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Cancer Immunity and Role of Micronutrients

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Abstract

Cancer and immunity are intricately linked, as the immune system plays a pivotal role in identifying and eliminating cancerous cells. However, cancer cells can evade the immune system through various mechanisms, such as expressing proteins that suppress immune responses or creating an immunosuppressive microenvironment. Micronutrients, including vitamins and trace minerals, play a crucial role in modulating the immune system's response to cancer. These essential nutrients support various cellular functions and biochemical pathways that are pivotal for maintaining immune surveillance and combating tumor growth. Vitamins such as A, C, D, and E, and minerals like zinc, selenium, and iron, have been shown to influence the activity of immune cells, including T-cells, B-cells, and increase the capacity of natural killer cells to identify and eliminate cancer cells. Additionally, micronutrients contribute to the regulation of oxidative stress and inflammation, both of which are critical in the tumor microenvironment. Micronutrients, also play complex roles in cancer processes such as tumorigenesis, angiogenesis, metastasis, and chemoresistance. However, the complexity of their interactions and the need for precise dosing highlight the necessity for further research to fully elucidate their role and optimize their use in cancer immunity.

Keywords: Cancer Immunity; Micronutrients; Chemoresistance

Abbreviations

IN: Immunonutrition; FA: Fatty Acids; QOL: Quality of Life; TME: Tumor Microenvironment; PLR: Platelet-to-Lymphocyte Ratio; DC: Dendritic Cells; OS: Overall Survival; BC: Breast Cancer; NKC: Natural Killer Cell; CT: Chemotherapy; GI: Gastro Intestinal; ROS: Reactive Oxygen Species; OM: Oral Mucositis; CRC: Colorectal Cancer; NOS_2: Nitric Oxide Synthase; SCFAs: Short Chain Fatty Acids; HSCT: Hematopoietic Stem Cell Transplantation; GVHD: Graft Versus Host Disease; RIOM: Radiation Induced Oral Mucositis; CARET: Carotene and Retinol Efficacy Trial; ATBC: Alpha Tocopherol Beta Carotene; AREDS2: Age Related Eye Disease Study 2; HCC: Hepatocellular Carcinoma; IAPEN: Indian Association for Parenteral and Enteral Nutrition; RT: Radiotherapy; N3-FA ; Omega 3 Fatty Acids; ATBC ; Alpha-Tocopherol, Beta-Carotene.

Introduction

Cancer, a multifaceted disease characterized by uncontrolled cell growth and metastasis, profoundly impacts the body's immune system, often leading to immunosuppression and increased susceptibility to infections [1]. Immunonutrition (IN), the strategic use of nutrients to modulate the immune response, has emerged as a pivotal component in the

comprehensive care of cancer patients. Traditional cancer treatments such as chemotherapy, radiation, and surgery, while effective in targeting malignancies, can further compromise immune function and nutritional status [2-4]. IN offers a therapeutic avenue that not only supports the immune system but also enhances overall patient outcomes. Key nutrients, including omega-3 fatty acids (n3-FA), arginine, glutamine, nucleotides, antioxidants, and pre-probiotics play crucial roles in modulating immune responses, reducing inflammation, and promoting tissue repair and gut integrity [5,6]. Antioxidants such as vitamins A, C, and E, along with trace elements like zinc and selenium, help mitigate oxidative stress and bolster immune defenses [7]. Clinical studies have shown that tailored IN can lead to improved tolerance to cancer treatments, reduced infection rates, and enhanced recovery post-surgery [8]. Furthermore, by addressing the metabolic demands of cancer patients and counteracting the adverse effects of cachexia and malnutrition, IN contributes to better quality of life (QOL) and potentially improved survival rates. Thus, integrating IN into cancer care protocols represents a holistic approach that not only targets the malignancy but also fortifies the patient's immune system, paving the way for more resilient and effective cancer treatment regimens.

Cancer and Immunity

Chronic inflammation is a hallmark of cancer. Cancer is a systemic condition that alters the immune system's overall composition and function in numerous ways [9]. Some malignancies significantly affect hematopoiesis, noticeable in the proliferation of immature neutrophils and monocytes in the periphery of tumor-bearing hosts, which ultimately promotes Tumor Microenvironment (TME) and contributes to local immunosuppression [10]. A meta-analysis of over 40,000 patients with elevated neutrophil-to-lymphocyte ratio (NLR), was associated with a poor cancer prognosis [11]. Another meta-analysis of 17079 Breast cancer (BC) patients suggested that elevated NLR and platelet-to-lymphocyte ratio (PLR) were associated with poor overall survival (OS) and greater risk of recurrence [12]. In animal experiments with BC, immunological remodeling was found, with increased neutrophils, eosinophils, and monocytes and decreased dendritic cells (DC), B cells, and T cells. However, surgical tumor excision or cytokine blocking therapy was able to reverse many of the alterations [13]. B cells are the tumor-infiltrating lymphocytes and play a key role in influencing the immune response to cancer. B cells that can limit tumor formation by producing tumor-reactive antibodies, boosting Natural Killer Cell (NKC) induced tumor death, macrophage phagocytosis, and priming CD4+ and CD8+ T cells. B lymphocytes can also support tumor development by producing auto antibodies and tumor growth agents. Regulatory B cells can inhibit Th1 and CD8+ cytolytic T cell responses [14]. As an antitumor immunity, the NKCs can directly kill tumor cells while also influencing the antitumorigenic behavior of other immune cells [15]. Tumor cells can reduce NKC receptor expression and with tumor cells induce reduction of NKC receptor expression and promote TME [16].

Impact of Cancer Treatment on the Immunity of Cancer Patients

Understanding the immune system's impact on cancer treatment is crucial for developing strategies to mitigate adverse effects and improve therapeutic outcomes. Surgery significantly strains the immune system, by releasing the stress hormones like cortisol and catecholamines, which can suppress the immune functions of NKCs, Lymphocytes, and other immune cells [17,18]. Postoperative immunosuppression can create a window of vulnerability where the risk of infections and metastasis increases. Studies have shown that the perioperative period is crucial; during this time, the immune system's ability to combat minimal residual disease and micrometastases is significantly compromised. Hence, strategies such as minimally invasive surgical techniques and perioperative immunomodulation are being explored to minimize the immunosuppressive effects of surgery. Chemotherapy (CT) drugs do not discriminate between cancerous and healthy dividing cells, leading to collateral damage to the bone marrow, gastrointestinal (GI) tract, and hair follicles, among other tissues. The bone marrow is particularly important for immunity, as it produces white blood cells, including neutrophils, lymphocytes, and other immune cells. CT induced myelosuppression leads to neutropenia, and lymphopenia, increasing patient susceptibility to infections, treatment delays, dose reductions, and treatment discontinuation [19]. CT can alter the activity and functions of innate immune cells like NKCs, DCs, macrophages, and neutrophils, potentially hindering their ability to produce a positive immune response [20]. CT impacts adaptive immune cell proliferation, activation, and effector activities, particularly T- and B-lymphocytes. Chemotherapeutic agents can cause thymic atrophy, affecting T-cell production for tumor surveillance, tolerance, and protection [21]. Radiotherapy significantly impacts the immune system, particularly in critical immune organs like the spleen, bone marrow, or thymus. It induces immunosuppression through DNA damage, inflammation, and fibrosis, altering the local immune environment and preventing immune cell trafficking. It also releases immunosuppressive cytokines and recruits regulatory T cells, inhibiting anti-tumor immune responses [22].

Cancer treatments reduce morbidity and mortality but can impair immune function and cause severe cytopenia, allowing opportunistic infections to impede healing in hospitalized cancer patients. Recognizing infection likelihood is crucial for selecting proactive nutritional and medicinal management.

Nutritional Consideration

Malnutrition is a major issue for patients with malignant tumors as they are more vulnerable to infections. Studies suggest patients with cancer who received IN therapy had improved immune responses and better nutritional status [23]. IN has been shown to control the body's inflammatory and immunological reactions and makes use of particular nutrients to enhance the nutritional status of cancer patients. IN has been experimented during various cancer therapies [23]. In addition to enhancing patients' nutritional status, some particular nutrients as discussed in this review have been shown to control the body's inflammatory and immunological reactions.

Glutamine (Gln)

Glutamine, an abundant amino acid, becomes conditionally essential in catabolic stress like cancer, trauma, sepsis, or burns due to rapid mobilization from muscle reserves [24]. Gln is crucial for maintaining intestinal integrity and promoting the differentiation and proliferation of intestinal stem cells into enterocytes and goblet cells. It enhances gut enterocyte proliferation by enhancing growth factors like epidermal growth factor and insulin-like growth factor-I, which regulate DNA, RNA, and protein synthesis and mucosal cell replication [25]. Gln boosts the immune system, promotes mucosal surfaces, prevents bacterial translocation, preserves gut integrity, and reduces sepsis risk by enhancing leukocyte, macrophage, and IgA production [26]. In the form of glutathione, Gln protects cells from reactive oxygen species (ROS) and inhibits proinflammatory cytokine production, making it a beneficial supplement for post-surgical trauma patients [27].

Patients with esophageal cancer receiving CT and high-dose oral Gln (30 g/day) have demonstrated improved lymphocyte mitogenic activity with lymphocyte counts being restored [28]. In a study by Chattopadhyay et al, the Gln supplementation group developed lower incidents of grade III and Grade IV oral mucositis (OM) and for a shorter duration, compared to the control group [29]. Similarly in a meta-analysis of 13 preventive and three therapeutic RCTs, prophylactic Gln supplementation significantly reduced the incidence of severe OM (grade ≥ 3) (RR = 0.53, 95% CI = 0.32–0.88) and, Gln supplementation on Chemo and radiation days lowered the incidence of severe OM (RR = 0.40, 95% CI = 0.19–0.86 and RR = 0.55, 95% CI = 0.41–0.74, respectively) [30]. However, in another study of patients with head and neck cancers (HNC), Gln did not lower the frequency of OM. (RR = 0.98, 95% CI = 0.94–1.03). However, it reduced the severity of OM (RR = 0.38, 95% CI = 0.2–0.74) [31]. A meta-analysis by Yarom et al found no significant benefits of parenteral Gln in HNC patients [32]. The above studies have shown Gln supplementation can reduce the incidence of grade III and IV OM, and also reduce the severity. A meta-analysis of colorectal cancer (CRC) patients undergone radical surgery observed that Gln significantly enhanced the humoral immune function indicators, such as IgA (SMD = 1.15, 95% CI = 0.72–1.58), IgM (SMD = 0.68, 95% CI = 0.48–0.89), and IgG (SMD = 1.10, 95% CI = 0.70–1.50). Significantly improved T cell immune function indicators, CD4+ T cells (SMD = 0.76, 95% CI = 0.53–0.99) and CD4+/CD8+ T cells (SMD = 0.92, 95% CI = 0.57–1.28). However, in contrast, the CD8+ T cells reduced significantly (SMD = −0.50, 95% CI = −0.91 to −0.10). There was a significant decrease in postoperative complications such as surgical site infection (RR = 0.48, 95% CI = 0.30–0.75), anastomotic leakage (RR = 0.23, 95% CI = 0.09–0.61), and LOS (SMD = −1.13, 95% CI = −1.68 to −0.58) [33]. These evidences indicates that beyond immunological regulation and reduced GI toxicity, Gln supplementation (10-30g/day) may have other advantages for patient well-being during cancer treatment.

Arginine (Arg)

Arginine, a semi-essential amino acid, enhances immune responses, supports nitric oxide production, aids wound healing, and plays a crucial role in infection control and overall immune health [34]. Growth hormone and IGF-1, along with enhanced proline and hydroxyproline synthesis, and the actions of Nitric Oxide (NO) and polyamines, can accelerate wound healing upon arginine stimulation [35]. Arg regulates T-cell receptor expression, B-cell development, NO generation by Nitric oxide synthase (NOS2), and antibody production by B-cells. Hence, Arg is crucial for both acquired and innate immunity [36]. Random supplementation of Arg and fiber in Seventy-two oral or laryngeal cancer patients along with controls who received isocaloric, isonitrogenous enteral formula after surgery reported reduced fistula formation in the Arg group (5.2% vs. 17.6%, p=0.026) and shorter length of postoperative stay [37]. Similar results of reduced incidence of fistula formation were observed in another study on oral or laryngeal cancer patients receiving high dose arginine enterally (20gm/day) vs an isocaloric, isonitrogenous enteral formula containing 12.3 g Arg/day (3.4% vs. 10.5%, p=0.006) [38]. Some other studies found Arg supplementation in sepsis patients had minimal benefit and potentially harmful effects on cardiovascular function and systemic blood pressure [39,40].

In summary, individuals with established sepsis may

experience negative consequences from Arg, particularly if they have hypotension. The use of Arg as a wound healing supplement showed that up to 20 g/day is safe and generally well tolerated in adults; however, currently, not enough information is available to determine the best doses and timing for delivery.

Nucleotides

Nucleotides, essential for DNA and RNA, play a crucial role in various cellular activities. Dietary nucleotides affect lymphocyte populations, maturation, and proliferation, and responses to malignancies and allografts. They also improve macrophage phagocytosis and delayed hypersensitivity, and enhance early life immunity against infections [41].

Nutritional formulas containing IN, a blend of Omega 3 fatty acids (n3-FA), glutamine, arginine, and nucleotides, can influence the body's inflammatory response to surgery, reducing non-infectious complications and infectious ones like surgical site infections [42]. A systematic review and meta-analysis of 61 RCTs found that IN significantly reduces postoperative infectious complications like wound, respiratory, and urinary tract infections and shortens hospital stays. However, sepsis and all-cause mortality did not differ between IN and standard nutrition. Patients receiving enteral IN, along with Arg, nucleotides, and n-3FA, had lower rates of respiratory tract and wound infections [43]. Matsuda et al. conducted a study to determine if a 5-day preoperative supplementation with IN could restore the balance between type 1 and type 2 CD4+ T cells (Th1/Th2). The study found that preoperative IN improved Th1/Th2 balance both on postoperative day 0 and by the end of the postoperative period (POD14) [44].

In contrast, in a meta-analysis of 27 studies involving 1,478 patients who underwent CT and Radiotherapy (RT) there was no significant difference observed in the overall incidence of OM, diarrhea, or esophagitis between the IN and standard nutrition/placebo groups. However, IN significantly reduced the incidence of diarrhea, esophagitis, weight loss > 5 %, and severe (grade ≥3) OM [45].

Probiotics

Probiotics are live microorganisms that, when administered in sufficient amounts, provide significant health benefits to the host through their metabolites like lactic acid and short-chain fatty acids (SCFAs) [46]. Lactic acid-producing bacteria like Propionibacterium, Bifidobacterium, Streptococcus, and Lactobacillus can help prevent cancer by altering the intestinal microbiota, enhancing metabolic activity, binding and degrading carcinogenic compounds, producing anticancer compounds, modulating the immune system, correcting intestinal dysfunction, altering host physiology, inhibiting cell proliferation, and inducing apoptosis in cancer cells [47,48].

A systematic review of 23 RCTs on probiotic supplementation in CRC found benefits such as reduced post-surgery infections, lower tumor incidence, enhanced immune modulation, improved QOL, and mitigation of side effects. However, study limitations like small sample sizes and pre-surgery bowel-cleansing often hindered the detection of significant clinical outcomes [47]. A meta-analysis of RCT found that probiotics can improve surgical outcomes and prevent chemotherapy-Induced diarrhea (CID) in gastric cancer patients. While they didn't significantly impact weight loss or prealbumin levels, they reduced postoperative complications, expedited recovery times, shorten hospital stays, and increased serum albumin levels [49]. Another meta-analysis of, 13 RCTs, with 1024 cancer patients concluded that probiotics reduced CID rate [RR=0.47, 95% CI (0.35, 0.63), p<0.00001] and grade III-IV diarrhea [RR=0.16, 95% CI (0.05, 0.42), p=0.0008], and shorten the diarrheal duration [MD= -1.92, 95% CI (-1.96, - 1.88), p<0.00001]; with statistical significance. But in patients with grade I-II diarrhea [RR=0.81, 95% CI (0.53, 1.24), p=0.34], statistical significance was not observed [50]. Le Noci V et al. found that probiotic aerosol therapy inhibits lung melanoma metastasis by enhancing the immune response. Lactobacillus rhamnosus activates T cells and NKC, boosting the antitumor effect. Combined with dacarbazine CT, this treatment significantly improves efficacy, making it a promising method to prevent lung metastasis in high-risk melanoma patients [51]. Probiotics have shown potential benefits in hematopoietic stem cell transplantation (HSCT) by supporting early neutrophil engraftment and reducing febrile neutropenia duration. Some trials found no significant impact on graft-versus-host disease (GVHD) or gut microbiota, while others showed probiotics can lessen oral mucositis severity [52]. Evidence suggests that probiotics like Lactobacillus plantarum can be safely used in HSCT patients, helping to enhance recovery and support gut health without causing adverse effects [53,54]. A clinical trial found that daily synbiotic supplementation reduces acute GVHD severity in allo-HSCT patients by enhancing regulatory T cell induction and modulating immune responses through SCFA production, suggesting synbiotics are beneficial in improving GVHD outcomes and overall survival [55].

To find specific strains of bacteria with anticancer properties that can survive the digestive tract, and to evaluate any possible negative effects in immunocompromised individuals, more research is needed.

Fibers

Dietary fibers, both insoluble and soluble, are carbohydrates that the body cannot digest due to lack of enzymes. Colon

bacteria break down soluble fiber to SCFA, which produce metabolites like propionate, butyrate, and acetate, which have anticancer properties [56].

Butyrate induces apoptosis in cancer cells, by eliminating damaged or abnormal cells. Butyrate can be broken down into acetyl-CoA, a cofactor that increases histone acetyltransferase activity, potentially altering gene expression patterns and increasing the antitumor properties of butyrate [57]. β-glucans, polysaccharides with antitumor, anti-inflammatory, and immunomodulating properties, have been shown to mediate tumor suppression in prostate carcinoma, and they and inulin enhance tumor control by activating pattern recognition receptors Alexander MP, et al. [58] and inhibiting activation of monocytes in mice and reducing the incidence of melanoma in metastatic lung cancers [59]. β-glucan from yeast enhances antitumor immunity by stimulating NKC through dectin-1 and TLR-4 receptors, releasing cytokines, and activating cytotoxic NK and CD8+ T cells. This enhances the immune response against tumors, reducing melanoma lung metastasis in a preclinical model [60-62]. Yeast-derived whole β-glucan particles were shown to reduce tumor weight and lower levels of immunosuppressive cells in mouse models of lung and BC [63].

A study on Hepatocellular Carcinoma (HCC) patients found that gut microbiota regulates dendritic cell cGAS–STING signaling, which in turn affects host cytotoxic T lymphocyte responses and RT sensitivity. Optimizing a patient's response to RT may involve altering gut flora through fecal transplantation, prebiotics, or personalized probiotics [64]. Gut microbiota translocation to distant organs may enhance antitumor immunity by disrupting gut barrier integrity and boost tumor responses to cyclophosphamide by promoting T helper cell immune responses [65].

SCFAs, primarily produced by gut microbiota, have anticancer properties. TME suppresses immune responses, allowing cancer cells to evade detection. Boosting immune responses with dietary fibers like β-glucans and inulin helps control tumors. By modifying immune responses, gut microbiota, and metabolic processes, dietary fiber can modify cancer treatment responses [66].

Omega-3 Polyunsaturated Fatty Acids (PUFA) (N3-FA)

N3FA are essential fatty acids. α-linolenic acid (ALA; 18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3) are the three different active molecules which forms n3-FA. ALA is synthesized from plants (seeds, nuts, seaweed, algae, and plant oils) and EPA and DHA are derived from cold-water fish. Small quantities of EPA and DHA can be produced from ALA by a series of elongation and desaturation processes [67]. n3-FA has anti-inflammatory properties by inhibiting NF-κB and producing pro-resolution mediators. These mediators lower cellular debris and leukocyte infiltration, stopping the inflammatory process. NF-κB promotes tumor proliferation, angiogenesis, and metastasis. EPA inhibits NF-κB, reducing IL-6 and pro-inflammatory cytokine production, and apoptosis of esophageal cancer cells and COX-2 enzyme, which leads to inflammation and neoplastic changes [68].

Supplementation of 1.8 g/day n3-FA to patients post-HSCT has been shown to decrease GVHD incidents [69]. A meta-analysis by Yue T, et al. [69] suggested that n3-FA improves the humoral immune functions in CRC postoperative patients [70]. Xie H and Chang YN's 2016 meta-analysis linked short-term n3-FA administration to reduced postoperative complications, inflammatory cytokines, and hospital stay after CRC surgery [71]. A meta-analysis and clinical trial demonstrated that lipid emulsions based on ω-3FA can preserve liver function, reduce inflammation, and reduce overall complications, resulting in shorter hospital stays and reduced overall complications [72,73]. A randomized, double-blind, and controlled trial found that supplementing BC patients with EPA and DHA, along with 0.32% vitamin E as an antioxidant, significantly changed plasma fatty acid composition, maintained CD4+ T cell levels, and reduced active inflammatory response, positively impacting the immune system [74]. In a HNCs RCT, n3-FA and arginine enhanced formulas postoperatively showed improved blood protein concentrations and lymphocyte levels Morsy BM, et al. [75] found that topical Omega-3 nanoemulgel treatment for HNC patients with radiation-induced oral mucositis (RIOM) reduced pain intensity and improved QOL, suggesting that n3-FA may influence oral microbial dysbiosis, potentially improving RIOM [76].

However, studies by Hanai N, et al [76] showed no effect on the maintenance of the nutritional status of HNC patients, of IN g n3FA w-3 fatty acids Schmidt Sørensen, et al. [77] showed no survival benefit in patients undergoing CRC surgery and a subgroup of patients treated with adjuvant CT with supplementation of n-3 FA [78]. A Systematic review of 12 RCTs involving 1456 patients on preoperative n-3FA fatty acids in major GI surgery concluded insufficient evidence to support routine n-3FA fatty acid supplementation [79].

The research on n3-FA in cancer treatment and prevention has shown mixed results. Organizations like ESPEN (European Society for Clinical Nutrition and Metabolism) and IAPEN (Indian Association for Parenteral and Enteral Nutrition) do recommend n3-FA as part of nutritional support for cancer patients, but they also emphasize the need for individualized treatment plans [80,81].

Micronutrients: Vitamins, Minerals and Antioxidants

Vitamins: The Carotene and Retinol Efficacy Trial (CARET), the Alpha-Tocopherol, Beta-Carotene (ATBC), and The Age-Related Eye Disease Study 2 (AREDS2) Cancer Prevention Study found that beta-carotene supplements increased the risk of lung cancer in smokers [82-84]. Some clinical trials found no relationship between vitamin A or beta-carotene supplements and the incidence of lung cancer or mortality [85]. An RCT of 22,071 male physicians on 50 mg beta carotene or a placebo for 12 years, with no differences in lung cancer cases or malignant neoplasms [86]. Another RCT 7,627 women on 50 mg of beta-carotene, 600 IU vitamin E, 500 mg vitamin C daily, or a placebo for 9.4 years, with no significant effect on total cancer incidence or mortality, including from lung cancer [87].

B vitamins and vitamers are essential for enzymes and cellular activities, but their protective role in cancers is unclear due to complex variables like absorption, bioactivity, and vitamer generation [88].

Vitamin C is essential for immune cell function, defense against infectious agents and cancers, and has significant epidemiologic evidence against non-hormonal-dependent malignancies [89]. Preclinical studies show vitamin C can inhibit cancer cell proliferation, but there is a lack of clinical evidence supporting its antitumoral effectiveness [90].

Vitamin E isomers possess strong antioxidant properties and can scavenge ROS and prevent oxidative damage to cells and tissues. Vitamin E metabolites, such as γ-tocopherol and δ-tocopherol, can activate Nrf2, enhancing the production of antioxidant enzymes like catalase, glutathione peroxidase, and phase II detoxifying enzymes. These enzymes help maintain cellular homeostasis and protect cells from oxidative damage. Vitamin E's ability to inhibit eicosanoids, which contribute to colon cancer progression, contributes to its ability to prevent carcinogenesis and reduce inflammation. Additionally, Vitamin E can inhibit inflammatory markers through various pathways, such as blocking PPARs and inhibiting inflammatory factors like cyclooxygenase 2, TNF-α, and IL-6 [90].

Vitamin D, a lipid-soluble vitamin, is found in two forms: ergocalciferol and cholecalciferol. Studies have shown that low levels of Vitamin D can increase tumor growth in solid and non-solid types. It has been demonstrated that Calcitriol (1,25-dihydroxy vitamin D3) inhibits the formation and development of tumors in animal models and has anti-proliferative and pro-differentiating actions on a variety of malignant cells, suggesting that it may find application as an anticancer drug [90,91].

Vitamin K Deregulated γ-carboxylation contributes to the development and progression of HCC, with vitamin K supplementation potentially offering survival benefits. Studies have shown that vitamin K supplementation can reduce circulating des-γ-carboxylated thrombin (a type of abnormal prothrombin that is secreted by Primary hepatocellular carcinoma cells) and extend survival time in HCC patients [92].

Minerals

Certain minerals play a crucial role in supporting the immune system and may help in cancer prevention. Here are some key minerals and their benefits:

Selenium is an essential trace mineral that plays a role in cellular antioxidant systems which protect cells from DNA damage and mutations and may reduce the risk of certain cancers. However, the evidence on selenium's effectiveness in preventing cancer is mixed. Some observational studies suggested that higher selenium levels might be associated with a lower risk of certain cancers. Despite this, more rigorous RCTs have generally found no significant effect of selenium supplementation on reducing cancer risk. Some studies have even indicated potential risks, such as an increased chance of high-grade prostate cancer [93].

Zinc: Essential for immune function, zinc supports the body's defense mechanisms and helps in DNA repair. For signaling mechanisms including cell development, proliferation, and death, zinc is essential. Zinc deficiency is a prevalent feature in multiple cancers, potentially serving as a biomarker for cancer risk identification, prognosis prediction, and treatment. Studies have also suggested that zinc supplements could be used as an adjuvant cancer treatment and some studies have shown no benefit of zinc supplementation in cancer prevention [94].

Magnesium (Mg): Important for many bodily functions, Mg helps maintain a healthy immune system and may have a role in cancer prevention. Mg deficiency has been shown to increase in ceramide formation, which is known to activate NFkB and trigger the release of several proinflammatory cytokines, including IL-1β, IL-6, and TNF-α. Systemic Mg deficiency also affects the microbiota, as evidenced by a decrease in bifidobacteria concentration in the colon and a disruption in the intestinal wall's barrier function, which increases TNF-α and IL-6 expression in the liver and intestine [95].

Copper: As a vital component of many biological processes, copper must be precisely regulated to prevent harmful health consequences and possible toxicity to cells. Increased concentrations, of copper toxicity lead to "cuproptosis". According to studies, elevated copper levels are seen in

various cancer patient's serum and tumor tissues. Copper plays an important role in the growth of tumors, metastasis, cell proliferation, and chemoresistance. Copper ions are involved in various signaling pathways within tumor cells by interacting and activating key molecules and influencing the biological behavior of cancers indirectly through various pathways, e.g. Notch pathway, that promotes the shedding of the notch ligand Jagged1, leading to tumor cell migration. Copper promotes tumor angiogenesis, through its interaction with hypoxia-inducible factor 1-alpha (HIF1α). Through NFκB pathway, copper influences inflammation and tumorigenesis. Copper also regulates tumor metabolism, impacting lipid and sugar metabolic pathways. Several researches are underway targeting Cuproptosis as a potential cancer treatment [96].

Calcium: Vital for bone health, calcium can help prevent osteoporosis, which is a common side effect of cancer treatment. Some studies suggest higher consumption of calcium can prevent colon cancer and it is believed that calcium has the potential to bind the hazardous chemicals in the gut and decrease their interaction with the colon's lining. Given that vitamin D facilitates the body's absorption of calcium, calcium and vitamin D may together lower the risk of CRC. However, some studies have indicated an increase in prostate cancer. The relationship between calcium and cancer is complex and not fully understood, more research is needed to determine if this link exists [97]. According to Warburg's theory, the rise in glycolytic rate represents a compensation mechanism for the defective mitochondrial metabolism seen in cancer cells. The building blocks and energy needed to support unchecked growth are provided by increased mitochondrial Ca2+ absorption, which also accelerates mitochondrial metabolism. Additionally, ROS are produced by mitochondrial metabolism and these ROS activate signaling pathways, including hypoxia and inflammatory pathways that encourage carcinogenesis [98].

Iron Abnormal iron homeostasis is a marker of cancer, as tumor cells have higher metabolism and proliferation rates, leading to increased iron demand and oxidative stress. They can upregulate antioxidant defenses for survival but are more sensitive to iron depletion, resulting in increased iron metabolism, affinity, and inhibition of iron output.

Conclusion

Cancer treatments, including surgery, CT, and RT, impact the immune system in a complex manner. However, these treatments also present opportunities for therapeutic intervention. Adequate micronutrients can improve patient immunity, treatment efficacy, and quality of life. However, micronutrients as adjuvants for oncology treatments are still in their infancy, requiring further research to explore their potential as safe, convenient, and affordable agents. This research is crucial for improving cancer patient outcomes and harnessing the immune system's full potential.

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Conflicts of Interest

The authors declare no conflict of interest.

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