Nutrition, Immunity, and Cancers

24

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Contents

24.1 **Introduction** 534

24.2 **Role of Nutrition in Predisposition of Cancer from an Immunologic View** 534

24.2.1 Protein–Calorie Balance 535

24.2.2 Essential Fatty Acids 535

24.2.3 Antioxidants (Selenium, Vitamin E, and Vitamin C) 535

24.2.3.1 Vitamin A 535

24.2.4 Vitamin D 536

24.2.5 Vitamin B6 536

24.2.6 Folate 536

24.2.7 Calcium 536

24.2.8 Nutrition Overdose in Cancer 536

24.3 **Aging as a Confounder of the Triangle of Nutrition, Immunity, and Cancer** 536

24.4 **Microbiota as a Confounder of the Triangle of Nutrition, Immunity, and Cancer** 537

24.5 **Role of Cancer in Predisposition to Malnutrition from an Immunologic View** 538

24.6 **Role of Nutritional Support in Immune Restoration of Cancer Patients** 539

24.6.1 Arginine 539

24.6.2 Glutamine 539

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24.6.3 Branched Chain Amino Acids..... 539
24.6.4 Nucleotides, Long-Chain..... 540
24.6.5 Fructooligosaccharides..... 540
24.6.6 Bioactive Compounds..... 540
24.6.7 Antioxidants (Vitamin E and Vitamin C)..... 540
24.6.8 Vitamin A..... 540
24.7 **Concluding Remarks**..... 540
References..... 540

24.1 Introduction

Changes in immunologic pathways play a leading role in all stages of cancer. Proper immune function also associates with quantitative and qualitative aspects of nutrition [1, 2]. Therefore, overnutrition and imbalanced nutrition may affect development, progression, and therapeutic response of cancer [2]. Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interferon-γ (IFN-γ), and interleukins 1 and 6 (IL-1 and IL-6) are important mediators of cancer complications such as cachexia [3]. A tumor can trigger the release of cytokines such as IL-6 [4], which is associated with an increase in lipolysis and proteolysis, which in turn affect the appetite and host neuroendocrine axis and induce anorexia and cachexia [4, 5]. Several neuropeptides such as neuropeptide Y (NPY) and adipokines such as leptin have been implicated in the pathogenesis of cancer cachexia syndrome [5, 6]. Thus, an imbalance of cytokine production, and neuropeptide and adipokine dysfunction as well as changes in microbiota (particularly in GI in the consequence of cancer and tumor suppressive agents) may be a major cause of the nutritional consequences of cancer.

24.2 Role of Nutrition in Predisposition of Cancer from an Immunologic View

One of the known risk factors for cancer is obesity, especially with the modern lifestyle and low physical activity [3]. Dietary patterns have a significant effect on the cytokine profile; for instance, the high intake of saturated fats, especially in obese people, leads to infiltration of adipose tissue by macrophages producing IL-1β, IL-6, and macrophage inhibitory factor (MIF) [4–6]. Moreover, a decrease in the secretion of anti-inflammatory adipokines such as adiponectin may maintain pro-inflammatory signals and activate the production of C-reactive protein (CRP) by the liver [7, 8]. Based on previous studies, this chronic inflammatory process is related to an increased susceptibility to various types of cancer, including cancers of the gastrointestinal, respiratory, and genitourinary systems [9–11]. It has been evident that the inflammation is promoted by saturated fatty acids and their binding to the Toll-like receptors (TLR 2 and 4) activating pro-inflammatory factors such as nuclear factor-kappa B (NF-κB) [12]. Moreover, downregulation of autophagy and decreased cytoplasmic recycling of damaged organelles accelerate activation of inflammasome and complement components [13, 14]. Chronic inflammation dysregulates immune function from immunosurveillance to carcinogenic inflammasome by stimulating cellular turnover, increasing stem cell divisions, enhancing production of reactive oxygen species and metabolic rate locally [15]. Unresolved inflammation due to overnutrition provides a local immunosuppressive microenvironment by production of transforming growth factor beta (TGF-β) and myeloid-derived suppressor cells within the tumor lesion [16, 17]. Obesity also affects the microbiota leading to an intestinal dysbiosis and diminishes the bacterial and endotoxin barriers, which increases the risk of procarcinogenic metabolites presentation [18, 19]. Decreased autophagy also enhances aging process affecting immune profile by decreasing

cytotoxic T-cells, thymic atrophy, and dendritic cells' dysfunction [19–21].

Vice versa, intermittent fasting and adjusted low-carbohydrate/hypocaloric diet has beneficial effects on antagonizing the chronic inflammation process mediated by increased ketone-bodies, decreased risk factors of metabolic syndrome [1, 22–25]. Surprisingly this method can be used for boosting chemotherapy since it can increase the remodeling of the immune-cell infiltrate by an increased infiltrating cytotoxic T-cells and local depletion of regulatory T-cells [26, 27]. Treatment with one or several fasting cycles diminishes tumor growth, prevents cellular transformation, and upregulates autophagy [28–30].

Influenced by this important effect of nutrition on the immune system, characteristics of the human diet can directly stimulate gastrointestinal malignancies [31]. A diet low in fiber and vegetables may affect the regulation of carbohydrate absorption and short chain fatty acid formation, which affects the metabolism of carcinogens [32]. This process is linked to colon cancer and its progression [33]; apparently, a decrease in fiber intake may allow more time for exposure of colon cells and the immune system to the potential carcinogens, affecting intestinal transit [34]. However, recently the anti-inflammatory effects of fiber and multiple distinct phytochemicals (e.g., enterolactone, flaxseed, lignin, and spermidine) on microbiome have been reported including increased proportion of *Lactobacilli* and *Bifidobacteria* [35, 36]. Moreover, based on the evidence used to draw conclusions about a gluten free diet in patients with celiac disease leading to cancer protection, it seems reasonable to consider gluten as a booster for cancer in celiac patients [37, 38]. Meat consumption is a risk factor for some cancers, especially colon, rectum, and prostate. Red meat consumption increases the risk of colon cancer by causing increased production of heterocyclic amines [39, 40]. On the other hand, a change in the normal diet and deficiency of vitamins or minerals may affect the adequacy of either innate immunity (phagocytic activity, chemotaxis of neutrophils, or release of cytokines from monocytes) or adaptive immunity (immunoglobulin production of B-cells or cell-mediated immunity) [41–44]. Many of the consequences of malnutrition in the regulation of signal transduction and immunoregulatory gene expression were first recognized in the early 1800s as nutrigenomics [44, 45]. The majority of these changes are reversible after administration of adequate nutrition supplements [46]. The following list of specific dietary factors has been studied in relation to the immune aspects of cancer.

24.2.1 Protein–Calorie Balance

The formation of lymphocytes, eosinophils, and vital immune system proteins such as thymic hormones, antibody (Ab) responses to T-cell dependent antigens (Ags), and Ab affinity are affected by protein–calorie imbalance [47]. It has long been recognized that caloric restriction with a well-balanced diet avoiding certain nutrient deficiencies can increase longevity and has cancer preventive effects in mammals [48].

24.2.2 Essential Fatty Acids

Essential fatty acids, mainly suggested by consumption of nuts, in our body can regulate the production of prostaglandins, prostacyclins, thromboxanes, and leukotrienes, causing a significant effect on the host immune system and regulation of inflammation and C-reactive proteins [49].

24.2.3 Antioxidants (Selenium, Vitamin E, and Vitamin C)

These nutrients have strong antioxidative effects and may reduce the risk of cancer by neutralizing reactive oxygen species or free radicals that can damage DNA [50, 51].

24.2.3.1 Vitamin A

Vitamin A plays an important role in protection against measles, white blood cell (WBC) function, resistance to carcinogens, and skin and mucous membrane defenses. Vitamin A precursor carotenoids, such as lycopene, have a potential effect on cancer prevention [52, 53].

24.2.4 Vitamin D

25-hydroxyvitamin D has been of interest based on ecologic studies on populations with greater exposure to ultraviolet light who had a lower risk of breast cancer, colon cancer, and prostate cancer. This vitamin regulates humoral Ab response, enhances organ specific cytotoxic T-cells, and supports a Th2-mediated anti-inflammatory profile of cytokines; therefore, its anticancer properties are strongly suggested [54–56].

24.2.5 Vitamin B6

Pyridoxine and its metabolite PLP (pyridoxal-5′ phosphate) induce immunosurveillance activation and Th1 cytokine-mediated immune responses. Epidemiologic studies and laboratory animal models have shown that vitamin B6 modulates the risk of cancer. It is not clear how vitamin B6 mediates this effect, but it has been reported that high dietary vitamin B6 attenuates and low dietary vitamin B6 increases the risk of cancer [55, 57–59].

24.2.6 Folate

Folate is important for DNA methylation, repair, and synthesis, which is also crucial for lymphocyte development [60, 61]. Epidemiologic studies have shown that low folic acid intake is associated with a higher risk of various cancers, most notably colon, breast, and probably cervical cancer. The fact that methylenetetrahydrofolate reductase, an enzyme predicted to reduce the risk of colon cancer, is associated with folate status supports the role of folate deficiency in cancers [62, 63].

24.2.7 Calcium

Many studies show that calcium may reduce the risk of colorectal cancer via direct and indirect effects. Calcium has a direct effect on proliferation, stimulating differentiation, and apoptosis in the colonic mucosa [64, 65]. Its indirect effect is binding to toxic secondary bile acids and ionized fatty acids to form insoluble soaps in the lumen of the colon [66].

24.2.8 Nutrition Overdose in Cancer

In addition to deficiency, an overdose of some micronutrients can also have an immunosuppressive effect, especially megadoses of vitamin E [67]. High doses of certain minerals such as chromium, copper, iron, manganese, and zinc also may induce cancer and immune dysfunction [68].

In summary, attenuated innate and adaptive immunity as a result of an inadequate diet leads to a higher risk of cancer and lower homeostasis for cancerous antigens, which could be resulted from reducing nutrient intake, increasing losses, and interfering with utilization due to altering metabolic pathways. Thus, nutrition may have a significant role in immune prevention and immune surveillance of cancer.

24.3 Aging as a Confounder of the Triangle of Nutrition, Immunity, and Cancer

Aging may be a confounder of the triangle of nutrition, immunity, and cancer (Fig. 24.1); however, neither the relationships nor the mechanisms of interaction are known. Unfortunately, only a few studies have considered that nutrition and immune function simultaneously decrease in elderly individuals [69]. It is known that increased age adversely affects the function of the immune system as well as nutrient intake habits [70]. Therefore, both immunosuppression (mainly due to decreased effectiveness of T and natural killer cells) and nutritional deficiencies (as defined by the 1989 recommended dietary allowances) in the elderly may have independent correlations with an increased risk of infection and neoplasia development [42].

One of the probable mechanisms that may affect both immunity and nutrition in old people is turn-

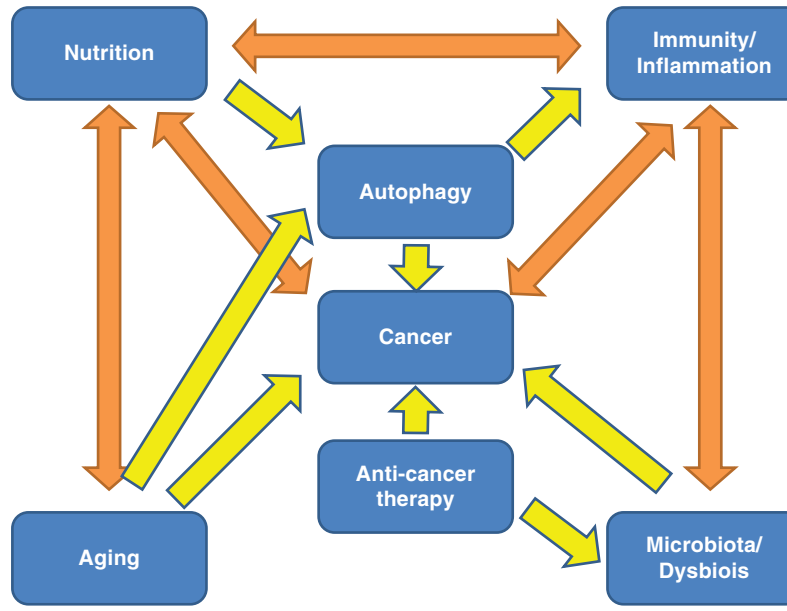

Fig. 24.1 Schematic overview of complex network of diet-immunity-cancer

over fluctuations of cellular components in lysosomes or autophagy. Advanced age leads to a reduction in the autophagy of loading viral Ags and cross presentation of tumor Ags into MHC class I molecules, as well as pathogen killing [71–73]. Similarly, the capability of autophagy for energetic balance recycling of amino acids to maintain protein synthesis under starvation conditions and the capacity of intracellular lipid stores or glycogen mobilization are disturbed [74, 75]. However, only minimal information has been produced concerning human cancer initiation as a direct result of a specific dietary etiology in the elderly.

24.4 Microbiota as a Confounder of the Triangle of Nutrition, Immunity, and Cancer

Studies examining the composition of alimentary elements on the intestinal microbiome and the role of dysbiosis in different diseases states have uncovered associations with inflammation and tumorigenesis [76, 77]. Moreover, the impact of immunosuppressive and anticancer agents on the microbiota profile has been recorded [78–81]. High protein diet can increase the microbial diversity and proportion of *Bifidobacteria*, *Lactobacilli,* and *Eubacterium Rectale* but can decrease *Bacteroides* species. Similarly most of natural sugar can enhance incidence of *Bifidobacteria* rather than *Bacteroides*. Moreover high fat diet inhibits propagation of the lactic acid bacteria but provide an environment in favor of *Clostridiales* and *Bacteroides.* Probiotics also can change the microbiota by overpresentation of *Bifidobacteria, Lactobacilli*, *aerobes/anaerobes,* and lower presentation *coliforms, Helicobacter pylori, Escherichia coli* [82, 83].

Immunosurveillance profile (low short chain fatty acids, low lipopolysaccharide levels, low IL-6, and high IL-10) is associated with specific microbiome molecular patterns which usually can be linked with Mediterranean diet with dominancy of *Bifidobacteria, Lactobacilli, Eubacteria, Bacteroides,* and *Prevotella.* Studies that involve intake of a specific dietary component demonstrate how certain bacteria tend to respond to the nutrient-specific challenge. Protein, fats, digestible and non-digestible carbohydrates, and probiotics all induce shifts in the microbiome with secondary effects on host immunologic and metabolic markers suggesting maintaining healthy gut microbiome is critical to human health [84, 85].

24.5 Role of Cancer in Predisposition to Malnutrition from an Immunologic View

Despite the role of nutrition in either preventing or causing cancer in humans, malnutrition is a common problem (global percentage of 56.5%), and weight loss is often predictive of shortened survival in these patients [86]. In advanced stages of cancer, up to 35% of related deaths may be linked to improper diet [87, 88]. Moreover, a proportion of patients with malignancy develop cachexia, a progressive involuntary weight loss status that is attributed to clinic-pathologic factors of the tumor (origin, metastasis, and size), host immunity, and antitumor treatment (Fig. 24.2) [89]. During the development of cancer-associated cachexia, several Th2-dominant condition mediators such as IL-2 and TNF (prognostic markers) are implicated in appetite loss and metabolic disturbances, as well as leptin, IL-1, IL-6, IFN-γ, leukemia inhibitory factor, NPY, and proteoglycan 24 K [90, 91]. These immunologic and metabolic changes induce cancer cachexia syndrome, which is characterized by patient tissue wasting, anorexia, appetite loss, prolonged fatigue and lethargy, insulin resistance, microcytic anemia, hyperlipidemia, and hypoalbuminemia [92, 93]. Metabolic features of this syndrome include increases in the heterogeneity of energy requirement, substrate cycling and turnover, Cori cycle activity, and hepatic protein synthesis, as well as decreases in peripheral muscle protein synthesis, serum protein lipase activity, and plasma concentration of branched chain amino acids. In general, the severity of malnutrition and cachexia in digestive neoplasias is in highest percentages (from 79% in esophageal cancer to 40% in rectum cancers) due to the involvement of all predisposing factors described in Fig. 24.2 during the development of cancer and in chemotherapy or tumor resection. It should be noted that antitumor agents with their side effect on cells with high turnover may exacerbate malnutrition [94]. This could be explained by the competition between cancerous regions and normal cells of the gastrointestinal system to use nutrients to repair the adverse effects of antitumor drugs (hypermetabolic state) [95]. Briefly, impaired caloric intake, side effects of therapy, changes in taste and mood, pain and other adverse consequences of eating, obstruction, fistula, and malabsorption all promote malnutrition in cancer patients; therefore, well-nourished cancer patients with intact gastrointestinal integrity have lower morbidity and mortality than others [96]. It should be noted that cachexia after cancer differs from cachexia following starvation. Increased protein and glucose turnover, high whole body synthesis and catabolism, accelerated hepatic protein production (especially acute phase

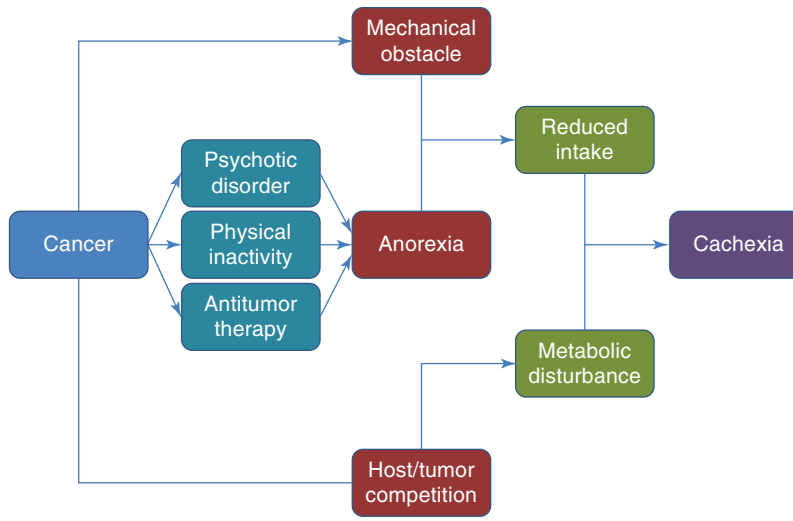

Fig. 24.2 The casual pathways of cachexia occurrence after malignancy

agents), increased serum free fatty acid levels, and depletion of fat stores were reported only in cancer patients. However, metabolic abnormalities and, paradoxically, impaired immune response are probable consequences of cancer cachexia, as explained in the previous section. Increased levels of immunosuppressive mediators (e.g., TGF-β), decreased C3 and delayed hypersensitivity response, and diminished numbers and activity of NK cells are the most common changes in the immune system of patients with cancer cachexia, leading to more infectious complications and poor prognosis [96]. Neutrophil chemotaxis, monocyte phagocytosis and cytotoxicity, number of T-cells, and proliferation of lymphocytes are also defective in patients with lung cancer. Phagocytic and bactericidal activities of neutrophils were low in hepatocellular carcinoma patients. In addition, surgical stress in cancer patients enhances Th2 and compromises the Th1/Th2 balance and expression of HLA-DR on monocytes, which is considered to be a central marker of immune paralysis after surgical trauma [97, 98]. Most of these immune parameters are also reduced during radiotherapy and chemotherapy because of their side effects on bone marrow. However, these factors are reversible after nutrition improvement [99].

24.6 Role of Nutritional Support in Immune Restoration of Cancer Patients

Adjuvant therapy of cancer patients by different nutritional support strategies (dietary counseling, oral nutritional supplements, enteral tube feeding, and parenteral tube feeding) is the mainstream recommendation to increase their quality of life and to obviate the risks associated with gastrointestinal complications and reverse malnutrition. However, there is no comprehensive approach based on the needs of cancer patients with cachexia or those with increased nutrient requirements. Several studies have shown the effectiveness of nutritional supply in groups of patients with malignancy that resulted in weight gain, increased appetite, increased energy and protein intake, reduced gastrointestinal toxicity, and enhanced immune function [100]. In the clinical setting with standard treatment protocols, it turns out that the implementation of nutrition support in patients with cancer is most effective when it is limited to special, well-described circumstances. Nonetheless, the potential advantages of some specific nutrients have been described and are outlined below [101].

24.6.1 Arginine

Arginine is a semi-essential amino acid with immunomodulatory potentials such as stimulated thymic growth and mononuclear cell response to mitogens, which enhances lymphokine-activated killer cell generation via a nitric oxide-mediated mechanism and stimulates the release of polyamines by the small intestine. In one randomized trial of malnourished patients with head and neck cancer, follow-up at 10 years indicated better survival in those who received supplemental arginine preoperatively [102].

24.6.2 Glutamine

Glutamine is the most abundant amino acid in the human body and the preferential fuel of rapidly dividing cells such as lymphocytes and macrophages [103]. However, supplementing glutamine in the diets of patients with cancer may be counterproductive because glutamine (which is essential for fast growing cells in culture) may promote accelerated tumor growth. A meta-analysis of studies that used parenteral glutamine postoperatively showed it was associated with a shorter hospital stay and a lower incidence of infectious complications [104].

24.6.3 Branched Chain Amino Acids

L-valine, L-leucine, and L-isoleucine can improve the immune response and maintain serum albumin level in the course of hepatocellular carcinoma recurrence [105].

24.6.4 Nucleotides, Long-Chain

Omega-3 polyunsaturated fatty acids and eicosapentaenoic acid. These lipid agents have anti-inflammatory, anticachectic, immunomodulating, and antitumor effects [106–108].

24.6.5 Fructooligosaccharides

This group of functional fibers associated with increased lactic acid bacteria acts as an immunomodulator by stimulating IgA synthesis, promoting mucin production, modulating inflammatory cytokines, and decreasing Ag absorption [90].

24.6.6 Bioactive Compounds

Agaricaceae fungus consisting of ergosterol, oleic acid, and triterpenes may inhibit neovascularization induced by tumors and therefore attenuate cancer progression [109].

24.6.7 Antioxidants (Vitamin E and Vitamin C)

Since chemotherapy may induce mucositis and bleomycin in particular induces chromosomal damage in lymphocytes, the administration of vitamins C and E may reduce the side effects of therapy [110].

24.6.8 Vitamin A

This fat-soluble vitamin can increase the numbers of NK cells or regulatory lymphocytes in cancer patients [89]. A recent study showed that all-trans retinoic acid can potentiate the chemotherapeutic effect of cisplatin by inducing differentiation of tumor initiating cells in liver cancer [111].

24.7 Concluding Remarks

In summary, due to the safety and cost-effectiveness of oral dietary therapies, nutrition counseling and the implementation of nutritional supplements should be the initial approaches to nutritional support [112]. Even though parenteral nutrition may also lead to weight gain and improvement in nitrogen balance in patients with cancer, it does not clearly improve serum albumin levels or alter whole body protein turnover even with prolonged administration. Therefore, when nutrition support is chosen as a therapy, the use of enteral nutrition is preferred if the gastrointestinal tract is functional [113, 114]. The use of parenteral nutrition should be limited to malnourished cancer patients who are receiving active anticancer treatment, whose gastrointestinal tract is not functional or who cannot tolerate enteral nutrition, and who are anticipated to be unable to meet their nutrient requirements for 14 days or more [113]. Moreover, it is proposed that preoperative and postoperative immune-nutrition intervention by total parenteral nutrition using a lipid-based regimen is the method of choice in cancer patients who have undergone major surgery to reduce immune dysfunction without enhancing tumor growth (increased augmentation of lymphocyte blastogenesis and production of helper T-lymphocyte lymphokine IL-2, increased ICAM-1 level, and decreased IL-4 and IL-10 values) [114, 115]. This observed preference of parenteral nutrition is marginal, and enteral methods are always the preferable route for cancer patients with an intact digestive system. It is also reported that complement components and lymphocyte response may be better with enteral rather than parenteral nutrition [115, 116].

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