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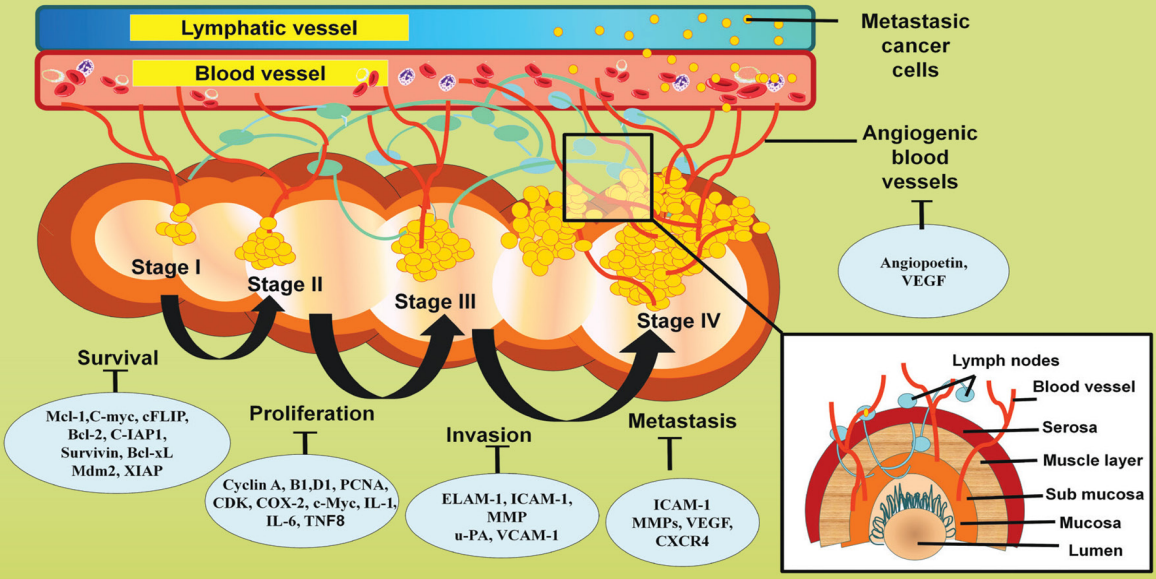

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Advances in Nutraceutical Applications in Cancer

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Recent Research Trends and Clinical Applications

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Preface

Nutraceuticals are the blended products that possess both nutritional and the medicinal value and formulated in the form of various dosage forms such as tablets, capsules including other dosage forms. These products are designed to help in improving the physical health, immunity, increase longevity, and fight against day-to-day challenges such as stress.

The popularity of nutraceuticals in society as well as healthcare providers has been increasing due to its complimentary role in enhancing the positive effects of medicines and health supplements. There are nutraceutical products with a wide variety of therapeutic values such as immunity booster, antidiabetic, anticancer, antimicrobial, and gastroprotective.

Dietary supplements and nutraceuticals such as vitamin A and D, omega-3, and probiotics are used as part of the cancer treatment as complimenting the main therapy. Regulatory T cells (Tregs) are a heterogeneous T-cell subpopulation that regulates the immune system in various ways. T cells protect us from infections and tumors. Recent report published in *Science* (March 29, Volume 363, issue 6434, 2019, 1395–1396) in which Baixaulli et al. have proposed that reduced nutrient uptake in T cells in high potassium concentrations induces a state of functional caloric restriction. This extends life span, induces autophagy, increases mitochondria quality control, supports optimal stem cell activity, improves immunological functions, and improves malignant transformation. Vodnala et al. showed that elevated potassium triggers a starvation response of T cells with engagement of autophagy and metabolic modeling that involves a reduction of mTOR signaling, activation of the energy sensors, AMPK (adenosine monophosphate-activated protein kinase), and enhanced mitochondrial metabolism (SK Vodnala et al., *Science*, 363, 6434, 1417, 2019). There can be new therapeutic strategies using nutraceuticals, herbal drugs, and minerals to metabolically induce stemness programs in antitumor T cells that enhance cancer immunotherapies.

In this scenario, nutraceuticals and dietary supplements may play a significant role. Valenzuela et al. (*J. Immunol*., April 1, 2009, 182 (1 Supplement) 90.30) tested the nutraceuticals resveratrol and cycloastragenol for their ability to enhance T-cell functions in vitro. In this study, they evaluated the effect of these compounds on cellular proliferative capacity, levels of telomerase activity, surface markers, and cytokine secretion of human CD4 and CD8 T cells. They reported that cycloastragenol moderately increase telomerase activity and proliferative capacity of both CD4 and CD8 T cells. These preliminary results suggest that nutraceuticals inhibit the onset of CD4 and CD8 cellular senescence and can be a good complimentary medicine with anticancer drugs.

Several nutraceuticals have shown to boost the immune responses such as beta-glucans, echinacea, astragalus, selenium, and many more. Emerging clinical studies and research suggests that some plant-based agents may, indeed, impact late-stage cancer, influencing molecular processes corrupted by tumor cells to evade detection, expand clonally, and invade surrounding tissues.

This book is an attempt to collect evidence and related clinical information of application of nutraceuticals to be used in cancer treatment or compliment the cancer treatment. It contains 16 chapters written by experts in related field's and covers many different aspects of the formulation and development of nutraceuticals for cancer applications. It covers efficacy, safety, and toxicological aspects of nutraceuticals. Details about novel drug delivery systems of nutraceuticals as anticancer agents or supplements used for cancer prevention or treatment are also covered.

Nutraceuticals can alter the gut microbiota. Gut microbiome undergoes changes during the disease status and followed by the cancer treatment. Nutraceutical's role in proliferation and prevention of gynecological cancers, nutraceutical's role in proliferation and prevention of prostate cancer, and role of micronutrients in cancer prevention pros and cons, are some of the topics discussed in various chapters in this book.

We think this will be a very good reference book for the readers and scientists and students who are working in the area of nutraceutical applications in cancer treatment.

We express our sincere thanks to Dean College of Pharmacy at USF health to encourage us to work on this project as well as our colleagues at CRC Press who helped us to make this book marketable. If you find any challenges in this book information, kindly do bring it to our notice and we will update it in the next edition.

We also would like to express our sincere thanks Mr Steve Zollo, and others from Taylor and Francis who helped through the publication of this book.

Sheeba Varghese Gupta and Yashwant V. Pathak

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1 Role of Micronutrients in Cancer Prevention and Intervention—Pros and Cons

Anjelika Chatwal and Yashwant V. Pathak

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1.1 INTRODUCTION

By the end of the twenty-first century, cancer, a noncommunicable disease, will be the leading cause of death among both men and women, surpassing the most common causes: heart disease and stroke. Of roughly 18 million incidences, approximately 9 million will lead to death [1]. With the rising incidences of cancer in both developing and advanced countries, the necessity for alternative types of therapies for prevention and intervention before and during treatments has grown immensely. There have been countless promising theories and hypotheses that have been developed to evaluate the efficiency of altering one's diet to include micronutrients and antioxidants to contribute to the prevention of cancer [2]. While other factors, such as alcohol consumption and smoking, act on cancer amplification, eventually leading to death, it has been suggested that preventing cancer through the diet has accounted for a percentage of those who have cancer [2]. Since any food that a person eats can

have direct impact on their health, patients tend to gravitate toward popular diets, such as the vegan, ketogenic, Paleolithic, and alkaline, that might contribute to their survival [3]. Some believe that combined with general treatments, natural substances can target cells within the body to elicit effects [4].

However, the efficacy of these alternate diets and supplemental treatments has been doubted, as the use of either could promote unrealistic outcomes and properties relating to cancer recovery [3]. Even worse, patients who rely on these diets for an alternative without consulting their physicians can become nutrient deficient, which can further compromise their treatments [3]. The role of adding micronutrients in the diet in order to prevent cancer from developing and becoming malignant has been controversial in cancer research. Most studies regarding this area of research express the need for further experiments to be done in order to establish more concrete conclusions and results about the varying micronutrients that can contribute potential effects on cancer. Some papers suggest that efforts to study the potential treatments for cancer prevention should begin with high-risk groups through different levels of population so that a broader scope is defined [5]. Does implementing these necessary dietary factors truly contribute to preventing diseases such as cancer? We will first need to understand the classification and characteristics of micronutrients to have a better insight of how our bodies utilize and metabolize these factors and what they can potentially do in the cancer mechanisms.

1.1.1 Micronutrient Background

Micronutrients are classified as elements that we cannot synthesize in our bodies [6]. Certain metabolic and biosynthetic pathways in our bodies require a variety of nutrients, antioxidants, and phytochemicals that have properties necessary for these pathways and mechanisms to function properly. What makes micronutrients special is that in order to maintain these processes, our systems only need small amounts for adequate growth and development—hence their name, micronutrients. Antioxidants, on the other hand, are substances that can delay or prevent the oxidation of a substrate when present in low concentrations, in comparison to substrates that are more likely to be oxidized [7]. These are also helpful in preventing more oxidative damages from occurring in the body, as they, themselves, are redox-active substances that can act as catalyzers and active cofactors for enzymes [8]. Some others act as stabilizing proteins and enzyme activators [8].

Since we cannot physically develop these factors in our bodies, we must ingest them through foods that are rich in vitamins A, B12, C, D, and E and various other substances and through supplements [9]. Micronutrients can be found as part of specific substances, such as antioxidant enzymes, which include superoxide dismutase and glutathione peroxidase. In layman's terms, superoxide dismutase includes elements such as manganese, copper, and zinc, while glutathione peroxidase includes selenium [10]. Additionally, phytochemicals, which are described as plant-based nutrients that are not essential for our overall diets, include carotenoids, flavonoids, curcumins, and resveratrol [11]. While these substances may seem far-fetched for the common person, they are actually found in most of the everyday foods. Carotenoids

are typically found in carrots, flavonoids in fruits, wine, green tea, and other dietary factors, and curcumin in turmeric [12].

The various metabolic processes within our bodies can generate chemical errors or toxic by products, such as superoxide, reactive oxygen, reactive nitrogen, or reactive chlorine species [10]. Although some parts of our body systems function by utilizing these reactive species in beneficial ways, like killing bacterial organisms, uncontrolled production of these species can spark the need for substances that act as defenses to protect the body's normal processes from spiraling out of control. Micronutrients, as part of antioxidants, work to recycle, protect against, or remove certain reactive species that build up past their needs [10]. These substances all have their own unique mechanisms of action that work on the cellular processes in order to protect against oxidative and environmental stressors [13]. For instance, selenium deficiencies can contribute to diseases like cancer, indicating that researching its molecular processes is significant in determining how implementing selenium in the diet can help prevent illnesses [14]. Selenoproteins, proteins that contain selenium, have important physiological roles in the body. These are redox-active proteins that have roles of repairing oxidatively damaged proteins, quality control, and protein folding and can act as targets for new therapies for a number of diseases [14].

1.1.2 The Cell Cycle and Tumor Growth

Comprehending how micronutrients affect the cellular processes within our bodies is essential to realizing the role they have in cancer prevention and intervention. Normally, the cells in our bodies undergo cell cycles, in which they grow, replicate their DNA, and divide. However, cancerous cells undergo these cycles without proper signaling pathways and mechanisms that regulate errors and uncontrolled proliferation [15]. The cycle includes four phases as explained below. There are the checkpoints and signaling pathways involving regulatory mechanisms that are meant to prevent unnecessary cell growth and encourage apoptosis of cells that are damaged. If genetic mutations arise, these mechanisms or proteins found at the regulatory checkpoints can malfunction, causing cell proliferation of potential tumor-causing cells [15].

G1—the gap phase, involving cell growth and preparation to synthesize DNA
S—synthesis phase, where the cell synthesizes DNA
G2—second gap phase, involving preparation for division
M—mitosis phase, where cell division finally occurs

The various micronutrients studied are likely to target various regulatory proteins, checkpoints, and signaling pathways that are found within the cell cycle, as well as other metabolic processes, such as glycolysis [16]. For instance, if vitamin A was to impact the cell cycle, it would most likely induce apoptosis or encourage cell differentiation, which would in turn limit cell proliferation [17]. This means that the G1 phase would be affected, as cell growth would shut down. Looking at the micronutrients in this manner, we can assess the ability of these factors and substances to limit tumor growth in individuals, and therefore the most effective ways they can be implemented in research and treatments.

1.2 USE OF MICRONUTRIENTS PROS VS CONS

1.2.1 Accessibility to Micronutrients

An obvious benefit of utilizing micronutrients as supplements to chemotherapy is the fact that they are widely accessible in the market. Vitamins and minerals can be found in varying doses over the counter. In this way, studies that demonstrate how micronutrients are involved in cancer prevention and alleviation, biologically, are significant so that people can understand that, if needed for treatments, these supplements are readily available to them.

With the development of evidence suggesting the powerful anticancer effects that micronutrients and phytochemicals carry through their cell signaling pathways, newer methods of incorporating these into the everyday lives of individuals combatting cancer are being tested. General plans may not have a strong effect for all patients, as they would have differing symptoms and reactions to their treatments. However, creating personalized supplements for patient according to their necessary clinical treatments and needs is a leading goal in terms of utilizing phytochemicals for clinical use [18]. Once the molecular actions of phytochemicals on specific cancer cell targets are proven, the next step of assessing the proper phytochemicals to use as supplemental treatments for each clinical case would introduce the ease of accessing these supplements for the diet. This study, expanding on previous studies of the usefulness of phytochemicals in health, demonstrates how healing supplements can be developed in a personalized manner to make it easier for those who have these illnesses to acquire the nutrients they need to act as anticancer agents. Thus, personalized evaluations based on the evidence are more useful for these kinds of treatments [19].

Apart from micronutrients available in the market as dosed supplements, the necessary vitamins and minerals that are studied in relation to certain types of cancers can be acquired through dietary intake. In fact, the lack of a proper diet can be a risk factor for some cancers, highlighting the significance of micronutrients stemming from a person's diet [20]. The quality of a patient's diet is studied in order to assess how their food intake affects mechanisms of their chemotherapy, if it does at all. Therefore, the accessibility one has to micronutrients, such as vitamins and minerals, is significant, as they can be found in most foods.

For instance, vitamin C is a powerful antioxidant that is commonly found in our everyday lives. Apart from being an antioxidant, vitamin C, also known as ascorbic acid, is classified as a "functional food." Functional foods refer to those that are natural or processed and contain biologically active substances that are proven to have some benefit for chronic illnesses [7]. Most people think of orange juice, since the citrus contains this valuable essence, but there is a variety of foods, including fresh greens, fruits, and vegetables, that allow for more absorption of this vitamin and other vitamins beyond that of just orange juice, especially compared to supplemental pills and tablets. Since this antioxidant is water soluble, it is eliminated quickly and is not able to be stored in our bodies. Aside from this, our bodies are unable to produce this vitamin naturally due to an absent catalyzer, gulonolactone oxidase, for the an enzyme in the last step in the biosynthesis pathway, so incorporating more

vitamin C-rich foods into our diets is the most significant way for us to gain its effects [7]. As mentioned, many foods contain numerous vitamins and minerals, and the best way our bodies can absorb the nutrients from the vitamins is in combination with others. For example, vitamins C and E inhibit oxidation together, and vitamin C helps to reestablish vitamin E levels if they start to decline [7].

1.2.2 Alleviation of Chemotherapy-Induced Symptoms and Influence of Response to Chemotherapeutic Agents

Physicians tend to lean on more tangible therapeutics when it comes to certain diseases, such as cancer. Their primary focus would be to utilize chemotherapy and drugs targeted for the specific kinds of cancers that they see, but newer studies are demonstrating a shift to incorporating micronutrients in diets, which could potentially enhance the efficacy of some of the drugs used in chemotherapeutic treatments and the outcomes of patients. While other factors, such as genetic instability, can affect how tumor cells replicate and proliferate, studies indicate that the intake of vitamins, minerals, certain antioxidants, specific natural phenols, such as resveratrol, and carotenoids, can in some way influence how tumor cells respond to antitumor drugs [20]. For instance, green leafy vegetables and fruits can impact responses, in that they are associated with low levels of cytogenetic damage [20], which occurs in cells when they are exposed to ionizing radiation with changing dose rates [21].

A number of cancer treatments can result in various diseases that affect all parts of one's body. One example is Chemotherapy-Induced Peripheral Neuropathy or CIPN, which is a frequently occurring effect of cancer treatments [22]. Two specific chemotherapy agents, taxane and platinum, are known to be both primary choice treatments and lead to neurological symptoms, such as neuropathies. Apart from the tiring effects of the chemotherapy treatments themselves, these treatments can induce these symptoms of neuropathy, including cognitive function impairments and a worsening of the quality of life [22]. The nerve damage was enhanced due to the low nutrition levels found in patients who were treated with taxane and platinum [22]. However, this study done by Velasco et al. suggests that vitamin E deficiency can be a culprit to the worsening effects of nerve damage after chemotherapy treatments. Results from the blood samples that they took before and after treatments demonstrated that axon regeneration coincides with more vitamin E in the diet, though it is not completely certain how the micronutrients and antioxidants are involved in the nerve-regeneration process.

Other antioxidants have shown to have some effects during chemotherapy, such as selenium, which has been shown to decrease blood toxicity. Antioxidant supplementation effects are not widely known as of yet and have been shown more in short-term rather than long-term studies, but some studies describe how the addition of antioxidants in the diet can decrease adenomas, for example, in patients with colon cancer who do not smoke but are drink alcohol [23].

Moreover, micronutrients and antioxidants are significant for a person's overall health maintenance, even more so for someone who is undergoing chemotherapy treatments. Since chemo can be so detrimental to a person's body, weakening their

immune systems, for instance, it is important that an adequate diet, supplemented with micronutrients, is maintained. Therapies are not as effective and may reduce tolerance, while also increasing the possible adverse effects and complications after treatments [24].

Patients who must receive surgery are also at risk of weight loss and postoperative decline in nutritional status. By admitting nutrition to them preoperatively, physicians can alleviate some of the postoperative changes that might occur and increase their tolerance [25]. As this study by Liu et al. explores, postsurgery in colorectal patients, cytokine responses can change and become detrimental to the body. Inflammatory reactions are more likely to occur in those patients who are poorly nourished before they had their surgery [25]. Intake of some vitamins and minerals, however, can alleviate these inflammatory responses. Having a deficiency of vitamin A, for example is associated with more prominent inflammatory responses, while a deficiency in vitamin D can increase the risk of inflammatory and infectious diseases associated with the immune cells [25]. Additionally, vitamin E is associated with a defect in naïve T cells, while zinc can affect the production of cytokines within the body. More specifically, when zinc supplements are administered, cytokines in plasma respond on a dose-dependent basis [25]. In the cases of malnourishment, a method of providing supplemental nutrients to the body, called total parenteral nutrition (TPN), is utilized. This is a preferred method preoperatively over enteral feedings for extremely malnourished patients who are receiving abdominal surgery. The solution typically includes a fat emulsion, vitamins, and elements that offer a broad range of nutrition to compensate for what the patients were lacking. While this can pose risks, such as infections, pneumothorax, or hemothorax, the amount of energy this method delivers is far greater than other methods that can potentially be used [25].

A study performed by Hansen et al. investigates the relationship between antioxidant consumption and the risk of colorectal cancer for both smokers and nonsmokers. While their findings had a stronger indication for a risk of colorectal cancer in individuals who smoked, little evidence suggested that the consumption of antioxidants or micronutrients posed an effect along with this [26]. It is possible that antioxidants alone might have a greater effect on the risk of this type of cancer, but in combination with numerous years of smoking, it is difficult to determine how helpful the antioxidants and micronutrients are. A separate study, on the other hand, following the relationship between diet and colorectal cancer shows that there is considerable evidence for promising, protective effects of vitamin D, fruits, vegetables, and folate, while red and processed meats are associated with increasing the risk for the disease [27]. The interaction of nutrients and foods within the body can also create an effect that can influence cancer cell generation through effects on inflammation and overnutrition [27].

A specific study by Tayyem et al. involving micronutrient consumption among Jordinians and the risk of colorectal cancer, 169 participants previously diagnosed with colorectal cancer were tested for the association between total energy and nutrient intake and the potential risk for the development of colorectal cancer. The results demonstrated that total energy ingestion, along with increased saturated fat, cholesterol, and sodium, was significantly correlated with a higher risk of developing the disease [28]. On the other hand, vitamin E and caffeine showed a more protective outcome against colorectal cancer [28].

The mangosteen fruit, widely popular in Asian countries, contains gamma-mangostin, a micronutrient. Evidence was found that showcased antiinflammatory and antibrain tumor actions of the gamma-mangostin micronutrient. A study by Chang and Yang expanded on this development further by researching the relationship between apoptosis and colorectal adenocarcinoma cells, made possible by the gamma-mangostin. The viability of this micronutrient was tested on the HT29 cells specific to the colorectal adenocarcinoma, showing that when treated with differing concentrations of the micronutrient, the HT29 cells experienced a substantial concentration-dependent inhibition in viability [29]. Due to the promising findings from this study regarding the decreased cell viability due to the apoptotic effects of gamma-mangostin and the inhibition of the colorectal adenocarcinoma cell proliferation, there seems to be enough evidence for developing anticancer drugs using xanthones and micronutrients that have similar properties as this one. This evidence is substantiated by previous discoveries of the antiinflammatory characteristics of the mangosteen plant as well [29].

When studying cancer prevention and the role of micronutrients, it is important to understand the mechanisms involved of specific transcriptional factors. Nuclear factor-like 2 boosts antioxidant enzyme and phase-2-detoxifying enzyme levels through mechanisms that could help to reduce oxidative stress and chronic inflammation that contribute to the development of carcinogenesis [30]. The significance of this involves the actions of antioxidant enzymes and phase-2-detoxifying enzymes. The former works to abolish the work of free radicals through catalysis, while the latter changes carcinogens to risk-free substances that are able to be eliminated from the body [30]. However, the enzymes cannot work alone, as their actions are not substantial enough on their own to produce an effect against highly oxidative environments. Simultaneous additions of dietary antioxidants are necessary to help activate the transcriptional factor that enhances these enzymes [30].

Lycopene, a particular kind of carotenoid found in tomatoes, also regulates transcriptional factors in a way that is involved with cancer prevention, specifically in terms of sex hormone-dependent cancers, like breast cancer, which is estrogen-dependent, and androgen-dependent prostate cancer [31]. The study found that, in general, a high intake of vegetables and carotenoids were associated with a lower risk for breast cancer, linked to the limitation of estrogen activity, since higher levels of estrogen contributed to increased breast cancer incidence [31]. Since it was shown that carotenoids impede on estrogen signaling and cell proliferation, lycopene and other tomato-containing foods are useful in obstructing tumor growth in these tissues [31].

Moreover, in terms of prostate cancer, the most common cancer found in males in the United States, androgens contribute to the advancement of this disease, and treatment involves blocking the action of this hormone or castrating it [31]. Lycopene also slowed the development of the disease in a study, meaning these compounds help to regulate carcinogenesis in the prostate.

A mixture of natural substances, such as quercetin, curcumin, green tea, cruciferex, and resveratrol, showed a pronounced inhibition of growth head and neck squamous cell carcinoma and cell proliferation [32]. This further enhances the idea that combinations of substances seem to combat the illnesses more effectively than

when individually supplied to the body, as also demonstrated by the combination of vitamin A and beta-carotene for lung cancer. Research involving the alpha-tocopherol, beta-carotene study also explores the involvement of vitamin D, as the lipid metabolites of this compound provide evidence that serum 25-hydroxy vitamin D is associated with certain health benefits, particularly with cancer, though results are mixed [33].

Retinoids in general have been shown to decrease and go against the typical process of detrimental transformation in epithelial tissues. In terms of skin squamous cell carcinomas and cervical cancer, a specific retinoic acid, 1,3-*cis*-retinoic acid, demonstrated the most prominent results when utilized in treatment [34]. Moreover, this same study researched a number of factors with their association to cancer and carcinogenesis. It was found that a typical outcome of developing infections had a significant negative correlation with nutritional status, influencing the idea of recommending nutritional support for children with cancer [34].

1.2.3 Overconsumption of Nutrients Affecting Cancer Prognosis and Mortality

Just as is common with any other drugs or prescription medications, treatments involving supplements of micronutrients can have associated risks. Depending on the type of cancer an individual has and the specific micronutrient that works best for them, overconsumption of these nutrients can interfere with the normal processes of the body, leading to worsening effects of the cancer. Furthermore, other factors, such as genetic instability and variability, aging, and overall health, can come into play when assessing how effective micronutrients and antioxidants are in a body with a chronic illness, like cancer.

Aging, for instance, increases the vulnerability of the body, making it more difficult for substances and supplements, such as micronutrients, to combat the disruptive actions occurring on our bodies. The sensory, physical, and psychosocial aspects that are altered in the body as the aging process occurs creates an environment that is more susceptible to damage and risk for increasing diseases [35]. Incorporating antioxidants and micronutrients in the diet before the aging process is amplified ensures that these nutrients are absorbed more efficiently and are actually being metabolized effectively for our bodies to utilize, whereas in bodies that are older, the processes can be slower and less effective [36].

In this way, having a middle ground in terms of the amount of micronutrient that is ingested during treatment is a significant aspect to understand when considering these supplemental nutrients. There are optimal levels at which these substances are more useful than detrimental for the body, and several studies have described that, at higher than optimal levels, the body's normal functions can deteriorate. As we explored, some antioxidants and micronutrients are protective, in that they limit the amount of oxidation occurring on substrates. However, even ingesting too much of any vitamin or mineral, especially with addition of supplementation and fortified foods on top of dietary intake, can leave a lasting impact on the functions of our bodies [37]. Guidelines and safe limits for the optimal amounts of the vitamins and minerals are provided by the Institute of Medicine.

Although more studies and research need to confirm, several studies have demonstrated positive associations between various types of cancers and the intake of differing micronutrients associated with those cancers. For instance, micronutrients seem to have some kind of positive impact on lung cancer, but more studies need to validate these findings further, as oxidative stress and physical activity can affect the outcomes [38]. Primarily, there have been mixed results in terms of the efficacy of micronutrients in decreasing the risk of cancer or having a definitive protective role, but there are promising findings that indicate statistically significant results in terms of reductions of outcomes [39]. The amount and type of micronutrient changes the effect on the cancer and its mechanisms on the body. One study from the American Society for Nutrition found that vitamin A had a 16% increased risk for cancer, while calcium supplements showed a decreased risk of cancer and no effect was shown for selenium, zinc, vitamin D, beta-carotene, vitamin C, folic acid, and vitamin K [40].

In patients with the highest intake of phosphorus and lowest intake of vitamin D, researchers found patients to have higher odds of getting bladder cancer [41]. Due to the processes of the bladder system, nutrients and dietary factors are metabolized and broken down in the urinary tract. Therefore, these micronutrients or their metabolites can potentially affect carcinogenesis, in that they can act as either inhibitory or promotive factors [41]. An important aspect of this study to consider is the idea that micronutrients such as calcium, phosphorus, magnesium, and vitamin D metabolically work in conjunction with each other and are derived from similar food sources. Results for intake of micronutrients separately did not show statistically significant results. However, when studied together, as metabolically interactive minerals, results showed statistically significant outcomes for the odds of bladder cancer [41].

Past observational studies and randomized clinical trials show opposing results in terms of whether antioxidants and micronutrient supplements actually make a difference in prolonging life and improving the overall health of patients. However, more recent studies describe the more lasting effects of supplements like these. Vitamins A and E and beta-carotene might have an adverse effect, as they are linked to an increased mortality rate [42]. It seems that a noteworthy key to supplementing diets with antioxidants and micronutrients is that they should arise from natural sources, and not pills or tablets. Ingesting antioxidant- and micronutrient-rich foods tends to show better effects, as they are maintained in a balanced diet, while supplemental pills can come in unmanageable doses that our bodies cannot process adequately [42].

While beta-carotene has mostly been shown to have a positive effect on cancer prevention, especially in terms of the effect on reactive oxidative species (ROS), in terms of head and neck cancer, preventative intake of beta-carotene poses an increased risk for cancer development [43]. Specifically, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trail (ATBC) provided the data that showed an increased incidence of lung cancer in men who smoke who were also taking alpha-tocopherol and beta-carotene compared to those who were getting placebo administrations. Beyond this, combining vitamin A and beta-carotene showed an increased risk of lung cancer for both men and women [43]. A distinct, 18-month study involving alpha-tocopherol and beta-carotene, specifically with ATBC, showed that in terms of lung cancer, alpha-tocopherol did not have an effect, while beta-carotene increased the cancer incidence by just shy of 20% during the intervention period [44]. The difference

was eliminated after the postintervention period began [44]. This chapter also studied the combination of vitamin A and beta-carotene and its effect on lung cancer. There was an approximate 30% increase of a lung cancer incidence, and it was found that the beta-carotene contributed to the elevated growth of preclinical tumors through supplements and the fact that this substance could improve the lung's function, allowing for better inhalation of the carcinogens from smoking [44].

The combination of beta-carotene and vitamin A was tested with prostate cancer as well, as previous studies showed inconsistencies in this area. Stemming from the Prostate Cancer Prevention Trial, serum retinol and carotenoid levels were tested against low- and high-grade risk for prostate cancer [45]. A positive correlation was discovered between serum retinol and high-grade prostate cancer, along with serum alpha-carotene and total prostate cancer [45].

A mixture of natural substances, such as quercetin, curcumin, green tea, cruciferex, and resveratrol, showed a pronounced inhibition of growth head and neck squamous cell carcinoma and cell proliferation [32]. This further enhances the idea that combinations of substances seem to combat the illnesses more effectively than when individually supplied to the body, as also demonstrated by the combination of vitamin A and beta-carotene for lung cancer. Research involving the Alpha-Tocopherol, Beta-Carotene study also explores the involvement of vitamin D, as the lipid metabolites of this compound provide evidence that serum 25-hydroxy vitamin D is associated with certain health benefits, particularly with cancer, though results are mixed [33].

In a separate study by Brasky et al., an association between lung cancer and long-term (10 years) supplemental use of vitamin B was investigated. Their hypothesis suggested that the long-term intake would disturb the natural balance of the vitamins in the body, leading to a substantial consequence on the cellular mechanisms and physiology of the cells involved, leading to potential cancer cell generation [46]. The baseline characteristics of the participants with and without lung cancer were assessed to compare to their characteristics after the long-term supplementation. Based on the results, there was an approximate 30% increase in the risk for lung cancer amongst men who took supplements of vitamins B6 and B12, while an association between women and a risk for lung cancer was not found [46]. There was also a more significant effect on men who were also smokers, as the mutated cells that were also present could be amplified from the high doses of B vitamins that would promote cell growth and carcinogenesis [46]. This study further describes how the mechanisms of B vitamins should, in theory, contribute to the prevention of cancer through carbon metabolism, but this is only beneficial when the intake is in the recommended levels and when patients are deficient of the vitamins. The negative effects, such as DNA damage and carcinogenesis, are more pronounced when intake exceeds the recommended amounts [46].

1.2.4 Specific Micronutrients Affect Certain Cancers

A drawback of utilizing micronutrients in treatments is that, while supported by evidence of beneficial characteristics, they can be specific to certain cancers, and may affect one type of cancer differently than another. This is why studying these

micronutrients in regards to a variety of cancers can allow physicians to understand which ones have a better overall outcome for their patients and which ones may be potentially more harmful in combination with the chemotherapeutic agents. A full dietary assessment is necessary to evaluate what kinds of food patients are consuming, how these foods are processed and cooked, and how the chemicals in these foods can affect aspects of treatments. For example, in the case of bladder cancer, it was found that the deficiency of vitamin B12, found in meat, poultry, milk products, eggs, and fish products, results in a risk for cancer. Since this micronutrient is necessary for the methylation of DNA, a deficiency might lead to uracil coming into the DNA and the ensuing chromosomal breakage, which can be avoided with adequate amount of vitamin B12 [47].

Similarly, folate, a type of B vitamin, is required for DNA methylation as well, and can be found in citrus, green vegetables, and liver. Since this micronutrient is involved in one-carbon reactions during DNA synthesis and methylation, a deficiency could promote cancer growth in normal tissue, specifically ovarian cancer in this study. However, it was also found that having too much folate in the body could also lead to adverse effects, such as the development of tumors or a decline in the survival rate after the cancer has already been established [48].

In studies involving lung cancer, there have been repeated studies that show fruits and vegetables defending against the harmful effects [49]. Specifically, the beta-carotene that can be found within these food sources can have both beneficial and harmful effects on lung cancer.

A study performed by O'Grady et al. explores the correlations between a variety of micronutrients and incidences of thyroid cancer. While there was no relationship found between selenium intake and the incidence of total thyroid cancer, there was a positive correlation found between an increasing intake of vitamin C and the risk of thyroid cancer or specific subtypes, particularly follicular and papillary [50]. Vitamin C tends to be associated with the improvement and mediation of unusual instances in terms of thyroid hormones. Additionally, no evidence of associations were observed among the risk for thyroid cancer and a number of other vitamins and minerals, such as calcium, vitamin E, vitamin D, folate, magnesium, and zinc [50]. This study, in particular, demonstrates the importance of the idea that micronutrients can affect cancers in diverse manners, as selenium, normally shown to have a preventative effect on most cancers, appears to have less of an effect on thyroid cancer and vitamin C intake tends to have both positive and negative correlations with thyroid cancer. Selenium actually aids in producing thyroid hormones and ensures the appropriate functions of these hormones, while also contributing its antioxidant effects [50].

In terms of breast cancer, the relationship between this specific disease and circulating levels of folic acid within the blood has been frequently studied, only to lead to inconclusive results. Aside from this, folate was perceived to have a preventative effect, and increased intake was associated with a lowered risk of having estrogen receptor negative breast cancer in premenopausal women [51]. Moreover, having higher plasma levels of vitamin B6 and riboflavin proved beneficial in combatting a risk of breast cancer for premenopausal women, while vitamin D allowed for lessened recurrence [51].

Although not studied thoroughly yet, some evidence suggests that the consumption of soya through the diet can have preventative effects for patients with triple negative breast cancer. The mechanism works on increasing the expression of tumor-suppressing genes, while decreasing expression of oncogenes [51]. More extensive research regarding this finding is necessary, but it does indicate that this specific food can have a protective measure against the risk for triple negative breast cancer.

Bladder cancer, developed from risk factors like smoking and the environment, has its own associated vitamins, particularly vitamins C, D, and E, investigated by Chen et al. in a study of close to 200,000 participants. This group studied three different focuses to determine the risk of bladder cancer in terms of the type of administration or delivery of the vitamins: diet with supplementation, supplementation only, or diet without supplementation. The background of this particular study suggested that vitamins C, D, and E have some individual protective effects against tumor development. Vitamin D supposedly inhibits the multiplication of cells and encourages apoptosis in human tumor cells from the bladder in in vitro experiments [52]. Vitamins C and E, as mentioned previously, tend to have better effects in combination. They protect against the development of cancer cells through their antioxidant properties [52]. Contingent on dose-dependent analysis, there was no association found between vitamin C and a risk for bladder cancer, while vitamins D and E from the diet had inverse relationships with the risk of bladder cancer, with an even stronger association among smokers. Conversely, γ-tocopherol, a prominent form of vitamin E found in plant seeds had a positive association with the risk of bladder cancer [52], as well as with lung, colon, prostate, and mammary [53]. Studies show that the gamma-tocopherol acts by trapping reactive oxygen species and creating "side-chain degradation products" that keep specific ring structure together [53].

While vitamin E had a more beneficial influence in the previous study, a few other findings suggest more variability when it comes to the vitamin E compounds. While a majority of vitamin E compounds have antitumorigenic properties for some cancers, such as prostate in this case, controlled trials have shown differing results. A Selenium and Vitamin E Cancer Prevention Trial (SELECT) explored the effects of selenium and vitamin E in respect to prostate cancer [54]. The trial demonstrated that there was a 17% higher incidence of prostate cancer in men who had these micronutrients supplemented daily compared to those who received a placebo [54]. Additional studies found no effect from administered drugs every other day while vitamin E indicated a reduced risk for prostate cancer, mainly among those who smoke. These trials illustrate that vitamins and minerals have varying effects; they can be both synergistic or antagonistic depending on the type of cancer they are associated with and the dosage given [54]. The results of the SELECT trial revealed a higher incidence of prostate cancer from supplemented alpha-tocopherol acetate, a compound of vitamin E, and the men with the highest level of plasma alpha-tocopherol were more likely to be diagnosed with prostate cancer with a selenium supplement [54]. High calcium doses on a daily basis also pose a risk for developing prostate cancer in a similar manner [55].

As mentioned previously, reactive oxygen species and oxidative stress are both factors in damaging cells. Skin cells are privy to these dangers, and UV exposure is a leading cause of skin cancer development, aside from other factors like genetics, as it