry, C.; Lynch, K. The role of diet in the development and management of gastroesophageal reflux disease: Why we feel the burn. J. Thorac. Dis. 2019, 11, S1594–S1601.
139. Dawsey, S.M.; Fagundes, R.B.; Jacobson, B.C.; Kresty, L.A.; Mallery, S.R.; Paski, S.; van den Brandt, P.A. Diet and esophageal disease. Ann. N. Y. Acad. Sci. 2014, 1325, 127–137.
140. Rosekrons, S.L.; Baan, B.; Muncar, V.; van den Brink, G.R. Esophageal development and epithelial homeostasis. Am. J. Physiol. Liver Physiol. 2015, 309, G216–G228.
141. Shirapia, N. The potential contribution of dietary factors to breast cancer prevention. Eur. J. Cancer Prev. 2017, 26, 385–395.
142. Hori, S.; Butler, E.; Mc Hughlin, J. Prostate cancer and diet: Food for thought? BJU Int. 2011, 107, 1348–1359.
143. Bilodeau, J.F.; Gevariya, N.; Larose, J.; Robitaille, K.; Roy, J.; Oger, C.; Galano, J.M.; Bergeron, A.; Durand, T.; Fradet, Y.; et al. Long chain omega-3 fatty acids and their oxidized metabolites are associated with reduced prostate tumor growth. Prostaglandins Leukot. Essent. Fat. Acids 2020, 164, 102215.
144. Matsushita, M.; Fujita, K.; Nonomura, N. Influence of Diet and Nutrition on Prostate Cancer. Int. J. Mol. Sci. 2020, 21, 1447.
145. Smith, R.J. Nutrition and metabolism in hepatocellular carcinoma. Hepatobiliary Surg. Nutr. 2013, 2, 89–96.
146. Casari, I.; Falasca, M. Diet and Pancreatic Cancer Prevention. Cancers (Basel) 2015, 7, 2309–2317.
147. Kich, D.M.; Vincenzi, A.; Majolo, F.; Volken de Souza, C.F.; Goetterm, M.I. Probiotic: Effectiveness nutrition in cancer treatment and prevention. *Nutr. Hosp.* 2016, 33, 1430–1437.
148. Vernia, F.; Longo, S.; Stefanelli, G.; Viscido, A.; Latella, G. Dietary Factors Modulating ColoRectal Carcinogenesis. *Nutrients* 2021, 13, 143.
149. Valdes, A.M.; Walter, J.; Segal, E.; Spector, T.D. Role of the gut microbiota in nutrition and health. *BMJ* 2018, 361, k2179.
150. Bradbury, K.E.; Balkwill, A.; Spencer, E.A.; Roddam, A.W.; Reeves, G.K.; Green, J.; Key, T.J.; Beral, V.; Pirie, K.; Banks, E. Organic food consumption and the incidence of cancer in a large prospective study of women in the United Kingdom. *Br. J. Cancer* 2014, 110, 2321–2326.
151. Baudry, J.; Assmann, K.E.; Touvier, M.; Alles, B.; Seconda, L.; Latino-Martel, P.; Ezzedine, K.; Galan, P.; Hercberg, S.; Lairon, D.; et al. Association of Frequency of Organic Food Consumption With Cancer Risk: Findings From the NutriNet-Sante Prospective Cohort Study. *JAMA Intern. Med.* 2018, 178, 1597–1606.
152. Lunet, N.; Valbuena, C.; Vieira, A.L.; Lopes, C.; Lopes, C.; David, L.; Carneiro, F.; Barros, H. Fruit and vegetable consumption and gastric cancer by location and histological type: Case-control and meta-analysis. *Eur. J. Cancer Prev.* 2007, 16, 312–327.
153. Vieira, A.R.; Abar, L.; Vogeliene, S.; Chan, D.S.; Aune, D.; Navarro-Rosenblatt, D.; Stevens, C.; Greenwood, D.; Norat, T. Fruits, vegetables and lung cancer risk: A systematic review and meta-analysis. *Ann. Oncol.* 2016, 27, 81–96.
154. Wang, M.; Qin, S.; Zhang, T.; Song, X.; Zhang, S. The effect of fruit and vegetable intake on the development of lung cancer: A meta-analysis of 32 publications and 20,414 cases. *Eur. J. Clin. Nutr.* 2015, 69, 1184–1192.
155. Maasland, D.H.; van den Brandt, P.A.; Kremer, B.; Goldbohm, R.A.; Schouten, L.J. Consumption of vegetables and fruits and risk of subtypes of head-neck cancer in the Netherlands Cohort Study. *Int. J. Cancer* 2015, 136, E396–E409.
156. Larsson, S.C.; Bergkvist, L.; Wolk, A. Fruit and vegetable consumption and incidence of gastric cancer: A prospective study. *Cancer Epidemiol. Biomark. Prev.* 2006, 15, 1998–2001.
157. Slavin, J.L.; Lloyd, B. Health benefits of fruits and vegetables. *Adv. Nutr.* 2012, 3, 506–516.
158. Baudry, J.; Debrauwer, L.; Durand, G.; Limon, G.; Delcambre, A.; Vidal, R.; Taupier-Letage, B.; Druësne-Pecollo, N.; Galan, P.; Hercberg, S.; et al. Urinary pesticide concentrations in French adults with low and high organic food consumption: Results from the general population-based NutriNet-Sante. *J. Expo. Sci. Environ. Epidemiol.* 2019, 29, 366–378.
159. Rebuillass, P.; Vidal, R.; Cravedi, J.P.; Taupier-Letage, B.; Debrauwer, L.; Gamet-Payrastre, L.; Touvier, M.; Hercberg, S.; Lairon, D.; Baudry, J.; et al. Estimated dietary pesticide exposure from plant-based foods using NMF-derived profiles in a large sample of French adults. *Eur. J. Nutr.* 2020, 1–14, doi:10.1007/s00394-020-02344-8.
160. Alavanja, M.C.; Bonner, M.R. Occupational exposures and cancer risk: A review. *J. Toxicol. Environ. Health B Crit. Rev.* 2012, 15, 228–263.
161. Mesnage, R.; ItSakiris, I.N.; Antoniou, M.N.; Tsatsakis, A. Limitations in the evidential basis supporting health benefits from a decreased exposure to pesticides through organic food consumption. *Curr. Opin. Toxicol.* 2020, 29, 50–55.
162. World Health Organization & Food and Agriculture Organization of the United Nations. *Global Situation of Pesticide Management in Agriculture and Public Health; World Health Organization,* 2019. Available online: https://apps.who.int/iris/handle/10665/329971. License: CC BY-NC-SA 3.0 IGO (11 February 2021).
163. Fenton, T.R.; Huang, T. Systematic review of the association between dietary acid load, alkaline water and cancer. *BMJ Open* 2016, 6, e010438.
164. Allen, J.; Montalto, M.; Lovejoy, J.; Weber, W. Detoxification in naturopathic medicine: A survey. *J. Altern. Complement. Med.* 2011, 17, 1175–1180.
165. Cohen, M. ‘Detox’: Science or sales pitch? *Aust. Fam. Physician* 2007, 36, 1009–1010.
166. Mishori, R.; Otubu, A.; Jones, A.A. The dangers of colon cleansing. *J. Fam. Pract.* 2011, 60, 454–457.
167. Ernst, E.Ear candles: A triumph of ignorance over science. *J. Laryngol. Otol.* 2004, 118, 1–2.
168. Bryant, S.M.; Kolodchak, J. Serotonin syndrome resulting from an herbal detox cocktail. *Am. J. Emerg Med.* 2004, 22, 625–626.
169. Fitzpatrick, M. The meaning of detox. *Lancer* 2003, 361, 94.
170. Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. How Cells Obtain Energy from Food. In *Molecular Biology of the Cell*, 4th ed.; Garland Science: New York, NY, USA, 2002.
171. Varghese, S.; Samuel, S.M.; Varghese, E.; Kubatka, P.; Busselberg, D. High Glucose Represses the Anti-Proliferative and Pro-Apoptotic Effect of Metformin in Triple Negative Breast Cancer Cells. *Biomolecules* 2019, 9, 16.
172. Ito, M.; Makino, N.; Matsuda, A.; Ikeda, Y.; Kakizaki, Y.; Saito, Y.; Ueno, Y.; Kawata, S. High Glucose Accelerates Cell Proliferation and Increases the Secretion and mRNA Expression of Osteopontin in Human Pancreatic Duct Epithelial Cells. *Int. J. Mol. Sci.* 2017, 18, 807.
173. Fadaka, A.; Aijobye, B.; Ojo, O.; Adewale, O.; Olayide, I.; Emuwohchere, R. Biology of glucose metabolism in cancer cells. *J. Oncol. Sci.* 2017, 3, 45–51.
174. Nagy, T.; Fisi, V.; Frank, D.; Katai, E.; Nagy, Z.; Miseta, A. Hyperglycemia-Induced Aberrant Cell Proliferation; A Metabolic Challenge Mediated by Protein O-GlcNAc Modification. *Cells* 2019, 8, 999.
175. Zhu, J.; Liao, M.; Yao, Z.; Liang, W.; Li, Q.; Liu, J.; Yang, H.; Ji, Y.; Wei, W.; Tan, A.; et al. Breast cancer in postmenopausal women is associated with an altered gut metagenome. *Microbiome* 2018, 6, 136.
176. Laborda-Illanes, A.; Sanchez-Alcoholado, L.; Dominguez-Reicio, M.E.; Jimenez-Rodriguez, B.; Lavado, R.; Comino-Mendez, I.; Alba, E.; Queipo-Ortuno, M.I. Breast and Gut Microbiota Action Mechanisms in Breast Cancer Pathogenesis and Treatment. *Cancers (Basel)* 2020, 12, 2456.
177. Weber, D.D.; Aminzadeh-Gohari, S.; Tulipan, J.; Catalano, L.; Feichtinger, R.G.; Kofler, B. Ketogenic diet in the treatment of cancer—Where do we stand? *Mol. Metab.* 2020, 33, 102–121.

178. Cabrera-Mulero, A.; Tinahones, A.; Bandera, B.; Moreno-Indias, I.; Macias-Gonzalez, M.; Tinahones, F.J. Keto microbiota: A powerful contributor to host disease recovery. *Rev. Endocr. Metab. Disord.* 2019, 20, 415–425.

179. Miro-Blanch, J.; Yanes, O. Epigenetic Regulation at the Interplay Between Gut Microbiota and Host Metabolism. *Front. Genet.* 2019, 10, 638.

180. Tang, Q.; Jin, G.; Wang, G.; Liu, T.; Liu, X.; Wang, B.; Cao, H. Current Sampling Methods for Gut Microbiota: A Call for More Precise Devices. *Front. Cell Infect. Microbiol.* 2020, 10, 151.

181. Fraher, M.H.; O’Toole, P.W.; Quigley, E.M. Techniques used to characterize the gut microbiota: A guide for the clinician. *Nat. Rev. Gastroenterol. Hepatol.* 2012, 9, 312–322.

182. Amoutzopoulos, B.; Steer, T.; Roberts, C.; Cade, J.E.; Boushey, C.J.; Collins, C.E.; Trolle, E.; de Boer, E.J.; Ziauddeen, N.; van Rossum, C.; et al. Traditional methods v. new technologies-dilemmas for dietary assessment in large-scale nutrition surveys and studies: A report following an international panel discussion at the 9th International Conference on Diet and Activity Methods (ICDAM9), Brisbane, 3 September 2015. *J. Nutr. Sci.* 2018, 7, e11.

183. Eldridge, A.L.; Piernas, C.; Illner, A.K.; Gibney, M.J.; Gurinovic, M.A.; de Vries, J.H.M.; Cade, J.E. Evaluation of New Technology-Based Tools for Dietary Intake Assessment-An ILSI Europe Dietary Intake and Exposure Task Force Evaluation. *Nutrients* 2018, 11, 55.