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1 Introduction

Summary and Quick Facts for Cancer Adjuvant Therapy

- Adjuvant cancer therapies are used to support and enhance the effects of primary cancer therapies in eradicating or reducing cancer's burden on the body, and to help prevent cancer recurrence and increase survival. For example, surgery to remove a brain tumor would be a primary therapy and chemotherapy given before, during or after the operation to help stop the cancer from coming back would be adjuvant therapy.
- Although adjuvant cancer therapy usually refers to conventional cancer treatments, the term can also refer to evidence-based integrative interventions used with the same goals. The intention of this protocol is to review integrative and novel therapies, including natural interventions and the off-label use of some common drugs, which have potential value in the setting of adjuvant cancer care.
- There are many integrative therapies that may be helpful in adjuvant cancer care; however, not all are appropriate for everyone. Although elimination of cancer is ideal, attaining equilibrium may be equally effective in terms of patient longevity and quality of life.

Adjuvant cancer therapies are used to support and enhance the effects of primary cancer therapies in eradicating or reducing cancer's burden on the body, and to help prevent cancer recurrence and increase survival. For example, surgery to remove a brain tumor would be a primary therapy, and chemotherapy given before, during, or after the operation to help stop the cancer from coming back would be adjuvant therapy.

Although *adjuvant cancer therapy* usually refers to conventional cancer treatments, the term can also refer to evidence-based integrative interventions used with the same goals. For instance, integrative interventions intended to improve immune function before and after cancer surgery can be considered adjuvant therapies.

The intention of this protocol is to review integrative and novel therapies, including natural interventions and the off-label use of some common drugs, which have potential value in the setting of adjuvant cancer care.

This protocol should be reviewed in conjunction with other relevant protocols, including:

- **Chemotherapy**
- **Radiation Therapy**
- **Cancer Surgery**
- **Cancer Immunotherapy**
- **Repurposing Drugs As Adjuvant Cancer Therapies**
- **Cancer Treatment: The Critical Factors**
- Protocol(s) specific to the type of cancer appropriate for the reader's situation

2 Background: Cancer Biology in the Context of Adjuvant Therapy

Cancer has a unique place in medicine. In 1971, President Nixon declared war on cancer and signed the National Cancer Act into law (National Cancer Institute 2016). For decades, this adversarial tone took us down a path that aimed to find "better bombs" (chemotherapy and radiation), rather than to try to understand the characteristics of this "enemy."

Through advances in scientific techniques and our ability to collect and analyze data, more is known about this "enemy" today than ever before. These developments have helped uncover much about how natural interventions may affect cancer.

Prevention of Cancer Recurrence

There are important biological differences between preventing cancer from developing in the first place (carcinogenesis) and preventing cancer from growing back (recurrence). The goal of adjuvant therapies is to prevent recurrence by controlling the growth of cancer cells that may be present already in the body.

The *tumor microenvironmen*t is the area around a tumor. It consists of cancer cells and non-cancerous cells, along with many other biological substances. The components in the tumor microenvironment influence whether or not the cancer cells will divide (Arvelo 2016). The tumor microenvironment presents many opportunities for adjuvant therapy (Balkwill 2012; Li 2007; Wang 2017). A key goal of adjuvant cancer therapy is to maintain a microenvironment that is not conducive to the growth of cancer and instead promotes its dormancy.

Immune Control of Cancer—Three Phases

It is now accepted that cancer cells arise in the body more often than previously thought, and that immune surveillance plays a key role in keeping them in check. Through a process called *immunoediting*, interactions between the immune system and cancer cells result in three possible outcomes (Schreiber 2011; Mittal 2014):

1. *Elimination*. Elimination is the successful removal of cancer cells by the immune system.
2. *Equilibrium*. Equilibrium is a dormant state in which some cancer cells have not been completely destroyed, but are not growing.
3. *Escape*. In this scenario, cancer cells have escaped immune control and begin to grow. Eventually, these cancer cells may be discovered as a tumor. Many emerging cancer immunotherapies target immune pathways that prevent escape from occurring (Beatty 2015).

Although elimination of cancer is ideal, attaining equilibrium may be equally effective in terms of patient longevity and quality of life. As the originators of the concept of immunoediting themselves wrote, "Equilibrium … may restrain outgrowth of occult cancers for the lifetime of the host" (Schreiber 2011).

The Role of Inflammation

Acute (short-term) inflammation is necessary for health. Acute inflammation allows us to heal injuries, repair wounds, and overcome infections. The key to the benefits of acute inflammation in these scenarios is that it eventually resolves (Serhan 2005). Chronic systemic inflammation causes ongoing tissue damage and is associated with many chronic diseases, including atherosclerosis and cardiovascular disease (Castro 2017; Tuttolomondo 2012; Tsoupras 2018), insulin resistance and type 2 diabetes (Caputo 2017), dementia (Walker 2017), depression (Berk 2013), sarcopenia (age-related muscle loss) (Dalle 2017), osteoporosis (Pietschmann

2016), and chronic kidney disease (Machowska 2016), as well as cancer (Leonardi 2018).

Minimizing systemic inflammation is an important goal of treatments to address chronic degenerative diseases in general, and cancer specifically (Castro 2017; Franceschi 2014). Accomplishing this is particularly challenging in cancer patients and survivors, because conventional cancer treatments often promote inflammation (Scuric 2017; Vyas 2014).

NF-kappaB is a protein complex that influences many aspects of cellular activity by regulating more than 150 genes involved in inflammation, cell survival, and immune function. Chronic activation or dysregulation of NF-kappaB signaling is a critical factor in cancer and other chronic diseases (Taniguchi 2018; Panday 2016). NF-kappaB overactivation is involved in cancer onset, growth, and metastasis, and it contributes to treatment resistance in cancer cells (de Castro Barbosa 2017). NF-kappaB is thus an attractive target to control the progression of cancer (Zeligs 2016; Durand 2017).

A wide range of natural compounds have been shown to reduce the activity of NF-kappaB. One well-studied natural agent is the polyphenol curcumin (Aggarwal 2007). Curcumin is found in the root of turmeric, and provides the familiar orange color of curry spice blends. Interestingly, many other compounds from spices have been found to inhibit NF-kappaB, including capsaicin, quercetin, piperine, black cumin oil, and thyme (Aggarwal 2007; Oliviero 2016; Agbaria 2015; Samykutty 2013; Chopan 2017; Comalada 2005; Majdalawieh 2017). The effects of these compounds may be a factor in the much lower cancer rates seen in some countries where these spices are consumed daily, such as India (Kunnumakkara 2018). A small study examined a combination of curcumin and quercetin in five patients with familial adenomatous polyposis, a hereditary condition characterized by hundreds of precancerous colon polyps. After six months taking 480 mg of curcumin and 20 mg of quercetin three times daily, all five participants had a decrease in the number and size of polyps in their colon. Overall, the average number of polyps decreased by 60.4% and the average size decreased by 50.9% (Cruz-Correa 2006).

Some other examples of natural agents that have been shown to inhibit NF-kappaB include chrysin, aloe, resveratrol, and epigallocatechin gallate (green tea extract; EGCG) (Tőzsér 2016; Ren 2013; Singh 2011).

Epigenetics

Epigenetics is the study of how changes happen in gene function, and how those changes are passed on through cell division and to offspring (Deans 2015). In practice, epigenetic regulation dictates whether genes get expressed (turned on) or silenced (turned off). Epigenetic changes over a lifetime due to factors related to diet, lifestyle, and environmental exposures influence cancer risk (Daniel 2015; Bishop, Ferguson 2015). Furthermore, there is mounting evidence that epigenetic dysregulation leading to widespread modification of gene expression in cancer cells plays a critical role in all stages of tumor progression (Timp 2013). Unlike genetic mutations, epigenetic modifications are potentially reversible, making them especially compelling as targets of conventional and natural therapies (Schnekenburger 2012; Hascher 2014). In fact, natural agents such as green tea, resveratrol, curcumin, lycopene, soy isoflavones, and others appear to improve cellular function through epigenetic mechanisms (Gerhauser 2012; Shukla 2014).

Tumor suppressor genes are segments of the genetic code that prevent and interrupt malignant changes in cells. If a tumor suppressor gene becomes damaged through genetic mutation or is inactivated through epigenetic mechanisms, cancer can develop and grow unchecked (Lee 2010; Morris 2015). Perhaps the best-known tumor suppressor gene is p53, which is mutated in more than 50% of human cancers (Parrales 2015). The polyphenols curcumin, resveratrol, and green tea catechins can reactivate p53 through epigenetic mechanisms in some circumstances (Thakur 2016; Gupta 2012; Das 2015; Thakur 2012; Hardy 2011; Boyanapalli 2015). Similarly, natural compounds may help reactivate other tumor suppressor genes that have been silenced through epigenetics (Dammann 2017; Meeran 2010; Pan 2013; Kim 2016).

Cancer Stem Cells

Cancer stem cells (CSCs) are cancer cells that have the properties of stem cells—namely, they can give rise to new cancer cells. CSCs may arise from existing CSCs or from fully differentiated cancerous cells through a process called dedifferentiation (Batlle 2017). They are thought to be responsible for treatment resistance, metastasis, and recurrence (Peitzsch 2017; Kleffel 2013; De Francesco 2018; Phi 2018).

CSCs are notorious for using multiple survival strategies to evade destruction by chemotherapy and radiation, such as pumping drugs out of their interiors, repairing DNA damage, resisting cell death signals, and entering a quiescent or suspended state (Zeuner 2015; Zhang, Feng 2017; Chen W 2016; Hu 2012). Several plant polyphenols have been shown to increase the sensitivity of CSCs to the tumor killing effects of chemotherapy or radiation, including curcumin (Kanwar 2011), apigenin (Erdogan 2017), and resveratrol (Mohammed 2018).

Targeting CSCs directly with natural therapies is an area of great interest in cancer research (Singh 2017). Agents such as lycopene, resveratrol, garlic, genistein, quercetin, and ginger (Mosehly 2015; Shen 2013; Jung 2014), as well as curcumin alone (Zhu JY 2017) and combined with green tea (Chung 2015), have shown promise in interfering with survival and self-renewal processes of CSCs (Singh 2017). Because CSCs also continue an inflammatory state in the tumor microenvironment by increasing activation of NF-kappaB, agents that block NF-kappaB might help disrupt tumor promotion by CSCs (Vazquez-Santillan 2015; Rinkenbaugh 2016).

3 The Value of Blood Testing in Monitoring Cancer

Blood tests can be helpful in monitoring the effectiveness of cancer therapy when used along with imaging and careful examination.

Tumor Markers

Some cancers produce molecules called tumor markers that can be detected in the blood and used to assess cancer activity. Tumor marker tests are not specific, however. This means that, in some cases, non-cancerous sources of a marker can increase the concentration of the marker and produce a false-positive result of cancer. Tumor marker tests should always be interpreted by a qualified healthcare provider.

Table 1. Types of cancer and tumor markers used for assessment

Type of Cancer	Tumor Marker
Breast cancer	Cancer antigen (CA) 27.29, CA15-3, carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125)
Bladder cancer	Bladder tumor antigen (BTA), NMP22 (urine tests); CA15-3 (blood test)
Colon, rectum, stomach, and cancers in some other organs	CEA, CA 19-9
Leukemia, lymphoma	Lactate dehydrogenase (LDH)
Liver cancer	Alpha fetoprotein (AFP)
Lung	Cytokeratin fragment 21-1
Ovarian cancer	CA-125, CEA, AFP
Prostate cancer	Prostate-specific antigen (PSA), prostatic acid phosphatase (PAP)
Pancreatic cancer	CA 19-9, CEA
Testicular cancer (and other germ cell	AFP, beta-human chorionic gonadotrophin (beta-HCG)

tumors)	
Thyroid cancer	Thyroglobulin, calcitonin (medullary form only)
Neuroendocrine tumors	Chromogranin A

(Vachani 2018)

Fasting Blood Glucose and Hemoglobin A1C

Hyperglycemia (high blood glucose level) and type 2 diabetes have been associated with worse outcomes in studies of people who have, or have had, various types of cancer (Ryu 2014; Storey 2012; Gallagher 2015; Healy 2015). In addition, hyperglycemia is associated with lower immune function (Jafar 2016; Turina 2005) and may increase the risk of infections in patients with cancer (Storey 2012). Both cancer and cancer treatment frequently cause hyperglycemia; therefore, it is important to monitor glucose control using blood tests such as fasting blood glucose and hemoglobin A1C (Sherwani 2016; Storey 2017; Gallo 2018). Although the normal range for fasting blood glucose is 65–99 mg/dL, and hemoglobin A1C is normal below 5.6% (NIH 2018c; NIH 2018d), some evidence suggests that glucose levels 80 – 86 mg/dL and a hemoglobin A1C of 5 - 5.4% may be ideal.

Lactate Dehydrogenase

Cancer cells have long been noted to metabolize glucose into energy differently from normal cells: normal cells mainly use a series of reactions called oxidative phosphorylation that requires oxygen and yields a high amount of energy per unit of glucose; cancer cells mainly use a less efficient pathway called glycolysis that does not require oxygen and produces lactate as an end product. This metabolic phenomenon, in which cancer cells depend on glycolysis even in the presence of oxygen, is known as aerobic glycolysis or the Warburg effect and results in high glucose demand and an increased production of lactate by cancer cells (Liberti 2016; Wulaningsih 2015).

Lactate dehydrogenase (LDH) is an enzyme that is used in the final step in glycolysis. LDH is overproduced in cancer cells and higher blood LDH levels are seen when cancer cells are active. High levels have been associated with worse outcomes in patients with several cancer types including lung, colorectal, prostate, gastroesophageal, gynecologic, kidney, and some breast cancers, as well as lymphoma and melanoma (Wulaningsih 2015; Liu R 2016; Li G 2016).

Normal values for the LDH test are 105–333 IU/L, but can vary slightly between laboratories. Importantly, several conditions other than cancer can cause LDH levels to rise (NIH 2018i), so high levels do not always mean that cancer cells are active in the body.

Alkaline Phosphatase

The enzyme alkaline phosphatase (ALP) is highly concentrated in cells of the liver and bones, two organs to which various cancer types often spread. An elevated ALP level in the context of cancer is not necessarily helpful in characterizing primary tumors, but suggests there may be metastases to the liver or the bones (Siddique 2012; D'Oronzo 2017). In a large meta-analysis of 19 studies including 3,268 patients with various solid tumors, higher ALP levels were significantly correlated with bone metastases (Du 2014). ALP may be useful in addition to the tumor marker cancer antigen 15-3 (CA15-3) for monitoring the recurrence of breast cancer (Keshaviah 2007). Elevated ALP levels are also considered a reliable indicator of bone metastasis in men with prostate cancer (Kamiya 2012). One study suggested that ALP levels of more than 90 U/L in men with newly diagnosed and untreated prostate cancer may indicate the cancer has spread to the bone, warranting a bone scan (Wymenga 2001). ALP is reported on routine metabolic panels as well as liver enzyme panels. If the ALP level is high, isoenzymes can be ordered to distinguish the source of the ALP (liver vs. bone) (Lowe 2017).

The normal range for ALP can vary between laboratories, but is generally 44–147 IU/L. ALP levels are normally higher in children during growth spurts and pregnant women, and can rise due to a number of conditions affecting bones or liver.

Vitamin D

Having a higher vitamin D level at or near the time of a cancer diagnosis results in an improved chance of survival

(Li M 2014). One large meta-analysis concluded that higher vitamin D levels were correlated with a 26% lower risk of death and a 16% lower risk of disease progression in patients with cancer (Vaughan-Shaw 2017). In addition, vitamin D insufficiency and deficiency may have other negative health effects in patients with cancer, potentially increasing risks of infection, depression, pain, and low quality of life (Bjorkhem-Bergman 2016). It is therefore recommended that patients with cancer have their vitamin D status tested periodically.

Vitamin D status is assessed by measuring levels of 25-hydroxyvitamin D. 25-Hydroxyvitamin D levels of 30–50 ng/mL is generally considered healthy; levels of 20–29 ng/mL indicate insufficiency; and, levels below 20 ng/mL indicate deficiency (NIH 2018b; Holick 2011).

Other Laboratory Measures

Common complications and side effects of cancer and its treatment, such as fatigue, neuropathy, immune suppression, and liver or kidney damage, can linger for years. An annual complete blood count (CBC) and blood chemistry test to check for anemia, immune competence, liver and kidney function, and blood glucose and lipid regulation is recommended in everyone who has had a diagnosis of cancer (Bhatia 2017; Han 2017). Additional specific tests for nutrients that are commonly deficient after cancer treatment may include an iron panel and zinc, folate, and vitamin B12 levels (Gilreath 2014; Costello 2012).

Inflammatory Markers

Managing systemic inflammation may improve health and prognosis in people with cancer. Several blood tests can help gauge the level of systemic inflammation in patients with a history of cancer (Sylman 2018; Gu 2017):

- **C-Reactive Protein (CRP).** CRP is a pro-inflammatory protein made in the liver that can be measured in the blood. High CRP levels have been associated with worse outcomes in a variety of cancers (Sylman 2018).

  While CRP production increases with inflammation, production of albumin, another protein made in the liver, often decreases. Tracking CRP and albumin at the same time may provide a better measure of systemic inflammation. A tool based on CRP and albumin levels, called the Glasgow Prognostic Score, has a proven track record in predicting outcomes in patients with a variety of cancers (Dolan 2017; Simmons 2017). The use of CRP to albumin ratio has also been shown to be useful for predicting prognosis in some patients with cancer. A meta-analysis of 25 studies assessing the use of the CRP to albumin ratio found that a higher ratio correlates with poorer outcomes for all cancers, except colorectal cancer (Xu 2017). Fish oil, containing omega-3 fatty acids, has been found to lower CRP levels and raise albumin levels, having a positive effect on the CRP to albumin ratio, in patients with gastrointestinal cancers (Mocellin 2013; Yu 2017; Mocellin 2016).

- **Platelets.** Platelets are blood cells that are well known for their role in blood clotting. Platelets also influence the inflammatory response by releasing both pro- and anti-inflammatory chemicals and interacting with immune cells and microbes (Pankratz 2016; Thomas 2015; Kapur Semple 2016; Franco 2015). Platelets can also be recruited and activated by tumor cells and are involved in stimulating the growth and spread of cancers (Li N 2016; Meikle 2017). High blood levels of platelets have been associated with poorer outcomes in many cancers (Riedl 2014). A platelet count is reported as part of a CBC and is normally 150–400 × 109/L (NIH 2018f).

- **Fibrinogen.** Fibrinogen is a protein that, along with platelets, is involved in blood clotting and inflammation and plays a role in cancer progression and metastasis (Zheng 2009; Davalos 2012; Palumbo 2000). A high fibrinogen level may be a marker for poor prognosis in patients with many different cancers (Perisanidis 2015). Fibrinogen levels are not checked as part of routine laboratory testing but can be easily added. A normal value is 200–400 mg/dL, or 2–4 grams/L.

4 Nutrients

There are many integrative therapies that may be helpful in adjuvant cancer care; however, not all are appropriate for everyone. It is always important to consult with a healthcare provider before undertaking a supplement program, especially if you have cancer.

The following interventions are listed alphabetically and not in order of importance.

Aloe

Topical aloe (*Aloe vera* and other species) may help heal mucous membranes damaged by radiation treatment for cancer. In one randomized controlled trial, 20 patients with rectal inflammation following radiation therapy for pelvic cancers were treated with either 1 gram of topical 3% *Aloe vera* ointment or placebo twice daily for four weeks. The aloe ointment was more effective than placebo at relieving rectal symptoms and related impairment (Sahebnasagh 2017). In another trial, an *Aloe vera* mouthwash was as effective as a standard mouthwash containing benzydamine, a locally acting nonsteroidal anti-inflammatory drug, at preventing radiation-induced oral mucositis in patients with head and neck cancer being treated with radiation therapy (Sahebjamee 2015). Oral mucositis, or inflammation of the mouth, is a painful and often severe side effect of radiation therapy in patients with head and neck cancer (De Sanctis 2016).

Taking aloe orally may sensitize cancer cells to chemotherapy. In one randomized controlled trial, 240 participants with various types of metastatic solid tumors were assigned to receive standard chemotherapy alone or with 10 mL of a solution containing 300 grams of fresh, crushed candelabra aloe (*Aloe arborescens*) leaves three times daily. Participants receiving the aloe solution had a partial or complete treatment response rate of 34%, whereas participants treated with chemotherapy alone had a treatment response rate of 19% (Lissoni 2009). In another trial, 50 individuals with untreatable advanced cancers were randomized to receive 20 mg of melatonin per day alone or with 1 mL of *Aloe vera* tincture twice daily. The survival rate after 1 year was 38% in the melatonin plus aloe group compared with 15% in the group receiving only melatonin (Lissoni 1998).

Other research suggests that aloe may increase the absorption of vitamins C and E and prolong the time that they stay in the blood (Vinson 2005), an effect that could also benefit patients with cancer.

Apigenin

Apigenin is a polyphenol found in citrus fruits, celery, culinary herbs like parsley and thyme, and many commonly used medicinal herbs including chamomile, peppermint, lemon balm, and yarrow (Kowalczyk 2017; Hostetler 2017). It has well-known anti-inflammatory and antioxidant properties, and has demonstrated anticancer effects such as inducing tumor cell death, inhibiting tumor cell movement and invasion, preventing tumor cell proliferation, and stimulating the immune response in preclinical studies (Yan 2017; Sung 2016; Tong 2013).

In one clinical trial, patients who had undergone surgery for colorectal cancer were monitored with follow-up colonoscopies for three to four years while receiving either a supplement providing 20 mg each of apigenin and EGCG per day or no supplement. An abnormal colonoscopy finding (a benign tumor) was found in only 7% (one of 14) of the patients receiving the apigenin/EGCG supplement, compared with 47% (seven of 15) of patients who did not receive the supplement (three cancer recurrences and four benign tumors) (Hoensch 2008).

Astragalus

Astragalus is a Chinese medicinal herb with a broad spectrum of actions that may protect against cancer (Li X 2014). In vitro and animal studies suggest that astragalus and its constituents may have anticancer effects related to their ability to increase the activity of the tumor suppressor gene p53 (Ye 2011; Cai 2018; Zhang, Han 2015; Yang 2014).

In a 2003 study, outcomes in patients with advanced lung cancer receiving astragalus injections in conjunction with standard chemotherapy were compared with those of similar patients receiving chemotherapy alone. Patients receiving astragalus injections had a better response to treatment, longer remission, a higher one-year survival rate (46.75% compared with 30.0%), and greater improvements in quality of life (Zou 2003). A review of 34 trials with a combined total of 2,815 participants with non-small cell lung cancer concluded that adjuvant treatment with astragalus may increase the effectiveness of platinum-based chemotherapy agents, improving tumor response and increasing survival at one and two years (McCulloch 2006). Similarly, a review of 17 randomized trials with a total of 1,552 participants found that astragalus-based herbal adjuvant therapies improved overall efficacy and decreased toxicity of platinum-based chemotherapy in patients with non-small cell lung cancer. Specifically, they found the addition of astragalus reduced risk of death by 27%, 67%, and 70% after one, two, and three years of treatment, respectively (Wang SF 2016). A review of 29 studies evaluating the use of astragalus-containing herbal preparations during radiation treatment for non-small cell lung cancer indicated that astragalus may decrease radiation toxicity, improve its effectiveness, and increase the likelihood of survival (He 2013).

Carotenoids

Carotenoids are yellow, orange, and red plant pigments found in high concentrations in colorful fruits and vegetables. The carotenoid family includes more than 700 compounds, about 50 of which are normally found in the diet (Fiedor 2014). Some carotenoids, such as α-carotene, β-carotene, and α-cryptoxanthin, are referred to as provitamin A carotenoids because they can be used to make vitamin A in the body. Vitamin A is needed to protect fatty tissues and lipid molecules from oxidative damage. Other carotenoids, such as lycopene, lutein, zeaxanthin, and astaxanthin, are not converted to vitamin A, but have their own anti-inflammatory and free-radical-scavenging properties (Murillo 2016; Tang 2010). Carotenoids have demonstrated anticancer properties both due to, and independent of, their effect on vitamin A status (Tanaka 2012; Olson 1989; Burri 2015; Tang 2010). Numerous studies have indicated that eating a diet high in carotenoids is correlated with lower risks of several types of cancers (Tanaka 2012; Milani 2017; Woodside 2015; Xavier 2016).

While vitamin A is toxic to the liver when taken in large doses, provitamin A carotenoids are not. Absorption and conversion of carotenoids into vitamin A appears to be carefully regulated, and excess carotenoids are stored in the skin. Very large amounts can cause a harmless yellow-orange skin pigmentation, visible mainly in the palms and soles (Allen 2002; Blomhoff 2001). Because carotenoids are fat-soluble, their absorption is increased when taken with dietary fats (Tanaka 2012; Wu H 2015).

Astaxanthin is a carotenoid that is particularly concentrated in microalgae and the marine organisms that eat them, such as salmon, shrimp, and crab (Zhang, Wang 2015; Ambati 2014). Astaxanthin has demonstrated anticancer effects against a variety of cancers in vitro and in animal models (Zhang, Wang 2015).

Astaxanthin reduces inflammatory and oxidative cell damage, and may induce tumor cell death (Zhang, Wang 2015; Wu J 2015). It has been shown to inhibit NF-kappaB, an inflammatory molecule involved in malignant cell activities (Zhang, Wang 2015; Nagendraprabhu 2011; Xia 2014). Astaxanthin may also prevent tumor progression by interfering with other cancer cell proliferation signals (Zhang, Wang 2015; Wu 2016; Li 2015), improving dysfunctional intercellular communication (Bertram 2005), and inhibiting enzymes that break down extracellular material and allow for tumor growth (Kowshik 2014; Chen YT 2017). Additionally, astaxanthin has multiple beneficial effects on the immune system, boosting the function of natural killer cells that patrol for cancerous cells (Park 2010; Lin 2015).

Lycopene is a carotenoid found mainly in tomatoes and tomato products but is present in other pink and red fruits, such as watermelon and pink grapefruit, in smaller amounts. Higher tomato consumption and higher blood levels of lycopene have been associated with a reduced risk of prostate cancer (Wang Y 2015; Rowles 2017), as well as a range of other cancers (Gajowik 2014). Findings from animal and laboratory research suggest lycopene has multiple anticancer effects, including interfering with cancer cell proliferation, promoting cancer cell death, decreasing inflammation, inhibiting new blood vessel growth, and preventing metastasis (Gajowik 2014; Sahin 2017; Bhatia 2015).

A number of clinical trials have investigated the possible benefits of lycopene as an adjuvant therapy in men with prostate cancer. A preliminary trial included 20 men with metastatic prostate cancer that was progressing despite prior treatment. Participants received 10 mg of lycopene daily for three months. One participant achieved a complete response, defined as a reduction of PSA to less than 4 ng/mL and the absence of any sign of the disease for at least eight weeks; six had a partial response, defined as a 50% reduction in PSA and alleviation of bone pain, if present; ten had disease stabilization; and three had progression of their cancer. Importantly, ten patients with bone pain were able to reduce their daily use of pain-suppressing drugs (Ansari 2004).

In a randomized controlled trial, 15 men with prostate cancer received 30 mg of lycopene daily for three weeks prior to prostatectomy, and 11 similar men who were untreated for three weeks before surgery were included as controls. Lycopene appeared to have positive effects during the pre-op period: prostate samples revealed that the cancer had spread beyond the prostate in 82% of controls but only 27% of the men taking lycopene. Moreover, tumor volume was less than 4 mL in 84% of lycopene-treated men, compared with 45% of controls (Kucuk 2001).

Another trial included 54 participants with metastatic prostate cancer who had undergone surgical removal of the testicles to eliminate testosterone stimulation of their cancer. Half of the participants were given 4 mg of lycopene daily for two years, and the others were not. At the end of the trial, 78% of the men receiving lycopene

had PSA levels below 4 ng/mL, compared with only 40% of the men not receiving lycopene. Additionally, the lycopene group had a higher survival rate than the control group (87% vs. 78%) (Ansari 2003). In a study in 71 men with rising PSA levels after initial treatment for prostate cancer, 30 mg of lycopene per day, with or without soy isoflavones, led to stabilization of PSA levels in most participants (Vaishampayan 2007).

A clinical trial that examined nutritional interventions in 79 patients with prostate cancer determined that the cancer's aggressiveness and an individual's ability to absorb and maintain high levels of lycopene in the blood were factors that influenced the effect of the lycopene. The participants consumed either tomato products containing 30 mg lycopene per day, the same tomato foods plus selenium and omega-3 fatty acid supplements, or a usual diet for three weeks before prostatectomy. A positive effect of the two intervention diets on PSA levels was seen only in men whose surgeries revealed non-metastasized cancer and men with the greatest increases in blood levels of lycopene, and the effect was more pronounced in men who also achieved the highest levels of selenium and omega-3 fatty acids (Paur 2017).

Another carotenoid, beta-cryptoxanthin, may also promote prostate health. A recent study looking at dietary intakes of lycopene and beta-cryptoxanthin showed that higher intake of either was correlated with less aggressive prostate cancer (Antwi 2016). A clinical trial examined the effects of oral lycopene supplementation in patients with advanced brain tumors known as gliomas. The study participants were randomized to receive radiation therapy along with either 8 mg of lycopene daily or placebo. After an average of 50 weeks, 28% of those in the lycopene group achieved a complete response and 16% achieved a partial response, but in the control group, only 8% achieved complete response and another 8% achieved a partial response. It was further noted that the time to progression was longer in the lycopene group (about 41 weeks) than in the placebo group (about 27 weeks). The authors concluded that lycopene may have therapeutic benefits as an adjuvant therapy for managing high-grade gliomas (Puri 2010).

Lycopene may reduce the toxicity of other cancer therapies. In a trial that included 120 patients receiving the widely used chemotherapy drug cisplatin, the addition of lycopene, at a dose of 25 mg every 12 hours beginning 24 hours before and ending 72 hours after receiving cisplatin, preserved some markers of kidney function compared with cisplatin treatment alone. Kidney toxicity is a potentially life-threatening side effect that frequently limits the use of cisplatin (Mahmoodnia 2017).

BETA-CAROTENE AND CANCER: A HISTORY OF CONTROVERSY

The safety of beta-carotene supplements in people at high risk of lung cancer came into question in the late 1990s. The concern stemmed from two large studies examining the possible protective effect of beta-carotene supplements in individuals at high risk of lung cancer. One of the trials, known as the Carotene and Retinol Efficacy Trial or CARET, was conducted in the United States and compared 30 mg (50,000 IU) of beta-carotene plus 7.5 mg (25,000 IU) of vitamin A (retinyl palmitate) with placebo in current or former smokers and asbestos-exposed workers (Omenn 1994). The study was halted early because of a 28% higher rate of lung cancer and a 17% higher rate of death in the group taking beta-carotene and vitamin A (Omenn 1996). The other trial, known as the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study, or Finnish Smokers Study, was conducted in Finland. Participants in this study were male smokers and received 50 mg (75 IU) of vitamin E (alpha-tocopherol), 20 mg (33,333 IU) of beta-carotene, the two combined, or placebo. Vitamin E had no effect on lung cancer incidence but beta-carotene was associated with a 16% increased risk (The ATBC Cancer Prevention Study Group 1994; Albanes 1996). Monitoring participants after termination of these trials revealed that the negative impact of beta-carotene supplementation on lung cancer risk may have persisted for as long as three years after stopping the supplements (Duffield-Lillico 2004).

The findings from these trials suggest excess beta-carotene from supplements may interact with known carcinogens (smoke and asbestos) in ways that exacerbate their cancer-promoting effects. Researchers have since found that beta-carotene can in fact exert DNA-damaging pro-oxidant effects in lung tissue already under a high degree of oxidative stress due to immune cell activation (van Helden 2009).

Nevertheless, high intake of carotenoid-rich foods continues to appear to be safe and cancer-protective. A follow-up analysis of the data from CARET showed that higher fruit and vegetable intake had a protective effect in participants randomized to the placebo group, but not the supplement group (Neuhouser 2003). In another

study, dietary intakes of beta-carotene, alpha-carotene, beta-cryptoxanthin, and lycopene were correlated with a lower risk of lung cancer in male smokers (Shareck 2017). A meta-analysis of studies concluded that higher blood levels of total carotenoids, alpha-carotene, beta-carotene, lycopene, and vitamin A are each associated with lower lung cancer risk, but could not draw conclusions about differing effects in asbestos workers or smokers versus nonsmokers (Abar 2016).

Until more is known about the causes for the findings from CARET and the ATBC Study, it is prudent for smokers and others at high risk of lung cancer to avoid supplementing with very large doses of beta-carotene. Multivitamins generally contain beta-carotene in safe doses ranging from one tenth to one one-hundredth the amounts used in these studies (Tanvetyanon 2008).

Chrysin

Chrysin is a polyphenol found in a variety of plants, and is particularly concentrated in the bee products honey and propolis. Like many other flavonoids, chrysin has free-radical scavenging, anti-inflammatory, antiviral, and anticancer activities (Mani 2018). Although few human studies have been conducted with chrysin, animal studies and in vitro studies suggest that it may protect against DNA damage (George 2017) and modulate several cell-signaling pathways involved in cancer progression, including those affecting inflammation, cell survival, cell growth, new blood vessel growth, and metastasis (Kasala 2015).

Chrysin, like other polyphenols, is poorly absorbed in the digestive tract; however, new techniques are being developed to improve its availability and uptake by cells, sustain higher levels in the blood over longer periods of time, and enhance its antitumor activities (Davatgaran-Taghipour 2017; Walle 2001).

Chrysin has been shown in human cell cultures to inhibit aromatase, an enzyme that converts testosterone into estrogen in both men and women (Campbell 1993; van Meeuwen 2008; Mohammed 2011). Aromatase inhibition is an important strategy in the treatment of tumors that are stimulated by estrogen, such as many breast cancers (Pistelli 2018; Manna 2016). If chrysin or a molecule derived from chrysin is found to inhibit aromatase in humans, it may be especially useful as an adjuvant therapy in people with estrogen-sensitive cancers (Mohammed 2011).

Coenzyme Q10

Coenzyme Q10, or CoQ10, is a biomolecule with a high capacity to reduce free radicals. It is found in cell membranes throughout the body and plays an integral role in cellular mitochondrial energy production through the oxidative phosphorylation pathway. CoQ10 is produced via the same chemical pathway that results in cholesterol production (Hernández-Camacho 2018).

Statin drugs, which are used primarily to lower high cholesterol levels, inhibit an enzyme on the cholesterol-synthesis pathway. While this action of statins may also suppress cancer progression, it poses the unintended consequence of interfering with CoQ10 production (Hernández-Camacho 2018; Muller 2017). Supplementing with CoQ10 has been shown to restore CoQ10 levels in statin users and mitigate some negative consequences of statin therapy (Skarlovnik 2014; Lee BJ 2013; Toth 2017). In addition, CoQ10 may have independent anticancer benefits.

Interestingly, even in the absence of statin therapy, people with cancer are more likely to have CoQ10 deficiency than healthy individuals. Dr. Karl Folkers, a pioneer in the study of CoQ10, was perhaps the first to demonstrate a relationship between low CoQ10 levels and cancer. A subsequent study noted a correlation between the degree of CoQ10 deficiency and breast cancer prognosis (Folkers 1997; Jolliet 1998). Dr. Folkers also showed that CoQ10 can improve a marker of anticancer immune function (Folkers 1991), and reported several case examples in which cancer progression was halted after treatment with CoQ10 (Lockwood 1995; Folkers 1993). A more recent study included 41 patients with various end-stage cancers who received CoQ10 along with a combination antioxidant supplement. Thirty-one of the subjects (76%) lived longer than predicted while the other 10 (24%) did not (Hertz 2009).

One of the mechanisms behind the apparent anticancer effects of CoQ10 may be its anti-inflammatory activity. In one trial, 41 patients undergoing surgery for liver cancer took either 300 mg CoQ10 or placebo daily for 12 weeks.

Blood levels of markers of oxidative stress and inflammation were significantly decreased in patients taking CoQ10 (Liu HT 2016).

CoQ10 may be of particular benefit for women taking the anti-estrogen drug tamoxifen. In one clinical trial, a combination of CoQ10 (100 mg/d), riboflavin (10 mg/d) and niacin (50 mg/d) was added to tamoxifen therapy in women with breast cancer. Tamoxifen alone, taken for one year or longer, reduced levels of two tumor markers (carcinoembryonic antigen [CEA] and cancer antigen 15-3 [CA15-3]) as well as markers of inflammation and of new blood vessel growth. The addition of the CoQ10 combination supplement resulted in further decreases in these levels after 45 days and again after 90 days, suggesting that the supplement may have enhanced the effect of tamoxifen. The supplement also appeared to trigger DNA-protective and epigenetic changes indicating less cancer in the body and better prognosis (Premkumar 2007a, 2007b, 2008a, 2008b).

CoQ10 may be helpful for patients treated with chemotherapy agents that are toxic to the heart, most notably doxorubicin (Adriamycin or Doxil). Heart muscle damage can develop slowly and can manifest 15 years or more after treatment (Kumar 2012). CoQ10 has been shown to protect against heart muscle damage in animals exposed to doxorubicin (Chen PY 2017; Mustafa 2017; Sugiyama 1995). Other research suggests CoQ10 does not interfere with the anticancer effects of doxorubicin. In fact, CoQ10 may increase tolerance to doxorubicin, allowing for longer or higher-dose treatment and enhancing the efficacy of doxorubicin (Conklin 2005). Given the value of CoQ10 in improving heart function and cardiovascular health in general (Sharma 2016), it may be beneficial as a co-treatment during chemotherapy with doxorubicin and is an essential consideration for supporting heart health for years, or even decades, after treatment with a heart-toxic chemotherapy agent (Conklin 2005).

Coffee

Coffee contains many phytochemicals that have demonstrated anticancer properties. Preclinical studies have shown that certain coffee constituents can promote cancer cell death, reduce the ability of cancer cells to invade and spread, reduce new blood vessel growth (which is required for tumors to grow), and improve anticancer immune activity (Gaascht 2015).

Although the data are inconsistent, some studies have found that coffee drinkers are protected against certain cancers. The strongest evidence for the cancer-preventive effects of coffee was found in regard to liver and endometrial cancers (Alicandro 2017; Arab 2010). Coffee may also protect against the most aggressive prostate cancers. In one study that included 47,911 men, drinking six cups or more of caffeinated or decaffeinated coffee daily was correlated with a 60% lower risk of lethal prostate cancer compared with drinking no coffee (Wilson 2011).

Coffee consumption has been associated with better colorectal cancer outcomes in two separate studies. The first study followed 953 people with invasive (stage 3) colorectal cancer. Participants who consumed four or more cups of coffee per day had a 42% lower risk of recurrence or death than non-coffee drinkers. A smaller benefit was seen in participants drinking two to three cups per day; participants drinking one cup or less daily did not derive any colorectal cancer outcome benefits (Guercio 2015).

The second study involved 1,599 participants diagnosed with invasive (stage 1–3) colorectal cancer. Over the course of 7.8 years of follow-up, participants who consumed at least four cups of coffee per day had a 52% lower risk of death due to colorectal cancer than participants who did not drink any coffee. In addition, patients whose intake before and after diagnosis was consistently more than two cups daily had a 37% reduced risk of cancer-related death and a 29% reduced risk of death from any cause than patients consistently drinking less than two cups daily (Hu Y 2018).

Coffee may also affect outcomes in some women with breast cancer. One study included 1,090 women treated surgically for breast cancer. Among a subgroup of participants with estrogen-sensitive cancer receiving tamoxifen followed for three to nine years after surgery, daily coffee intake of two or more cups per day was associated with a lower risk for breast cancer recurrence (Rosendahl 2015). A separate study also found that coffee consumption appeared to lessen the number of recurrences during 3–6 years of monitoring in women taking tamoxifen after breast cancer surgery (Simonsson 2013).

Women carrying breast cancer susceptibility gene (BRCA) mutations, which are linked to breast cancer risk, may derive particular benefit from coffee. A research analysis that included data from 40 clinics in four countries and

involved 1,690 carriers of BRCA1/2 mutations found coffee intake was correlated with lower breast cancer risk, and the protective effect rose with increasing levels of coffee consumption: Compared with women who did not drink coffee, the likelihood of being diagnosed with breast cancer was 10%, 25%, and 69% lower in participants who habitually drank one to three, four to five, and six or more cups of coffee, respectively (Nkondjock 2006).

Conjugated Linoleic Acids

Conjugated linoleic acids (CLA) are a group of fatty acids derived from the essential omega-6 fatty acid, linoleic acid. CLA has been shown in several studies to have anticancer properties. These include decreasing cell proliferation, causing cell death, suppressing metabolic pathways, and inhibiting metastasis (Lehnen 2015; Belury 2002; Lee 2005).

In a preliminary clinical trial, women with breast cancer were given 7.5 grams of CLA per day for at least ten days before surgery. When tumor tissue from surgery was compared with tissue from the original tumor biopsies, markers of cancer cell proliferation were reduced. In addition, CLA appeared to alter regulation of fatty acid synthesis, which may have been a contributing factor in its anti-proliferative effect (McGowan 2013). Other research suggests CLA may reduce the proliferation of estrogen-sensitive breast and endometrial cancer cells by affecting estrogen receptors (Kim 2015; Wang J 2013).

In a randomized placebo-controlled trial, 34 patients with rectal cancer received either three grams of CLA per day or placebo, beginning one week before a six-week regimen of chemotherapy plus radiation therapy. Patients taking CLA had lower levels of inflammatory markers and enzymes involved in tumor progression and metastasis. These findings suggest that CLA may be useful as an adjuvant therapy for rectal cancer (Mohammadzadeh 2013).

Through its actions on fatty acid metabolism, CLA has been shown to increase fat burning and decrease fat deposition in the body (Mądry 2016; den Hartigh 2017; Mizunoya 2005). Healthy body composition, with greater weight from muscle and bone and less from fat, is ideal for limiting systemic inflammation (Lehnen 2015).

CLA has also been found to improve liver function in patients with non-alcoholic fatty liver disease, a metabolic disorder in which fat accumulates on the liver (Ebrahimi-Mameghani 2016). Many cancer survivors have an increased risk for fatty liver, including those who have received high-dose steroids, those on tamoxifen, and those with elevated fasting glucose (Woods 2015; Zhao 2014; Bhatt 2015).

Fish Oil and Omega-3 Fatty Acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the major omega-3 fatty acids found in fish oil. EPA and DHA are incorporated into cell membranes where they help to maintain fluidity, support normal cell membrane activities, are a source for anti-inflammatory compounds, and disrupt membrane structures called lipid rafts. Lipid rafts are discrete regions—composed mainly of cholesterol and saturated fatty acids—which form in cell membranes and affect membrane function. Lipid rafts are thought to play a role in cancer promotion by influencing cell survival, immune cell activation, and the movement of proteins and lipids across the cell membrane (Walker 2015; Calder 2010; D'Eliseo 2016; Turk 2013). Lipid rafts can also harbor proteins that promote cancer growth, known as oncoproteins. DHA has been noted to displace several lipid raft-associated oncoproteins in the laboratory (Lee 2014).

Inflammation is a central mechanism for cancer progression, and omega-3 fatty acids from fish reduce inflammation in multiple ways, including suppressing NF-kappaB, regulating inflammatory enzyme activity, and acting as precursors to molecules that deactivate the inflammatory process (Nabavi 2015; Serini 2017). DHA has also been found to inhibit enzymes needed for glycolysis, reducing the ability of cancer cells to make energy from glucose (Manzi 2015). In addition, omega-3 fatty acids may act epigenetically to alter cancer risk (Weylandt 2015).

Higher intake of omega-3 fatty acids from fish has been associated with lower risks of colon, prostate, and breast cancers in some, but not all, studies (Lee JY 2017; Aucoin 2017; Fabian 2015). Inconsistent findings may be related to genetic differences in the ability to metabolize these fatty acids, differences in baseline intake levels and supplement dosages, and differences in omega-3-to-omega-6 fatty acid intake ratios (Weylandt 2015; Lenihan-Geels 2016).

EPA, DHA, and fish oil have been found to increase cancer cells' sensitivity to, reduce resistance to, and improve

effectiveness of various chemotherapy agents in animal and laboratory models of brain, colorectal, breast, lung, and bladder cancers, as well as leukemia and lymphoma (Corsetto 2017; Song 2016; Hajjaji 2013). EPA and DHA have been shown to induce DNA damage in cancer cells but not normal cells, potentially making cancers more sensitive to chemotherapy and radiation without increasing toxicity to normal tissue (Song 2016; Hajjaji 2013; Cai 2014).

The daily use of oral omega-3 fatty acids for supportive care in patients with cancer continues to hold promise. A controlled clinical trial with 46 participants found that adding 2.5 grams per day of combined EPA plus DHA to standard chemotherapy for advanced non-small cell lung cancer led to better outcomes than chemotherapy alone: participants receiving EPA plus DHA had a higher response rate with greater clinical benefit, and appeared to have better one-year survival rates (Murphy 2011). In another study, 30 patients with colorectal cancer received 2 grams of fish oil, providing 600 mg per day of combined EPA and DHA for 9 weeks during standard chemotherapy or chemotherapy alone. Participants taking the fish oil had a significantly longer time until progression of their disease (Camargo 2016). A research review noted clinical evidence that fish oil fatty acids improve immune activity, prevent loss of muscle mass, and increase quality of life and overall survival in patients with colorectal cancer and pancreatic cancer treated with standard therapies (Eltweri 2017).

Omega-3 fatty acids may reduce negative side effects and toxicities related to cancer treatment. One study found a connection between higher intake of omega-3 fatty acids and lower levels of post-treatment fatigue in breast cancer survivors (Alfano 2012). In a trial including 61 patients with esophageal cancer, taking an enriched nutritional formula providing 900 mg per day of omega-3 fatty acids for 15 days during chemotherapy was associated with fewer mouth ulcers and lower levels of markers of liver damage compared with a nutritional formula providing 250 mg of omega-3 fatty acids (Miyata 2017).

Several studies have shown that omega-3 fatty acids can prevent or reverse cachexia, a wasting syndrome commonly seen in patients with advanced cancers and associated with poor outcomes (Gartner 2016). In patients with advanced colorectal cancer, taking an EPA-enriched nutritional supplement providing 1 gram of EPA per day for 12 weeks during chemotherapy resulted in weight gain and appeared to improve quality of life scores more than chemotherapy alone (Trabal 2010). In a controlled trial including 111 patients with head and neck cancer, participants who also received a nutritional supplement enriched with EPA plus DHA during standard treatment with chemotherapy and radiation reported better quality of life and experienced less weight loss after 14 weeks of treatment than patients receiving an unenriched nutritional supplement (Fietkau 2013).

Omega-3 fatty acids may support positive outcomes after cancer surgeries. A review of the research found that nutritional formulas enriched with omega-3 fatty acids reduced post-surgical complications and infections and shortened hospital stays in patients undergoing liver surgery for both benign and malignant conditions (Zhang, Chen 2017). Anticancer effects of omega-3 fatty acids may also improve the status of patients with cancer before surgery. In a randomized controlled trial, patients with colorectal cancer awaiting surgery to remove liver metastases were given either 2 grams of EPA per day or placebo for 12 to 65 days before surgery. Although no difference was noted in the proliferation of the cancer cells between the groups, patients taking EPA had fewer blood vessels in their tumors (Cockbain 2014).

Enzymatically Modified Rice Bran

Enzymatically modified rice bran, which contains an immune-modulating polysaccharide called arabinoxylan, has demonstrated anticancer potential and may enhance chemotherapy effectiveness. Some evidence also suggests the formulation may reduce some of the negative side effects of radiation and chemotherapy (Ooi 2018).

A number of studies have found that modified rice bran can activate the anticancer immune response and inhibit tumor formation and growth in animals (Badr El-Din, Abdel Fattah 2016; Badr El-Din 2008; Kim 2007; Noaman 2008). In particular, enzymatically modified rice bran may stimulate natural killer cells and dendritic cells, two types of immune cells that are critical for the body's response to cancer (Ghoneum, Agrawal 2011; Ghoneum 2000; Cholujova 2009; Ghoneum 2004). In a three-month randomized controlled trial with 48 participants who had multiple myeloma, treatment with enzymatically modified rice bran increased natural killer cell activity, blood levels of dendritic cells, and levels of some beneficial immune molecules (Cholujova 2013). Laboratory research indicates enzymatically modified rice bran may also inhibit the formation of new blood vessels, which would limit

tumor growth (Zhu X 2017).

Preclinical and clinical studies suggest enzymatically modified rice bran may be useful in combination with standard cancer treatment. In a randomized controlled trial, 68 patients with liver cancer were treated with conventional therapies either alone or with the addition of one gram per day of rice bran arabinoxylan for 12 months. After three years, patients who received rice bran arabinoxylan had a greater decrease in tumor size, lower tumor marker levels, and lower recurrence rates. In addition, the two-year survival was 35% in patients taking rice bran versus 6.7% in patients receiving the conventional therapies alone (Bang 2010). In laboratory research, enzymatically modified rice bran increased susceptibility of breast cancer cells to the chemotherapy drugs paclitaxel and daunorubicin (Gollapudi 2008; Ghoneum 2014). In an animal model of cancer, modified rice bran demonstrated stronger antitumor activity than low-dose paclitaxel, and the combination of modified rice bran plus low-dose paclitaxel was more effective than either alone (Badr El-Din, Ali 2016).

Enzymatically modified rice bran worked synergistically with curcumin to promote cancer cell death in laboratory research (Ghoneum, Gollapudi 2011), and the combination helped to improve immune cell numbers in a preliminary clinical trial in patients with early-stage blood cancers (Golombick 2016).

Garlic

The first paper to describe the anticancer activity of garlic constituents was published in 1958 (Weisberger 1958). Other laboratory and animal research has shown that garlic also acts indirectly, by reducing inflammation and stimulating anticancer immune function, to inhibit tumor growth (Fallah-Rostami 2013; Gdula-Argasinska 2017; Saud 2016; Arreola 2015). In addition, garlic appears to alter epigenetic regulation of immune function, cell death, and toxin metabolism in ways that may reduce cancer development and progression (Charron 2015).

Consumption of garlic and related vegetables may be associated with lower risks of certain cancers. The best evidence of a protective effect is for esophageal, stomach, and colorectal cancers (Nicastro 2015). Garlic contains nutrients that could contribute to its possible benefits, including magnesium, selenium, amino acids, and vitamins B, A, and C (Petrovska 2010). In addition, garlic is a rich source of sulfur compounds with anticancer effects. These active sulfur compounds are formed through enzymatic activity when garlic is cut or crushed (Puccinelli 2017; Cao 2014; Yagdi 2016).

Aged garlic extract may be helpful for individuals prone to precancerous colorectal polyps known as adenomas. In a randomized trial, participants with a history of colorectal adenomas treated with 2.4 mL daily of aged garlic extract had fewer and smaller new adenomas after 12 months than participants treated with 0.16 mL daily (Tanaka 2006).

In a small clinical study that enrolled 50 participants with inoperable colorectal, liver, or pancreatic cancer, supplementation with aged garlic extract increased natural killer cell numbers and activity compared with placebo (Ishikawa 2006). Natural killer cells play an important and complex role in the immune response to cancer (Stabile 2017).

Inositol Hexaphosphate

Inositol hexaphosphate, or IP-6, is also known as phytic acid or phytate and is a naturally occurring fiber component and storage form of phosphorus. IP-6 is found in almost all plants and is abundant in plant foods such as whole grains, vegetables, and legumes. Although IP-6 has long been considered an anti-nutrient because of its propensity to bind to minerals and proteins, it is now also recognized for its important health benefits and its anticancer potential (Silva 2016; Bohn 2008).

High-fiber foods are rich sources of IP-6 and have been associated with lower risk of cancer, especially colorectal cancer, in numerous studies (Deschasaux 2014; Pan 2018; Wang, Qiao 2015; Chen, Chen 2016; Tuan 2016). IP-6 is active against many types of cancer cells in the laboratory (Nawrocka-Musial 2012). Preclinical studies suggest IP-6 may enhance the body's ability to defend itself against cancer through several mechanisms, including lowering oxidative stress levels, activating natural killer cells, altering cancer cell function and signaling, inhibiting tumor growth and metastasis, and stimulating normal cell division and cell death. Additionally, studies show IP-6 increases levels of tumor suppressor gene p53 and inhibit inflammatory signaling via NF-kappaB (Silva 2016; Nawrocka-Musial 2012; Bizzarri 2016).

IP-6 may be particularly helpful in conjunction with other cancer therapies. IP-6 plus inositol was compared with placebo in a trial with 14 women receiving chemotherapy for breast cancer. Patients receiving IP-6 had less bone marrow toxicity, reflected by higher numbers of blood cells, including platelets and white blood cells. In addition, overall quality of life was preserved to a significantly greater extent in the IP-6-treated women (Bacić 2010).

Early reports of the benefits of IP-6 as part of adjuvant therapy after cancer surgery were presented at the Seventh International Conference of Anticancer Research in 2004. IP-6 plus inositol, at a dose of 1,530 mg four times daily during chemotherapy and twice daily for one year after treatment, was noted to prevent treatment-related side effects and preserve quality of life in patients with colorectal cancer (Druzijanic 2004). Similarly, in patients with breast cancer, 2,040 mg of IP-6 plus inositol three times daily during chemotherapy and radiation and 510 mg three times daily after the end of treatment reduced side effects and prevented a decline in quality of life (Juricic 2004). In these small studies, IP-6 was taken 30 minutes before meals to minimize its anti-nutrient effects.

Lactoferrin

Lactoferrin is an iron-binding protein that helps to defend the body against microbial invasion. Lactoferrin is found in secretions like milk, tears, sweat, saliva, and digestive juices, on the body's surfaces, circulating in blood, and in some immune cells. The protein is antimicrobial, stimulates the immune response, reduces inflammation, and promotes wound healing (Albar 2014; Hao 2018). In addition, the ability of lactoferrin to reduce cancer initiation, growth, and metastasis has been studied extensively. Bovine lactoferrin (from cows' milk) is often used as a nutritional supplement, mainly to support immune health (Giansanti 2016).

Cancer onset and progression is associated with suppressed lactoferrin production (Giansanti 2016). As an immune system modulator, lactoferrin stimulates anticancer immune activity, yet may reduce inflammation in the tumor microenvironment (Drago-Serrano 2018; Siqueiros-Cendón 2014; Garcia-Montoya 2012). The other anticancer effects of lactoferrin include promoting healthy cell division and cell death, suppressing formation of new blood vessels by tumors, and interfering with the ability of cancer cells to spread (Hill DR 2015; Yin 2013). The antibiotic, anti-inflammatory, and immune-modulating properties of lactoferrin appear active against *Helicobacter pylori*, a bacterium that can lead to gastritis, ulcer, and cancer (Dial 2002). By scavenging free radicals and binding to iron, which promotes oxidation, lactoferrin also prevents DNA damage that can lead to cancer (Ogasawara 2014).

Studies in animals and humans indicate lactoferrin may be effective as an adjuvant cancer therapy. In a randomized controlled trial, 104 people with precancerous colon polyps received three grams of bovine lactoferrin, 1.5 grams of bovine lactoferrin, or placebo for 12 months before surgical polyp removal. At the end of the trial, in a subgroup of 55 participants who were 63 years old or younger, polyps from those receiving the higher dose of lactoferrin had grown less than polyps from those receiving the lower dose or placebo (Kozu 2009). In a mouse model of breast cancer, bovine lactoferrin enhanced the response to tamoxifen (Sun 2012).

Lignans

Lignans are plant chemicals found in the fibers of almost all plants. They occur in the diet mainly in legumes and seeds, with flaxseed being an especially rich source. Lignans can act as free-radical scavengers and are phytoestrogens, which means they are structurally similar to human estrogens. Lignans are converted into biologically active compounds, known as enterolignans, by certain gut bacteria (Goyal 2014; Landete 2016; Lecomte 2017). One lignan of particular interest for its powerful free-radical-scavenging capacity is secoisolariciresinol diglucoside.This lignan, found mainly in flaxseeds, may reduce the risks of cardiovascular disease and metabolic syndrome, and has demonstrated several anticancer properties (Goyal 2014; Adolphe 2010).

Like all phytoestrogens, enterolignans can bind and stimulate estrogen receptors in the body. Because they compete with estrogen for receptor sites and are weak stimulators of those receptors, their effect can be anti-estrogenic or mildly estrogenic, depending in part on the level of estrogen in the body. Phytoestrogens also appear to have varying effects on different types of estrogen receptors located in different tissues (Lecomte 2017; Landete 2017). In addition, flaxseed and its enterolignans have been shown to reduce tumor formation and growth, inhibit new blood vessel formation, and promote cancer cell death (Goyal 2014; Landete 2016).

High intake of flaxseed or lignans has been associated with reduced risks of breast (Flower 2014; Calado 2018)

and colorectal cancers (Jiang 2016; DeLuca 2018). Higher lignan intake may also be correlated with lower ovarian and uterine cancer risks (Neill 2014; Horn-Ross 2003). In addition, men with higher blood levels of an enterolignan, reflecting both lignan intake and gut microbial balance, may have a lower risk of prostate cancer (He 2015).

In a randomized controlled trial, 32 postmenopausal women awaiting surgery for newly diagnosed breast cancer were randomized to receive either a muffin containing 25 grams of ground flaxseed or a muffin without flaxseed every day from the time of their first biopsy until surgery, which ranged from 13 to 76 days. Postoperative analysis of the cancerous tissue revealed that tumor markers were reduced by 30%–71% in the flaxseed group, and tumor cell death was increased. The researchers concluded that dietary flaxseed has the potential to reduce breast cancer growth (Thompson 2005). In a similar trial, 147 men awaiting surgery for prostate cancer were given 30 grams per day of ground flaxseed for about 30 days before surgery. Surgical tissue samples showed that tumor aggressiveness, measured by the number of cells actively dividing, was reduced as urinary levels of enterolignans increased (Azrad 2013).

Regular consumption of high-lignan foods may improve cancer prognosis. One study assessed lignan intake during a one- to two-year period before cancer diagnosis in 1,122 women with breast cancer and followed their progress for seven to ten years. Among participants who were postmenopausal, women who reported the highest intake of lignans were half as likely to die for any reason and 71% less likely to die from breast cancer compared with postmenopausal women with the lowest lignan intake (McCann 2010). In another study in 1,140 postmenopausal women with breast cancer, higher blood levels of one enterolignan were correlated with a higher survival rate during four to eight years of monitoring. Interestingly, in this study, the correlation between likelihood of survival and enterolignan levels was significant only in women whose cancers did not express estrogen receptors (Buck 2011). A meta-analysis that included data from this and four similar studies concluded that patients with breast cancer who had higher enterolignan levels were less likely to die from breast cancer or from any cause (Seibold 2014).

Some breast tumors have high concentrations of receptors known as human epidermal growth factor receptor 2 (HER2), and are referred to as HER2+. Research in HER2+ cancer cells and animal models of HER2+ breast cancer suggests that flaxseed oil may enhance the tumor-reducing effect of trastuzumab (Herceptin), an immunotherapy agent used to treat this type of breast cancer (Mason 2014).

Melatonin

Melatonin is a molecule produced by the pineal gland, a pea-sized gland located in the brain, as well as by cells in a variety of tissues throughout the body (Najafi 2017). Melatonin synthesis is affected by many conditions, including light exposure, food, stress, age, reproductive status, health status, and use of medications. The molecule can act as both a neurotransmitter and a hormone, and has demonstrated broad anticancer effects such as reducing oxidative stress, the ability of cancer to grow and spread, and the formation of new blood vessels, as well as promoting cancer cell death and triggering favorable epigenetic changes (Reiter 2017; Yeh 2017; Su 2017; Goradel 2017; Wang RX 2016).

In clinical trials in patients with such cancers as primary brain tumors, colorectal cancer, non-small cell lung cancer, breast cancer, and brain metastasis, researchers found that melatonin, in doses up to 40 mg daily, worked well with conventional treatments or improved quality of life when no other treatment was available (Barni 1990; Lissoni 1991; Lissoni, Barni 1994; Lissoni 1995; Lissoni 1996; Lissoni, Barni, 1999; Lissoni 1997; Lissoni, Tancini, 1999). In two separate reviews of clinical trials assessing the use of melatonin during chemotherapy or radiation for the treatment of solid tumors, melatonin was found to decrease negative side effects such as fatigue and low platelet counts, improve response to treatment, and increase one-year survival (Wang 2012; Seely 2011).

Melatonin has a particularly well-studied role in protecting against breast cancer (Ball 2016). By altering estrogen receptor function, melatonin has been shown in the laboratory to reduce proliferation of estrogen-sensitive cancer cells. It may also reduce tissue estrogen levels by inhibiting enzymes involved in estrogen synthesis (Hill SM 2015). In a small study in 14 women with metastatic breast cancer that was progressing despite treatment with tamoxifen, the addition of melatonin to tamoxifen led to tumor regression in four of the participants (Lissoni 1995).

Melatonin may stabilize cancer growth in part by resetting the cortisol circadian rhythm. In a trial involving 14 patients with advanced cancer who had no more conventional treatment options, 20 mg of melatonin was given nightly for 3 months. Six of the 14 participants had stabilization of disease, and this effect was correlated with normalization of daily patterns of cortisol release (Brivio 2010).

Through its strong free-radical-scavenging ability, melatonin may protect immune cells from the damaging effects of cancer therapies such as radiation. In addition, melatonin has direct effects on immune cell numbers and activity, giving it great potential as an adjuvant therapy (Najafi 2017). For example, melatonin may complement the use of agents called checkpoint inhibitors, which are now used to treat some cancers that are otherwise difficult to treat, such as lung cancer and metastatic melanoma (Nagai 2018; Lissoni 2017). Melatonin has also shown promise in combination with the immune-modulating agent interleukin-2 in patients with solid tumors and in those with blood cell cancers (Lissoni, Meregalli 1994; Lissoni 2000). In a controlled trial, patients with advanced or metastatic cancer treated with interleukin-2 plus melatonin were more likely to have a positive response to treatment and had a higher survival rate at one year than those treated with interleukin-2 alone (Lissoni, Meregalli 1994).

Modified Citrus Pectin

Modified citrus pectin (MCP) is a complex polysaccharide derived from pectin obtained from the peel and pulp of citrus fruits (Glinsky 2009; Altern Med Rev 2000). Through changes in pH and temperature, pectin is broken down into shorter, absorbable pieces—MCP—that can bind to some cancer cells and possibly interfere with their ability to spread (metastasize) (Leclere 2013). MCP may also have direct toxic effects on cancer cells (Leclere 2013; Leclere 2015).

In order for cancer to spread, cancer cells need to bind together and with other cells. Protein projections on the outer surfaces of cells allow them to stick to one another (Ahmed 2015; Takenaka 2002). MCP appears to cover these "sticky" projections on cancer cells so they are unable to bind to each other or to other tissues. Deprived of the ability to stick together, cancer cells thus have a reduced ability to metastasize (Leclere 2013). In animal models, MCP decreased metastasis of several cancers, including breast (Glinsky 2009), colon (Liu 2008), and prostate (Pienta 1995).

In one study, seven of ten men with prostate cancer who took approximately 14 grams of MCP daily had a slowdown in the doubling time of their PSA levels. The slowing of the PSA doubling time represents a decrease in the rate of cancer growth (Guess 2003). In another study involving 35 men with prostate cancer who took 4.8 grams of MCP three times a day, the PSA doubling time stabilized or improved in 79% of participants (Keizman 2017).

Panax ginseng

Panax ginseng, also known as Asian, red, Chinese, or Korean ginseng, has been widely used as a medicinal herb by Asian cultures for thousands of years (Chang 2003; Helms 2004; Chen, Wang 2014).

Panax ginseng has been shown to stimulate anticancer immune function, decrease inflammation, and inhibit the formation of new blood vessels (Kang 2012; Dai 2017). Ginseng may also improve outcomes in patients with cancer undergoing chemotherapy. In one trial, patients treated surgically for stomach cancer received chemotherapy with or without *Panax ginseng* after surgery. The overall survival rate five years later was 76.4% in the *Panax ginseng* group compared to 38.5% in the control group (Suh 2002). Findings from animal studies suggest ginseng may reduce metastasis risk (Yun 2015; Mochizuki 1995; Seo 2011) and increase survival (Nakata 1998).

One of ginseng's main traditional uses is for building stamina and increasing energy (Li 2009; Kim 2013; Viale 2013). Several studies show ginseng decreases fatigue both during and after conventional cancer treatments (Kim YH 2017; Yennurajalingam 2015).

In a randomized trial in 53 people with different cancers, participants took either *Panax ginseng* at a dose of 3,000 mg or placebo daily for 12 weeks. Participants taking the ginseng had markedly better physical and mental functioning (Kim 2006). In a placebo-controlled clinical trial that enrolled 30 women who completed chemotherapy for ovarian cancer, the participants took red ginseng (3,000 mg daily) or a placebo for 3 months.

Women taking the ginseng had less fatigue, nausea, vomiting, sleepiness during the daytime, anxiety, and shortness of breath, as well as improved emotional functioning (Kim HS 2017).

A small trial that enrolled 30 participants with cancer-related fatigue found that 800 mg of ginseng daily for 29 days led to improvements in fatigue, appetite, and sleep (Yennurajalingam 2015); however, ginseng may be less helpful at lower doses: A randomized controlled trial in patients with advanced cancer found that 400 mg of ginseng extract twice daily for 28 days was ineffective for improving energy (Yennurajalingam 2017).

A related plant, American ginseng (*Panax quinquefolius*), has also reduced cancer-related fatigue at doses of 2,000 mg daily (Barton 2013). In addition, American ginseng improves immune function (Wang 2001), and in one study it decreased the risk of moderate or severe respiratory infections in people living chronic lymphocytic leukemia (High 2012).

Pomegranate

Pomegranate, a fruit that is rich in antioxidants, has gained widespread popularity as a functional food—a food with particular health benefits. Pomegranate fruit, juice, and extracts have been studied in relation to a variety of chronic diseases, including cancer (Adhami 2012; Syed 2013; Johanningsmeier 2011).

Pomegranate has been best studied for its potential role in preventing and treating prostate cancer. Pomegranate extracts have been found to suppress prostate cancer initiation, proliferation, growth, and invasion, and inhibit new blood vessel formation and prostate cancer cell survival (Wang 2014; Turrini 2015). Even the oil from pomegranate seeds reduced malignant activities of prostate cancer cells in the laboratory (Albrecht 2004). Synergistic effects between pomegranate components were identified by Israeli researchers, who noted that chemicals from various parts of the whole fruit acted in concert to reduce the invasive ability of prostate cancer cells (Lansky 2005).

Researchers have demonstrated that pomegranate polyphenols can induce epigenetic changes leading to reduced activity of genes involved in the production of androgens (male hormones), like testosterone, and the androgen receptors that many prostate cancers need to survive and grow (Hong 2008). In addition, scientists have found that pomegranate promotes cancer cell death in androgen-dependent prostate cancer cells in part by inhibiting inflammatory signaling (Rettig 2008).

In an important clinical trial, researchers studied men who had already undergone surgery or radiation treatment for prostate cancer, but nevertheless had rising levels of PSA, the serum marker of tumor growth or recurrence. Men drank 8 ounces of pomegranate juice daily, and the researchers measured their PSA levels every three months for 33 months, calculated their rates of PSA increase, and estimated the time it would take for their PSA levels to double. A longer doubling time indicates slower cancer growth. The average PSA doubling time lengthened from 15 months (1.25 years) at the beginning of the trial to 54 months (4.5 years) at the end (Pantuck 2006).

In a similar study, 101 men with rising PSA levels after initial treatment for prostate cancer received either one or three grams of pomegranate extract daily for up to 18 months. The PSA doubling time increased overall and by more than 100% in almost half of the participants. Both doses resulted in the roughly the same benefit in doubling times (Paller 2013).

Preclinical research suggests pomegranate extracts may be helpful for people with other types of cancer. Pomegranate seed oil, an extract from the oil, and a polyphenol-rich fermented juice have all demonstrated anticancer activities in breast cancer cells and animal models of breast cancer. These activities include suppressing growth, proliferation, and new blood vessel formation (Kim 2002; Mehta 2004; Grossmann 2010; Toi 2003). In addition, a pomegranate fruit extract enhanced the effects of the anti-estrogen drug tamoxifen in an estrogen-sensitive breast cancer cell culture (Banerjee 2011).

Pomegranate seed oil and peel extract have been shown to suppress experimentally induced colon cancer and precancerous colon lesions in rats (Kohno 2004; Waly 2012). In mice exposed to cigarette smoke, supplementation with pomegranate juice decreased lung nodule formation and a marker of tumor growth (Husari 2017). Pomegranate fruit extract has also been found to reduce tumor growth in other animal models of lung cancer (Khan, Afaq 2007; Khan, Hadi 2007).

Pomegranate polyphenols known as ellagitannins are digested by gut bacteria into compounds with strong anti-inflammatory and oxidative stress-reducing effects. Breakdown products of pomegranate ellagitannins have been shown to reduce inflammatory signaling and promote cell death in colon cancer cells (Adams 2006; Larrosa 2006). These compounds may also suppress estrogen-sensitive breast cancer by inhibiting aromatase, the enzyme that converts testosterone into estrogen (Adams 2010).

Proteolytic Enzymes

Proteolytic enzymes are enzymes that break down proteins. Both mammalian and plant-derived proteolytic enzymes have been used in cancer studies. The use of some of these enzymes in adjuvant cancer care has received particular attention in Europe (Moss 2008): one study found that, in a group of 2,339 patients with breast cancer, 55% had received proteolytic enzymes as part of their cancer treatment, along with standard chemotherapy, radiation, or surgery (Beuth 2001).

The role of supplemental enzymes in reducing inflammation is well established (Edakkanambeth Varayil 2014). Studies have reported that proteolytic enzymes taken during radiation therapy may reduce mucositis (inflammation of mucous membranes). This effect has been demonstrated in two controlled clinical trials involving patients receiving radiation for head and neck cancers (Gujral 2001; Kaul 1999) and one trial involving women receiving radiation for cervical cancer (Dale 2001). However, not all studies have demonstrated this protection (Martin 2002). Nevertheless, findings from a small preliminary trial suggest a combination of trypsin and bromelain may decrease elevated levels of inflammatory markers, including CRP in healthy adults (Paradis 2015). Higher levels of CRP have been associated with increased risk of recurrence in various cancers (Kong 2016; Asegaonkar 2015; Janik 2017; Shrotriya 2015).

One study examined the effect of proteolytic enzymes in people treated with standard chemotherapy for multiple myeloma. After a follow-up period of about three to five years, an approximately 60% lower risk of death was noted in those who supplemented their treatment with proteolytic enzymes for at least six months. In the most advanced cases, median survival was 83 months with proteolytic enzymes and 47 months without (Sakalová 2001).

A review of the effects of proteolytic enzymes in cancer care concluded that enzyme therapy can significantly decrease cancer-related and treatment-related symptoms such as nausea, other digestive problems, fatigue, weight loss, and restlessness, and improve quality of life. The effectiveness of proteolytic enzymes for increasing response rate and longevity in patients with plasmacytoma, a condition related to multiple myeloma, led to the inclusion of an enzyme product as an orphan drug (one intended for treatment of a rare condition) to advance research into its use (Beuth 2008).

PSK and PSP: *Coriolus versicolor* Polysaccharides

Mushrooms have been used as food and medicine in cultures around the world for thousands of years (Valverde 2015; Qin 2014). Several mushroom species have been used in integrative cancer care (Guggenheim 2014). A wealth of evidence has been gathered in support of the usefulness of *Coriolus versicolor* (turkey tail) in particular, and numerous clinical trials show that turkey tail may improve survival in people with cancer (Eliza 2012; Fritz 2015).

Coriolus contains polysaccharides—abbreviated PSK and PSP—that have demonstrated immune-enhancing and anticancer potential and have been used routinely in cancer care in both Japan and China for decades (Chang 2017). Preclinical and clinical studies suggest PSK and PSP have direct antimetastatic effects and promote anticancer immune activity (Pandya 2018). Because PSK and PSP stimulate healthy immune function (Lu 2011; Saleh 2017), they may be beneficial combined with chemotherapy, radiation, or surgery, which weaken the immune system (Kang 2009; Formenti 2013; Hogan 2011).

In a systematic review of 13 randomized, placebo-controlled, double-blind trials in patients receiving *Coriolus versicolor* for various cancers, the risk of dying due to cancer was lower in patients taking the mushroom. This finding was particularly true in patients with breast, colorectal, and gastric cancers (Eliza 2012). In a study of patients with advanced liver cancer who had poor liver function or could not take standard treatment, *Coriolus versicolor* improved social and emotional function, appetite, pain, and quality of life compared with placebo (Chay 2017).

A review of 28 studies, including six randomized controlled trials, five non-randomized trials, and 17 preclincial studies, noted important benefits from PSK in lung cancer treatment. In general, PSK demonstrated safety in patients undergoing radiation therapy or chemotherapy, had beneficial effects on immune function, helped with symptoms caused by the tumor, and appeared to extend survival in patients with lung cancer (Fritz 2015).

A meta-analysis of 23 randomized controlled trials that included a combined total of 10,684 patients with colorectal, gastric, or esophageal cancers found that PSK improves survival. The benefits were most dramatic in patients treated with both chemotherapy and PSK (Ma Y 2017). One trial specifically looked at individuals older than 70 years. After colon cancer surgery, study participants who received adjuvant chemotherapy plus PSK had a three-year survival rate of 81% while participants who received adjuvant chemotherapy alone had a three-year survival rate of 53% (Yoshitani 2009). PSK, at a dose of three grams daily for two weeks each month, was also reported to improve survival in a study of patients with cervical cancer being treated with radiation (Okazaki 1986).

Quercetin

Quercetin is a flavonoid found in almost all plants and present in a broad range of foods, from grape skins and red onions to green tea and tomatoes (Li Y 2016; Zhu L 2012). Like other flavonoids, quercetin has free-radical-scavenging, anti-inflammatory, antimicrobial, and immune-modulating characteristics. Quercetin has been found to interfere with cancer cell division, promote cancer cell death, and interrupt tumor signaling necessary for cancer growth and spread (Anand David 2016; Niedzwiecki 2016; Khan 2016). Also, quercetin may enhance the effectiveness of some chemotherapy drugs for various cancers (Niedzwiecki 2016; Kashyap 2016).

Quercetin has demonstrated anticancer effects against various types of cancer cells in the laboratory, including lung, liver, prostate, and breast cancer cells. The effects appear to be related to the ability of quercetin to reduce oxidative stress and inflammation (Zheng 2012; Granado-Serrano 2012b; Granado-Serrano 2012a; Granado-Serrano 2010; Senthilkumar 2011; Chou 2010). In prostate cancer cells, quercetin has also been found to reduce hormone receptor function and alter gene activity in favor of tumor suppression (Yuan 2010; Nair 2004). In breast cancer cells, quercetin exposure reversed resistance to tamoxifen (Wang, Tao 2015) and increased sensitivity to the chemotherapy drug doxorubicin (Li 2013). It also inhibited breast CSCs, which are thought to play a major role in cancer metastasis, recurrence, and progression (Li 2018; Wang 2018).

Findings from animal research suggest quercetin may protect the liver from carcinogenic toxins, inhibit liver cancer growth, and improve sensitivity to the chemotherapy drug 5-fluorouracil (Dai 2016; Carrasco-Torres 2017). In animal models of breast cancer, quercetin has been found to inhibit tumor growth, strengthen the immune response to cancer, and increase the effectiveness of doxorubicin (Zhong 2003; Du 2010).

Reishi

Reishi (*Ganoderma lucidum*) is a mushroom used for thousands of years in many parts of Asia as a remedy to treat an array of diseases and prolong life (Bishop, Kao 2015; Martinez-Montemayor 2011). Polysaccharides from reishi, like those from other mushrooms, have immune-modulating properties (Pandya 2018). Furthermore, reishi has been shown in preclinical research to be toxic to cancer cells, inhibit new blood vessel formation, reduce proliferation other activities of malignant cells, and protect healthy cells from toxic damage, making reishi a promising adjuvant cancer therapy (Boh 2013; Xu 2011).

Reishi polysaccharides may have a beneficial effect on bone marrow, the source of red blood cells and most immune cells. In an animal study, after bone marrow eradication by chemotherapy, reishi improved recovery of both red and white blood cells (Zhu 2007). Reishi increases the number and function of certain immune cells, including natural killer cells, antibody-producing B cells, and some T cells (Kladar 2016; Xu 2011; Jin 2016). Reishi has also been shown to inhibit several aspects of the inflammatory response (Zhang 2018; Rossi 2018). Through these mechanisms, reishi may suppress a variety of pro-cancer cellular pathways and decrease some harmful effects of conventional cancer treatments (Zeng 2018; Rossi 2018).

In addition to polysaccahrides, reishi contains compounds known as triterpenoids that may contribute to its health benefits (Ma 2011; Sanodiya 2009; Wu GS 2013). Reishi triterpenoids have free-radical-scavenging capacity and have demonstrated the ability to reduce proliferation, induce cell death, suppress signaling needed for new blood vessel growth, and inhibit metastasis in cancer cells (Wu GS 2013; Cör 2018). Laboratory and animal studies

indicate that reishi triterpenes are also anti-inflammatory (Dudhgaonkar 2009). In a randomized, placebo-controlled clinical trial, a triterpenoid- and polysaccharide-enriched reishi preparation increased the activities of antioxidant enzymes in healthy volunteers (Chiu 2017).

A Cochrane review of five randomized controlled trials that met the strict criteria for the highest level of evidence concluded that, while reishi may not be effective when used alone as a first-line treatment for cancer, the evidence supports its possible adjuvant use to enhance tumor responsiveness, preserve strong immune function, and improve quality of life in patients with cancer undergoing conventional therapies (Jin 2016). This conclusion is important, as Cochrane reviews are often used as high-quality evidence-based guidance for medical decision-making. Another review of findings from both preclinical and clinical studies reached a similar conclusion regarding the use of reishi as an adjuvant breast cancer treatment (Rossi 2018).

A small human study reported that a reishi extract enhanced immune function in patients with advanced cancers (Gao 2003). In a study involving patients with precancerous colorectal polyps (adenomas), a water-soluble reishi extract decreased the number and size of the adenomas seen on colonoscopy (Oka 2010). In another study of patients with advanced colorectal cancer, the administration of 5.4 grams of reishi for 12 weeks improved several markers of immune function, including the activity of natural killer cells (Chen 2006).

Resveratrol

Resveratrol is a non-flavonoid polyphenol and phytoestrogen (Ataie 2016). Resveratrol is one of a diverse group of plant compounds called phytoalexins that function like a plant immune system, defending against microbial invasion and activated by other stressors (Wei 2018; Piasecka 2015). Resveratrol has been identified in at least 72 species of plants, including cocoa, peanuts, Japanese knotweed, a variety of berries, and red grapes (Dybkowska 2018).

Because of its oxidative stress-reducing and anti-inflammatory properties, resveratrol may have a role in preventing and treating chronic degenerative diseases such as cardiovascular disease, neurological disorders, and possibly cancer (Berman 2017; Dybkowska 2018). Resveratrol inhibits inflammatory signaling through the NF-kappaB pathway, and this effect increases with higher doses of resveratrol (Ren 2013). In addition, the compound has been shown to directly inhibit cyclooxygenase-2 (COX-2), an enzyme involved in inflammation and cancer cell metastasis (Dybkowska 2018).

Resveratrol has been shown to inhibit proliferation and promote cell death in a variety of cancer cells in vitro. It also appears to induce epigenetic reprogramming that favors healthy cell function (Huminiecki 2018). In addition, resveratrol may help sensitize cells to the effects of chemotherapy (Ko 2017; Delmas 2011).

In a randomized, double-blind, placebo-controlled trial involving 39 women at increased risk for breast cancer, participants received 5 mg or 50 mg of trans-resveratrol twice daily for 12 weeks. The women then underwent a procedure to collect ductal cells for analysis. Increased activation of a tumor suppressor gene and decreased production of a pro-inflammatory and pro-malignancy chemical called prostaglandin E2 were seen in the cells taken from women receiving both doses of resveratrol (Zhu W 2012).

As is the case with many other polyphenols, resveratrol is poorly absorbed and largely digested into other compounds by gut microorganisms. Some of the health benefits of polyphenols may be due to their ability to improve gut microbial composition. In addition, compounds that result from microbial digestion of resveratrol may in fact be responsible for many of the health benefits attributed to resveratrol. Emerging research into the potential therapeutic role of breakdown products from resveratrol and other polyphenols is ongoing (Chen, Wen 2016; Stevens 2016; Bode 2013).

Selenium

Selenium is an essential trace mineral involved in numerous reactions and incorporated into many functional molecules in the body (Lu 2009; Rayman 2000). Seafood and Brazil nuts are among the richest sources of selenium, but many other plant and animal foods contribute to selenium intake (NIH 2018a). The role of selenium in cancer became apparent when it was discovered that populations lacking this mineral in their diet, such as people living in geographical areas with low soil levels, had higher rates of certain cancers (Semnani 2010; Cech 1984; Cui 2017).

Selenium compounds regulate the balance of pro-oxidant (oxidation) and antioxidant (reduction) chemical reactions in cells (Gandin 2018; Fernandes 2015). Some selenium compounds promote cancer cell death, regulate immune and inflammatory pathways, and prevent new blood vessel growth and tissue changes that can lead to cancer spread (Gandin 2018; Chen 2013). Other selenium compounds protect DNA from oxidative damage (Ferguson 2012). The exact effects depend on the nature of the selenium compound and the dose (Fernandes 2015).

In the Nutritional Prevention of Cancer Trial, participants with a history of basal or squamous cell carcinoma of the skin were given 200 micrograms of selenium per day, as selenium-enriched yeast, for an average of 4.5 years. After 6.4 years of follow-up, the occurrence of these two types of skin cancer did not change, but there were reductions in new diagnoses of lung, prostate, and colorectal cancers (Clark 1996). A later analysis of the data found the benefit of selenium supplementation for lowering prostate cancer risk was limited to men who began the trial with lower circulating levels of selenium (Duffield-Lillico 2003).

A meta-analysis that included 12 studies totaling more than 13,000 individuals found that, compared with men with blood selenium levels of about 60 ng/mL, men with levels of 135–170 ng/mL had a 15%–25% lower prostate cancer risk, and a 40%–50% lower risk for advanced prostate cancer (Hurst 2012). A study that assessed selenium levels in patients with newly diagnosed laryngeal cancer found that patients with levels higher than about 70 ng/mL were more likely to survive for five years (Lubiński 2018). People with higher selenium levels have also been found to have a lower risk of precancerous colon polyps (adenomas) and colorectal cancer (Ou 2012).

Soy

A number of studies have noted a correlation between greater soy intake and lower risks of certain cancers (Qadir 2017; Sarkar 2003; Sarkar 2002). Soybean constituents have demonstrated properties that may reduce cancer development and progression of cancer, such as inhibiting cancer cell growth, proliferation, and metastasis; suppressing new blood vessel formation; and promoting cancer cell death (Uifălean 2015; Mahmoud 2014; Varinska 2015).

Soybeans, like all legumes, contain compounds classified broadly as phytoestrogens. Phytoestrogens are plant chemicals that are structurally similar to, but not identical to, human estrogens. There are four main categories of phytoestrogens: isoflavones, stilbenes, coumestans, and lignans (Hwang 2015). Soy is a major source of the isoflavones genistein and daidzein, while all beans and lentils are rich in lignans (Lampe 2003).

One mechanism by which soy and its phytoestrogens may lower risk of cancer development and recurrence is by inhibiting aromatase, the enzyme that stimulates conversion of testosterone into estrogens (Lephart 2015; Liu 2012). Aromatase inhibition is an important strategy in breast cancer treatment, especially in postmenopausal women, in whom aromatase activity is a major contributor to the estrogen pool (Pistelli 2018).

Phytoestrogens appear to have either estrogenic or anti-estrogenic effects, depending in part on the types of estrogen receptors present in a particular tissue. Soy isoflavones have been shown to be strong activators of a receptor type called estrogen receptor-beta (ER-β) and weak activators of another type called estrogen receptor-alpha (ER-α). Tissues such as ovaries and lungs typically have more ER-β, while uterine and breast tissues have more ER-α, and bone has similar amounts of both. Emerging evidence suggests that ER-β activation may suppress tumor development and growth (Sareddy 2015; Rietjens 2013).

Because of their ability to stimulate different effects in different tissues and cells, phytoestrogens are sometimes described as natural selective estrogen receptor modulators, or phyto-SERMs (An 2016). Tamoxifen is a well-known drug SERM, and the soy isoflavone genistein is an example of a phyto-SERM (Oseni 2008; Hernandez 2018; Chang 2011). Despite theoretical concerns and some preclinical data suggesting soy intake might stimulate breast cancer cells, several reviews of evidence from human research have concluded that soy food consumption is safe and potentially beneficial in patients with breast cancer and breast cancer survivors (Messina 2016; Braakhuis 2016; Messina 2013; Fritz 2013; Magee 2012).

Soy consumption has been linked with decreased risk of recurrence and improved survival in women with a history of breast cancer (Guha 2009; Messina 2016; Nechuta 2012). A study that included more than 6,200 women with breast cancer found a 21% decreased risk of death among women with the highest dietary intake of isoflavones. The effect was strongest in women with a non-hormone-sensitive, and typically more aggressive,

form of breast cancer (Zhang, Haslam 2017). Preclinical research suggests soy isoflavones may enhance the effectiveness of chemotherapy agents commonly used to treat breast cancer, such as doxorubicin, docetaxel, and tamoxifen (Spagnuolo 2015), and clinical trials have shown that soy intake does not interfere with the effects of tamoxifen (Fritz 2013; Magee 2012).

Soy intake has also been correlated with reduced prostate cancer risk (Hwang 2015; Vaishampayan 2007; Yan 2009; Applegate 2018). In a randomized controlled trial, supplementation with isoflavones decreased inflammatory markers and improved markers of immune function in men with prostate cancer, effects that could improve their prognosis (Lesinski 2015). Soy isoflavones may inhibit prostate cancer through several mechanisms, including modulating hormone signaling, inhibiting growth and metastasis, and inducing cell death. In addition, soy isoflavones have been shown to induce epigenetic changes in prostate cancer cells that diminish their malignant activities in the laboratory (Mahmoud 2014; Karsli-Ceppioglu 2015).

In a clinical trial that enrolled men with rising PSA levels after prostate cancer treatment, considered a sign of recurrence, drinking 8 ounces of soy milk three times daily for 12 months led to a slowing of the PSA rise (Pendleton 2008). A soy-based combination supplement was found in another randomized controlled trial to slow rising PSA levels in men who had been treated previously for prostate cancer (Schröder 2005). In a trial involving men with active prostate cancer, consuming tomato products providing at least 25 mg lycopene daily along with soy food providing 40 grams of soy protein daily led to a significant reduction in blood levels of a protein that stimulates the formation of new blood vessels (Grainger 2008).

Soy and its isoflavones have a potential role in preventing or improving outcomes in patients with a broad range of cancers, including bladder cancer (Su 2000), stomach cancer (Wada 2015; Huang 2014), colorectal cancer (Yu 2016), and lung cancer (Yang, Shu 2013; Wu SH 2013). Although soy has known anti-thryoid effects, clinical trials in adults suggest that consumption of soy foods does not compromise thyroid function in individuals with adequate iodine intake (Messina 2006).

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin found in fruits and vegetables that acts as a cofactor for many enzymatic reactions in the body, helping to balance oxidation and reduction reactions. Vitamin C also plays essential roles in cellular energy production, protein assembly, and epigenetic regulation (Banhegyi 2014; Gillberg 2017). Vitamin C may benefit patients with cancer by exerting direct toxic effects in cancer cells, enhancing the effects of chemotherapy and radiation, strengthening immune defenses, and reducing inflammation (Mikirova 2013; Klimant 2018; van Gorkom 2018).

Patients with cancer have been noted to have exceptionally low vitamin C levels, which have been correlated with shorter survival. Intravenous administration of vitamin C can raise levels higher than those achievable with oral doses. When high doses are administered intravenously, vitamin C has a pro-oxidant action with more damaging effects on cancer cells than healthy cells. Evidence from cell culture studies suggests vitamin C does not reduce the effectiveness of chemotherapy and radiation. Furthermore, intravenous vitamin C can improve immune function and may suppress new blood vessel growth (Schoenfeld 2017; Chen 2005).

Laboratory research indicates that certain fast-growing cancers may be particularly susceptible to the toxic effects of vitamin C (Schoenfeld 2017; Polireddy 2017). Although the ability of vitamin C to inhibit different cancer cells can vary, the anticancer properties of vitamin C have been noted specifically against melanoma cells and stomach, prostate, brain, lung, and pancreatic cancer cells (Schoenfeld 2017; Polireddy 2017; Lee 2009). High-dose intravenous vitamin C was first reported to improve long-term cancer survival in the 1970s; however, this benefit has not been noted with high-dose oral vitamin C (Lee 2009; Moertel 1985; Creagan 1979; Cameron 1978; Cameron 1976). In a more recent clinical trial, 25 women with ovarian cancer received chemotherapy alone or combined with intravenous vitamin C, given during chemotherapy at increasing doses of up to 75 or 100 grams per infusion depending on each participant's blood level. Women who received the vitamin C had less chemotherapy-related toxicity (Ma Y 2014). A possible synergism between intravenous vitamin C and the platinum-based chemotherapies used in that trial was observed in an in vitro study using mice tumors as a model (Wang G 2016).

Intravenous vitamin C therapy is safe in most people; however, such therapy is contraindicated in individuals with

kidney disease, a rare genetic disease called glucose-6 phosphate dehydrogenase deficiency, and possibly an iron storage disease called hemochromatosis (Geeraert 2014; Michels 2015).

Boosting Vitamin C's Benefits with Intermittent Fasting

While vitamin C remains a promising cancer adjuvant, its clinical application awaits further high-quality controlled trials of pharmacologically-dosed vitamin C in specific types of cancer. A 2020 mouse study may offer a solution to improving the efficacy of vitamin C: combining it with a fasting-mimicking diet (FMD). A FMD—one that is plant-based, calorie-restricted, low-sugar, low-protein, and high-fat—was shown to increase the effectiveness of pharmacologically-dosed vitamin C treatment in a mouse model of KRAS-mutated colorectal cancer. While both the FMD and vitamin C delayed tumor progression when used alone, the combination was even more effective. Interestingly, the combinations of FMD or high-dose vitamin C with the common chemotherapeutic drug oxaliplatin were all equally effective. However, the combination of FMD, vitamin C, and oxaliplatin was the most effective at delaying tumor growth and improving survival, indicating potential synergism between traditional drugs and these non-toxic adjuvants (Di Tano 2020).

Vitamin D

Vitamin D is a fat-soluble vitamin with two major forms: Vitamin D2, ergocalciferol, which is obtained from a few plant sources such as mushrooms and is the more common form in supplements and fortified foods; and vitamin D3, cholecalciferol, which is generated in sun-exposed skin and obtained from food sources such as egg yolks and oily fish. Vitamin D3 is also increasingly used in supplements. Both forms pass through the liver and kidneys, where they are converted into 25-hydroxyvitamin D (calcidiol) and 1,25-hydroxyvitamin D (calcitriol), respectively. Calcitriol binds to vitamin D receptors on cell surfaces and is responsible for functions such as regulation of calcium metabolism (Balvers 2015; Veldurthy 2016; Tripkovic 2012).

Vitamin D has many beneficial effects that may inhibit the onset and progression of cancer. Among these are its ability to interfere with cancer cell signaling pathways, stimulate cancer cell death, promote normal cell division and maturation, and inhibit new blood vessel growth. Low vitamin D levels have been associated with greater risks of and higher mortality from some cancers, including skin, breast, prostate, colorectal, bladder, kidney, pancreatic, lung, and ovarian cancers (Moukayed 2017). In a large meta-analysis of studies in women with breast cancer, increasing vitamin D levels were strongly correlated with decreasing mortality rates (Hu 2018). In a study published in the *Journal of Clinical Oncology*, vitamin D supplementation was shown to decrease cancer-related mortality. The meta-analysis of 10 randomized controlled trials included nearly 80,000 participants given vitamin D supplements for at least three years. Vitamin D did not affect cancer incidence, however, those who took vitamin D experienced a 13% reduction in cancer-related deaths compared with placebo (Samji 2019). A review of studies found strong evidence for a relationship between sun exposure and lower risks of 15 types of cancer, and weaker evidence for nine other types (Grant 2012). In addition, people diagnosed with cancer in the summer or fall, when vitamin D production is highest, have been reported in some, but not all, studies to have a greater chance of favorable outcomes compared with individuals diagnosed in the winter or spring (Moukayed 2017).

Although findings from clinical trials are limited, vitamin D supplementation appears to reduce the occurrence and progression of some types of cancer (AlMatar 2017; Jacobs 2016). In conjunction with conventional treatments, vitamin D supplements have been shown in some studies to benefit individuals with breast, prostate, and colorectal cancers, as well as melanoma (Jacobs 2016; Pandolfi 2017). Supplement-induced improvements in cancer treatment outcomes are likely to be more pronounced in persons with vitamin D insufficiency and deficiency (Brenner 2017; Helde-Frankling, Bjorkhem-Bergman 2017).

Vitamin D supplements may help patients receiving palliative care for incurable cancer by decreasing pain, preventing infection, and improving overall well-being (Bjorkhem-Bergman 2016). In patients with advanced incurable cancers and vitamin D insufficiency or deficiency (levels <75 nmol/L or 30 ng/mL), adding 4,000 IU per day of vitamin D reduced cancer-related pain and use of opioid medications to control pain, and increased quality of life after one month, as well as reduced infections and use of antibiotics after three months (Helde-Frankling, Hoijer, 2017). Vitamin D has been proposed to help limit cancer treatment-induced bone loss in patients using hormone therapies to manage breast and prostate cancers (Handforth 2018; Hadji 2017).

Chemotherapy itself appears to decrease production of vitamin D in the body (Fakih 2009; Kennedy 2013). In a study involving 77 women with locally advanced breast cancer, nearly 80% of the participants had vitamin D insufficiency at the start of chemotherapy. After 7 cycles of chemotherapy, 97.4% of the women had vitamin D insufficiency (Jacot 2012). In another study, 81.5% of patients newly diagnosed with acute myeloid leukemia receiving chemotherapy had vitamin D deficiency (levels <20 ng/mL) at the beginning of treatment. After 28 days of treatment, the average vitamin D level had decreased below the pre-treatment average. Patients with higher levels of vitamin D responded better to treatment (Seyedalipour 2017). In patients with colorectal cancer, severe vitamin D deficiency was found in one study to be 3.7-fold more likely in patients who had received chemotherapy than those who had not, leading the authors to conclude that patients with colorectal cancer, especially if they are receiving chemotherapy, should consider vitamin D supplementation (Fakih 2009).

A secondary analysis of the VITAL randomized controlled trial was performed between November 2011 and December 2017 to assess the effect of daily supplementation with vitamin D3 (2,000 IU) on advanced or fatal cancer incidence (Chandler 2020). A total of 25,871 subjects with a mean age of 67 years participated in the intervention period, which occurred over a mean of 5.3 years. The results showed no significant difference for cancer occurrence between groups; however, there was a significant 17% reduction in a composite of metastatic and fatal cancer incidence in the treatment group compared with placebo. When stratified by body mass index (BMI) in comparison with placebo, there was a 38% reduction in metastatic and fatal cancer for those with normal BMI, but no statistically significant difference for those who were overweight or obese. These results may be explained in part by the disparate vitamin D storage patterns in overweight and lean individuals: those with greater amounts of adipose tissue may require higher dosages to achieve optimal serum 25-hydroxyvitamin D because adipose tissue serves as a reservoir for vitamin D (Abbas 2017; Carrelli 2017).

Monitoring vitamin D status with blood tests and adjusting the dose based on results may be the most effective means of achieving and maintaining adequate levels (Jacot 2016).

Vitamin E

Vitamin E is a fat-soluble vitamin that occurs in eight different forms in nature: four tocopherols (alpha, beta, gamma, and delta) and four tocotrienols (alpha, beta, gamma, and delta) (Caraffa 2016). Nuts, seeds, and plant oils are rich sources of vitamin E. The vitamin is best known for protecting fatty molecules and tissues from oxidative damage and for reducing inflammation. Although alpha-tocopherol is the most studied form of vitamin E, other forms appear to have unique properties, in some cases superior to alpha-tocopherol, related to preventing and treating chronic disease (Jiang 2014). Both tocopherols and tocotrienols have been found to have anticancer effects (Zarogoulidis 2013).

Although a number of studies have noted a relationship between low vitamin E intake or levels and increased risks of various cancers (Dong 2017; Chen, Jiang 2016), clinical trials with alpha-tocopherol supplements have yielded disappointing results (Yang, Suh 2013). In one trial, the combination of 400 IU per day of alpha-tocopherol plus 200 micrograms per day of selenium actually increased the risk of high-grade prostate cancer, but 50 IU per day of alpha-tocopherol reduced both the risk of, and risk of death from, prostate cancer in another trial (Albanes 2014).

Emerging evidence suggests that non-alpha-tocopherols, particularly gamma-tocopherol and delta-tocopherol, may be more important and effective for preventing cancer progression. Gamma- and delta-tocopherols inhibit the activity of a major inflammatory enzyme known as COX-2 and are more versatile free-radical scavengers than alpha-tocopherol (Das Gupta 2016; Abraham 2018). Gamma- and delta-tocopherols have been shown to interfere with hormone signaling, suppress growth and proliferation, and promote cell death in several cancer cell lines (Yang, Suh 2013; Das Gupta 2016). In addition, gamma-tocopherol and a tocopherol mixture emphasizing gamma-tocopherol have demonstrated tumor-inhibiting effects in animal models of prostate, breast, and colorectal cancers (Das Gupta 2016). The observed negative effects of high-dose alpha-tocopherol supplementation may be due in part to a resulting depletion of gamma-tocopherol from blood and tissues (Jiang 2014).

Tocotrienols also appear to be promising anticancer agents. Not only do tocotrienols inhibit inflammatory enzymes like COX-2, laboratory experiments show they also suppress inflammatory signaling involving NF-kappaB; reduce cancer cell proliferation; stimulate cancer cell death; interfere with cancer cell metabolism;

suppress CSCs; and inhibit invasion, metastasis, and new blood vessel formation (Abraham 2018; Jiang 2017; Husain 2017; De Silva 2016).

In a early-stage trial in patients with pancreatic cancer, 200–1,600 mg per day of delta-tocotrienol taken for two weeks before pancreatic surgery led to increased tumor cell death in surgical tissue samples (Springett 2015). Laboratory research further suggests that tocotrienols may sensitize cancer cells to chemotherapy drugs (Sailo 2018). Findings from a prostate cancer cell study suggest that gamma-tocopherol may enhance the anticancer effects of delta-tocotrienol, indicating that synergism between different vitamin E forms may be important to their anticancer effects (Sato 2017).

Vitamin K

Vitamin K is a fat-soluble vitamin with a well-known role in blood clotting (Dahlberg 2017). The importance of vitamin K in other aspects of health, including bone, cardiovascular, joint, cognitive, and metabolic health, have more recently been recognized, and some of its functions are still being discovered (DiNicolantonio 2015; Kaneki 2006; Schwalfenberg 2017). Vitamin K occurs in two main forms: vitamin K1, phylloquinone, which is found in green leafy vegetables and other plant foods; and vitamin K2, a family of molecules called menaquinones (MK-4 through MK-13) made from vitamin K1 by bacteria, including some that reside in the intestine, and animals. Vitamin K2 is found in some fermented and cultured foods as well as animal products (Schwalfenberg 2017; Okano 2016; Shea 2016).

In a study that followed more than 7,200 participants for 2.8–5.8 years, higher dietary vitamin K1 intake was associated with a lower risk of death due to cancer, as well as death from any cause (Juanola-Falgarona 2014); however, for prostate cancer specifically, vitamin K2 may be more effective at reducing cancer development and progression (Dasari 2017; Nimptsch 2010).

Several clinical trials have examined the effects of vitamin K in patients with liver cancer. A review of four trials in patients with liver cancer reported that treatment with vitamin K1 led to slowing of tumor growth and longer survival. All of these trials used the extraordinarily high dose of 40 mg per day; nevertheless, no toxicity was reported (Lamson 2003). Case studies have reported beneficial effects from high doses of vitamin K2 (45–90 mg per day) in individuals with blood cell cancers (Lamson 2003).

A synthetic vitamin K2 analog called menatetrenone has been investigated as a potential adjuvant therapy for liver cancer. In a meta-analysis of six randomized trials with a combined total of 930 participants, menatetrenone was found to reduce long-term recurrence rates and improve survival rates in patients with liver cancer treated with surgery (Zhong 2013). In one randomized controlled trial, the use of 45 mg of menatetrenone daily after liver surgery led to fewer recurrence over five years of monitoring (Ishizuka 2012).

Vitamin K has demonstrated anticancer activity against several cancer cell types in the laboratory, including lung (Nimptsch 2010; Yoshida 2003), breast (Kiely 2015), pancreatic, and colon cancer cells. The anticancer effects of vitamin K are induced by increasing oxidative stress, inhibiting cell division and proliferation, promoting cell death, and modulating cellular signaling pathways in cancer cells (Dasari 2017; Jinghe 2015). Furthermore, vitamin K has been found to enhance the effectiveness of the chemotherapy agent sorafenib in liver cancer cells in the laboratory (Ha 2015).

Update History

The protocols raise many issues that are subject to change as new data emerge. None of our suggested protocol regimens can guarantee health benefits. Life Extension has not performed independent verification of the data contained in the referenced materials, and expressly disclaims responsibility for any error in the literature.

References