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*INVITED REVIEW ARTICLES*

# Complementary and Integrative Medicine in Lung Cancer: Questions and Challenges

Moshe Frenkel, MD,[1,2] Robert Slater, MD,[1] Kenneth Sapire, MD,[3] and Victor Sierpina, MD[1]

**Abstract**

Lung cancer represents 13% of all cancers, making it the second most common type of malignancy in the United States. Lung cancer is the leading cause of cancer death in men and women in the United States and accounts for nearly 18% of all deaths from cancer. Because of its high mortality rate, lung cancer is associated with an increased rate of distress. Patients use various strategies to cope with this distress during and after cancer treatments, and complementary and integrative medicine (CIM) has become a common coping strategy. This review covers major questions and challenges of incorporating CIM during and beyond treatment for lung cancer. The questions revolve around determining the value of nutrition and nutritional supplements, assessing the role of exercise, addressing the mind–body connection, enhancing the benefit of immunotherapy, and determining the benefit of incorporating complementary therapies such as acupuncture and homeopathy. This review may provide a basis for discussion that can enhance patient–doctor dialogue regarding the use of CIM during and after treatment for lung cancer.

**Keywords:** complementary medicine, alternative medicine, lung cancer, immunotherapy, patient–doctor communication, nutrition



## Introduction

Lung cancer is the most common cancer, comprising more than 13% of new cancer cases worldwide.[1,2] It is a highly lethal cancer because nearly 80% of cases are discovered in advanced stages. In the United States, lung cancer is the leading cause of cancer deaths in both men and women; the 5-year overall survival rate is 18.1% but can be up to 55.6% for localized disease.[3]

Because of its high mortality rate, lung cancer is associated with an increased rate of distress. Patients use various strategies to cope with this distress during and after cancer treatments, and complementary and integrative medicine (CIM) has become a common coping strategy. Most patients with lung cancer experience various symptoms related to either the disease or its treatment. The most commonly reported symptoms are pain, fatigue, weakness, depression, anxiety, nausea, and poor well-being.[4–7] As a result, there is a constant search for additional options for care that can be incorporated into the treatment plan. This search may be associated with patients' core beliefs of how to restore their wellness and effectively manage their symptoms. The use of CIM falls into this category. Studies show that 23%–66% of lung cancer patients turn to CIM interventions such as the use of medicinal herbs, dietary supplements, and other complementary therapies in conjunction with conventional treatments.[4–7] Patients use these interventions to reduce symptoms and the toxic effects of standard therapies and improve their ability to heal, as well as for an increased sense of autonomy and control.[5,8–10]

The use of CIM in patients with lung cancer raises multiple questions. Most of these questions surround six main areas of CIM: nutrition, nutritional supplements, physical activity, mind–body therapies, enhancing immunotherapy, and complementary therapies. Currently there is not enough evidence to support the use of any of these treatments in obtaining a cure. However, multiple studies suggest that CIM may be beneficial for patients with lung cancer. This

[1]Department of Family Medicine, The University of Texas Medical Branch at Galveston, Galveston, Texas.
[2]Integrative Medicine Program, Institute of Oncology Meir Medical Center, Kfar Saba, Israel.
[3]Department of Anesthesia and Perioperative Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas.

review addresses the main questions and challenges related to the use of CIM, in its various forms, in patients with lung cancer. The authors anticipate that this information will be helpful to clinicians seeking to counsel their patients with lung cancer using a patient-centered and informed approach.

## Nutrition

One of the main issues that patients affected by cancer request an integrative oncology consultation relates to the issue of nutrition.[6–9] Although few studies have evaluated nutritional interventions in patients with active lung cancer, many studies have examined which foods and dietary patterns affect the risk of developing the disease. The 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Report, ''Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective,'' which was first published in 1997, updated in 2007, and updated again in 2018, provides a comprehensive review of the relationship between certain food groups and lung cancer, in prevention as well as survivorship. In that document, the authors cited studies that discuss the role of fruits, vegetables, carotenoids, flavonoids, red meat, and others.[11] The main possible beneficial foods, as well as foods that have a possible detrimental effect as hinted in the research arena, are listed in Table 1.

### *Fruits and vegetables*

A recent systematic review and meta-analysis evaluated the impact of fruit and vegetable consumption on the risk of lung cancer. Across the 18 studies included, high intake of fruits and vegetables reduced the risk of lung cancer by 14% (relative risk [RR] = 0.86; 95% confidence interval [CI] = 0.78–0.94).[12] A dose–response association was observed, although consumption of more than 400 g (about 1 pound) per day did not confer additional protection. This beneficial effect was significant in current smokers, but not in former or never smokers.[12]

In terms of lung cancer prevention, fruits had a more beneficial effect than vegetables, with a risk reduction of 18% (95% CI = 0.76–0.89; $n = 29$ studies and 15,599 cases) when comparing the highest intake of fruits with the lowest intake.[12] A 15% reduction in lung cancer risk (95% CI = 0.78–0.93; $n = 15$ studies and 12,021 cases) was observed when examining citrus fruits in isolation, and a dose–response relationship was observed with intakes up to 70 g.[12]

Vegetable intake is also helpful for lung cancer prevention, with a summary RR estimate of 0.92 (95% CI = 0.87–0.97; $n = 25$ studies and 19,095 cases) between the highest and lowest intake, although this association was statistically significant only for current smokers. A dose–response association was observed for vegetables; the risk was decreased by 18% for intakes of up to 300 g (two-thirds of a pound) per day.[12] The 2018 report suggests that there is limited but generally consistent that lung cancer risk is decreased with increased intake of nonstarchy vegetables (specifically green leafy vegetables) and nonstarchy root vegetables, such as tubers and beets, carrots, artichokes, asparagus, avocados, beans, and others. Data extracted from 10 studies showed a significant inverse association per 80 g of vegetables consumed per day, but this was a nonlinear dose response for intakes of up to 300–400 g/day.[11] Regarding particular types of vegetables, green leafy vegetables reduced the risk by 15% (95% CI = 0.75–0.96; $n = 9$ studies and 5783 cases), slightly

Table 1. Foods and Supplements That May Be Beneficial or Harmful in Patients with Lung Cancer

| | *Recommended* | *Avoid* |
|---|---|---|
| Foods | Fruits[11,12]<br>Nonstarchy vegetables (green leafy vegetables, nonstarchy root vegetables, tubers, and carrots)[11,12]<br>Foods high in carotenoids (carrots, cantaloupe, sweet potatoes, tomatoes, pumpkins, spinach, apricots)[11,13]<br>Foods high in selenium (Brazil nuts, cremini mushrooms, tuna, halibut, salmon, scallops, organic eggs, shiitake mushrooms, barley, grass-fed beef, turkey)[11]<br>Foods high in quercetin (capers, dill, kale, buckwheat, sweet potatoes, apples)[14,15]<br>Green tea[83]<br>Spices: turmeric,[84] black cumin[85]<br>Soy[86]<br>Garlic[87]<br>Pomegranate[88] | Red meat[11,16]<br>Processed meat[11,16]<br>Diets high in Glycemic Index[89] |
| Supplements | Astragalus[47,48]<br>Omega 3 (EPA:DHA ≥4:1)[36–41]<br>Curcumin[84]<br>Ginseng[90]<br>Sun soup[91]<br>*Trametes versicolor*[49,50]<br>Homeopathic remedies[73,78–82]<br>Melatonin[42–46]<br>Vitamin D (early stage)[30–34]<br>Probiotics[68–71] | Selenium[11]<br>Vitamin A[11]<br>β-carotene[11,22]<br>Vitamin D (advanced stage)[35] |

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more than the 13% reduction seen for cruciferous vegetables (95% CI = 0.79–0.97; $n = 11$ studies and 11,467 cases).[12]

### *Carotenoids*

A substantial amount of evidence shows that food containing carotenoids (e.g., sweet potatoes, carrots, tomatoes, pumpkins, spinach, cantaloupe, and apricots) has a protective effect against lung cancer.[11] Fruits and vegetables high in β-carotene provide a 23.2% reduced risk of lung cancer (95% CI = 0.675–0.874; $n = 18$ studies and 9372 cases) when comparing the highest with the lowest dietary intake, according to a 2015 meta-analysis.[13] A clear dose–response relationship is evident from cohort studies. The more one consumes dietary carotenoids, the more the risk of developing lung cancer is reduced. Data extracted from several studies with a total of 400,000 participants, including 3100 lung cancer patients, with a follow-up period of 7–16 years, suggest that those who consumed the most carotenoids had a 24% decreased risk of developing lung cancer.[11]

Supplements of β-carotene, however, are not recommended. Findings from the new edition of WCRF/AICR document reveal that high-dose beta carotene supplements are a convincing cause of lung cancer in current and former smokers.[11] The protective effect of dietary intake of carotenoids may be lost or reversed by the higher doses that pharmacologic supplementation provides.[11]

### *Flavonoids*

Flavonoids, which are phytochemicals in food products derived from plants, often contribute to the color of the foods. Foods such as berries, dill, buckwheat, red onions, kale, cranberries, sweet potatoes, apples, and others contain flavonoids. Flavonoid intake has been shown to be associated with a decreased risk of lung cancer, particularly for current smokers. A 2013 meta-analysis of dietary flavonoid intake showed a marginally significant reduction in lung cancer risk of 16% (95% CI = 0.71–1.00; $n = 8$ studies),[14] which differs from a prior meta-analysis that showed a statistically significant 24% risk reduction with a dose–response association.[15] For flavonoid subclasses, lung cancer risk appears to be most significantly reduced by the flavonols quercetin (34% risk reduction; 95% CI = 0.47–0.92; $n = 5$ studies) and kaempferol (22% risk reduction; 95% CI = 0.64–0.95; $n = 5$ studies).[15]

### *Red meat and processed meat*

In the 2018 WCRF report, there was limited but consistent evidence that consumption of red meat and processed meat increases risk of lung cancer. The dose–response meta-analysis showed a significantly increased risk of lung cancer per 100 g of red meat and 50 g of processed meat.[11]

Other studies suggest that among current and former smokers (the COSMOS screening study), there is a significant 73% increased risk (CI = 1.15–2.61; $p = 0.002$; $n = 178$ cases) of lung cancer for those with the highest meat consumption.[16]

### *Mediterranean diet*

In terms of overall dietary patterns, the Mediterranean diet is well established for the prevention of cardiovascular disease[17] and likewise appears promising for lung cancer prevention. The COSMOS screening study of 4336 heavy smokers revealed an 80% lower risk of lung cancer diagnosis among participants with a strong adherence to the Mediterranean diet.[18] That study also suggested that a high dietary inflammatory index increases the risk. An earlier case–control study of individual components of the Mediterranean diet showed protective effects with high consumption of carrots, tomatoes, and white meat and statistically significant protection with high consumption of sage and the exclusive use of olive oil.[19]

Additional beneficial foods are listed in Table 1.

## Nutritional Supplements

Nutritional supplements include herbal remedies, minerals, vitamins, and certain other substances. Supplements are one of the easiest type of CIM therapies for cancer patients to use, and 20%–90% of patients affected by cancer use supplements.[20] Patients tend to use nutritional supplements as a type of psychologic support; they want to feel hopeful or have a sense of control in the decision-making process, so that they feel they are doing everything possible.[20,21] Patients also use supplements to help reduce side effects of conventional treatments and enhance their quality of life. Typically patients are not seeking a cure for their disease with supplements.[21]

Although foods high in vitamins and minerals appear to reduce the risk of lung cancer, studies of micronutrient supplements thus far have not shown convincing evidence for the prevention of lung cancer. A 2012 Cochrane review of randomized controlled trials of vitamin A, vitamin C, vitamin E, and selenium supplementation found no significant risk reduction for the general population and a small but significant increased risk with β-carotene supplementation in smokers and individuals exposed to asbestos.[22] However, a few other studies suggest that adding nutritional supplements could reduce the risk of lung cancer or improve the benefit of conventional care during and after treatment.[23–29]

A meta-analysis from 2014 showed a 17% lung cancer risk reduction (95% CI = 0.734–0.937; $n = 21$ studies and 8938 cases) when comparing highest and lowest intake of vitamin C, with a linear 7% dose–response reduction with every 100-mg increase per day, but the analysis did not distinguish between dietary and supplemental intake.[23] In addition, a 2017 meta-analysis of vitamin E intake showed a 16% lung cancer risk reduction (95% CI = 0.76–0.93; $n = 11$ studies and 4164 cases), with a dose–response decrease in risk of 5% for every 2-mg increase per day in dietary vitamin E intake.[24]

Preliminary studies suggest that the use of antioxidant vitamins and minerals following a diagnosis of cancer reduces chemotoxicity and radiotoxicity during treatment; positive findings were observed in 34 of 46 trials in a 2016 systematic review.[25] However, there remains a concern that antioxidant supplementation could reduce the therapeutic effects of free radical-generating radiotherapy or chemotherapeutic agents such as the platinum compounds (e.g., cisplatin), and current evidence regarding treatment outcomes is not definitive.[25]

For lung cancer specifically, two preliminary Mayo Clinic cohort studies showed improved survival in patients with small-cell lung cancer (SCLC; RR = 0.65; 95% CI = 0.43–

1.00; $p = 0.05$; $n = 178$) and non-SCLC (NSCLC; RR = 0.74; 95% CI = 0.44–0.65; $p < 0.01$; $n = 1129$) who used vitamin or mineral supplements, along with improved quality of life in the NSCLC cohort.[26,27] An early study of 18 patients with SCLC showed improved survival with supplementation of vitamins, trace elements, and fatty acids,[28] and a randomized controlled trial of 136 patients with advanced NSCLC showed improved survival with supplementation, although this was not statistically significant.[29] More research is needed to determine whether antioxidant supplementation is appropriate during curative regimens, although use in palliative settings is likely worth consideration.

Nutritional supplements that have a possible benefit are listed in Table 1. Leading nutritional supplements such as vitamin D, fish oil, *Astragalus*, and melatonin are discussed in more detail.

### *Vitamin D*

Three meta-analyses published in 2017 examined the relationship between vitamin D and lung cancer. Regarding the prevention of lung cancer, high serum 25-hydroxyvitamin D levels were associated with a 16% risk reduction (95% CI = 0.74–0.95; $n = 17$ studies and 4368 cases), and each 10 nmol/L increase in 25(OH)D levels conferred an 8% reduction in lung cancer risk and a 7% reduction in lung cancer mortality.[30] One meta-analysis showed a nonsignificant correlation between overall survival in patients with lung cancer and low circulating 25(OH)D levels (adjusted hazard ratio = 1.25; $p = 0.13$; $n = 8$ studies),[31] and another showed no relationship at all (RR = 1.01; 95% CI = 0.88–1.16; $p < 0.001$; $n = 5$ studies).[30] Finally, high vitamin D intake was associated with a 28% reduced risk of lung cancer (95% CI = 0.61–0.85; $p < 0.001$), particularly in nonsmokers.[32]

One group of researchers took another approach to the question of vitamin D supplementation: they found that the stage of disease was an important factor. In their studies, in the early stages of the disease, surgery combined with dietary vitamin D intake was associated with significantly improved survival rates in patients with NSCLC.[33] In addition, levels of circulating vitamin D in the early stages of disease were directly correlated with survival in these patients.[34] In patients with advanced-stage NSCLC, the situation was more complex. The *C/C* genotype of the *Fok*I polymorphism, which is thought to have increased vitamin D receptor activity, was associated with improved survival. However, the *G-T-C* (*Cdx-2-Fok*I-*Bsm*I) polymorphism, which is thought to have reduced vitamin D receptor activity, was associated with poor survival. This suggests that in patients with certain types of advanced disease, supplementation with vitamin D might increase mortality and those patients should avoid the use of vitamin D. Thus, caution is needed. Researchers concluded that further studies are needed to confirm vitamin D's role in improving outcomes in patients with advanced lung cancer.[35]

### *Fish oil*

Multiple *in vitro* studies have shown that omega-3 polyunsaturated fatty acids (fish oil) have activity against lung cancer cell lines.[36–38] There is also some evidence that adding fish oil in clinical care carries some benefit. Lung cancer patients who used fish oil supplements during chemotherapy showed significantly higher rates of response and objectively longer overall survival. These benefits were not accompanied by any increase in dose-limiting toxicities.[39]

In a double-blind experiment with 40 patients with stage III NSCLC, patients were randomized to receive an oral nutritional supplement containing n-3 polyunsaturated fatty acids (2.02 g eicosapentaenoic acid +0.92 g docosahexaenoic acid per day) or an isocaloric control supplement during multimodality treatment. Patients in the intervention group reported a significantly higher quality of life, physical and cognitive function, global health status, and social function than those in the control group.[40] In a small multicenter, randomized, double-blind trial with 33 patients diagnosed with advanced inoperable NSCLC and undergoing chemotherapy, eicosapentaenoic acid + docosahexaenoic acid supplementation was associated with a significant increase in weight, as well as anti-inflammatory and antioxidative effects.[41]

### *Melatonin*

Melatonin is a hormone produced within the pineal gland from tryptophan, which is converted to 5-hydroxytryptophan and finally to melatonin. Numerous recent *in vitro* studies have shown promise for the use of melatonin in the treatment of lung cancer.[42–44] Earlier human studies by Lissoni et al. showed significantly increased survival and quality of life among lung cancer patients who used melatonin supplementation.[45] However, a 2014 randomized controlled trial of 151 patients with NSCLC that showed improved quality of life with treatment with melatonin (either 10 or 20 mg) revealed no significant difference in median survival.[46]

### Astragalus

*Astragalus* is a unique herbal remedy that has been used in Traditional Chinese Medicine for thousands of years. *Astragalus* is an adaptogenic herb that is thought to play a role in protecting the body against various stressors, including physical, mental, or emotional stress. The *Astragalus* root has antioxidant effects and also affects the immune system. It contains a variety of components, including saponins such as astragaloside, polysaccharides, multiple trace minerals, flavonoids, and amino acids.[47]

A 2016 meta-analysis of *Astragalus* use in patients with advanced NSCLC showed improved overall survival (hazard ratio = 0.61; 95% CI = 0.42–0.89; $p = 0.011$; $n = 17$ studies and 1552 patients), improved performance status (RR = 0.43; 95% CI = 0.34–0.55; $p < 0.001$), and tumor overall response rate (RR = 0.7982; 95% CI = 0.715–0.89; $p < 0.001$), and fewer side effects compared with platinum-based chemotherapy alone.[48]

### Trametes versicolor (Coriolus versicolor)

*Trametes* (*Coriolus*) *versicolor* is a mushroom, also known as turkey tail, that contains several polysaccharides, including polysaccharide peptide and polysaccharide krestin, both shown to have antitumor and immunomodulating effects.[49] A 2015 systematic review of polysaccharide K from *T.* (*C.*) *versicolor* showed supportive evidence for activity against lung cancer in 15 of 17 preclinical studies, improved survival

in 5 nonrandomized clinical trials, and objectively improved quality of life and survival in 6 randomized controlled trials.[50]

### Physical Activity

Physical activity is known to improve quality of life during and after cancer therapy. These effects include alleviating physical and mental fatigue, reducing anxiety, increasing cognitive function, improving self-esteem, increasing muscle tone and balance, helping manage weight, enhancing the immune system, and even reducing the chances for other illnesses such as heart disease, adult-onset diabetes, and osteoporosis.[11,51] In a systematic review of 45 U.S. National Cancer Institute-designated comprehensive cancer center websites, researchers found that the most common CIM therapy, that is being discussed, is exercise (97.8%).[52]

Evidence from prospective and case–control studies has shown that the risk of lung cancer is reduced with increasing levels of physical activity. The 2007 WCRF/AICR report mentioned 5 cohort studies investigating the relationship between total physical activity and lung cancer, 2 cohort studies investigating nonrecreational activity, and 11 cohort studies and 4 case–control studies investigating recreational activity as it relates to lung cancer risk. Overall, most studies showed a decreased risk with increased physical activity.[11] Extrapolating from other studies investigating different types of cancer, clinicians often suggest 150 min of walking per week at a speed of 2–2.9 miles/h (3.2–4.6 km/h).[53]

Exercise training can be beneficial at all stages of treatment for lung cancer. Before surgery, after surgery, during treatment, and even during palliative anticancer therapy in patients with advanced (inoperable) lung cancer who have compromised lung function, supervised exercise-based pulmonary rehabilitation is thought to improve cardiorespiratory fitness and functional capacity.[54] A recent randomized controlled study examined the effects of a 12-week exercise intervention on sleep and quality of life in 111 patients with lung cancer. In that study, the intervention included home-based walking exercise and weekly exercise counseling. Researchers found that sleep in the exercise group was significantly improved at 3 and 6 months after the intervention. The researchers concluded that walking is an effective intervention for improving subjective and objective sleep quality in patients with lung cancer and can be considered an additional element of lung cancer rehabilitation.[55]

### Mind–Body Therapies

Mind–body therapies, including stress reduction, meditation, yoga, massage, and music therapy, are commonly used in most comprehensive cancer centers in the United States. This increased use reflects the current understanding that these therapies have an essential role in approaching cancer patients in general.[52] Stress, when experienced chronically, leads to the activation of neuroendocrine pathways, including the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis. Biologic mechanisms identified as having potential direct carcinogenic effects on the sympathetic nervous system include DNA repair, oncogene activation, inflammation and immune response, hematopoiesis, angiogenesis, survival, and apoptosis.[56]

In a recent study, researchers found that prolonged employment in a stressful job was associated with increased odds of developing cancers of the lung.[57] In addition to stress being a possible etiologic factor in lung cancer development, the diagnosis of lung cancer by itself is a cause for emotional reactions such as anxiety, stress, depression, and fear.[58] Untreated mood disorders can negatively affect a patient's quality of life, level of pain, and response to chemotherapy. Reducing negative emotions, such as depression, may increase survival.[59,60]

Animal studies also support this observation; psychologic distress was shown to be associated with faster tumor growth and spread in mice.[61,62] Because most patients are diagnosed with lung cancer in the advanced stage, when the prognosis is poor, the stress and anxiety that these patients experience are quite high. Most CIM practitioners agree that integrating mind–body therapies in cancer care is an essential element in caring for patients with cancer, especially in patients with a poor prognosis.[63]

Some argue that current research includes a limited number of controlled studies in oncology populations, and thus, no clear conclusions can be drawn. However, the few published trials appear to show that mind–body therapies have promising effects on the immune system, health-related quality of life, functional capacity, and mood. As a result, most cancer centers do combine mind–body therapies into their CIM care plan. In a study of 265 patients, including those with lung cancer, conducted at The University of Texas MD Anderson Cancer Center, patients' distress was shown to be relieved by using a patient-centered communication style and integrating mind–body therapies into the patients' care.[64]

A recent review of the literature suggested that mind–body modalities as part of a multidisciplinary approach can help reduce anxiety, mood disturbance, pain, nausea, vomiting, sleep disturbance, and general well-being in patients with lung cancer.[54] Most of the research on mind–body therapies such as meditation, mindfulness-based stress reduction, yoga, massage, *t'ai chi*, *qigong*, and others suggests that these therapies are safe and beneficial for patients with lung cancer if performed by skilled practitioners.[54] The authors of the American College of Chest Physicians guidelines expanded on this idea and suggested that for lung cancer patients whose anxiety or pain is not adequately controlled by usual care, the addition of massage therapy performed by trained professionals can be helpful in reducing anxiety and improving well-being, as part of a multimodality cancer supportive care program.[54]

### Enhancing Immunotherapy

Immunotherapy is the use of medicines to stimulate a patient's own immune system to recognize and destroy cancer cells. Immunotherapy has moved to the center stage of cancer treatment with the recent success of trials of PD-1/PD-L1 axis blockade in solid tumors. This type of approach is becoming one of the leading new advances in treating some forms of NSCLC.[65] However, despite improvements in tumor response leading to the initial excitement about immunotherapy, these therapies also induce a range of responses that are hard to predict, accompanied with multiple toxic effects in the skin, gastrointestinal tract, lungs, and endocrine system.[66]

Information about the benefits of incorporating CIM to reduce these toxic effects and improve therapeutic coverage

is limited because this field is still in its infancy. One recent study examined the safety of adding treatment with *Viscum album (European Mistletoe)*, a botanical commonly used in Europe to improve quality of life during cancer treatment, to immune checkpoint inhibitors. This herbal therapy neither altered nor increased the toxic effects of the immune checkpoint inhibitors.[67]

Another CIM treatment of interest in immunotherapy is probiotics. According to mouse studies and some early human studies, the gut microbiome helps to enhance the efficacy of immunotherapy. Two recent studies revealed that gut microbiota may enhance the antitumor immune responses to checkpoint inhibitors, resulting in tumor regressions.[68] In patients who were treated with antibiotics or were germ free, immune checkpoint inhibitors lost their therapeutic efficacy.[69]

Researchers have found that certain gut bacteria increase the therapeutic benefit of CTLA-4 blockade (Bacteroides) in melanoma,[69] whereas others enhance the effect PD-1 blockade (Clostridiales)[70] and PD-L1 blockade (Bifidobacterium).[68] These individual differences in microbiome composition may be one of the reasons that immunotherapies work better in some patients than others. Understanding this principle can lead to innovative approaches that may improve the efficacy of immunotherapy.

Current evidence already suggests that optimizing the gut microbiome might improve the therapeutic coverage of immune checkpoint inhibitors.[71] These studies suggest that manipulating the microbiome by adding a specific probiotic might lead to improvement in immunotherapy but requires further research, specifically in the context of lung cancer. Additional research is needed to provide an educated answer to this question.



## Complementary Therapies

In a recent guideline document from the American College of Chest Physicians on the use of CIM in lung cancer patients, the reviewed evidence revealed that CIM therapies can be beneficial to patients during and after treatments.[54]

### *Acupuncture*

In acupuncture, a technique derived from Traditional Chinese Medicine, trained practitioners stimulate specific points on the body by inserting thin needles into the skin. Acupuncture has been in use in various forms for more than 3000 years. In the past decade, acupuncture has become one of the most common CIM therapies used by patients affected by cancer. This technique is considered safe for use in the general population when practiced by an experienced practitioner.[52,72–74]

In response to the severity and persistence of symptoms related to cancer care, patients usually try acupuncture in conjunction with standard treatments. This use is generally considered safe when conventional treatment fails or has intolerable side effects.[72–74] In a set of American College of Chest Physicians guidelines, which are backed by clinical evidence, acupuncture was suggested as an adjunct treatment option for patients experiencing nausea and vomiting caused by chemotherapy or radiotherapy, as well as for patients with cancer-related pain and peripheral neuropathy that are poorly controlled.[54]

A more recent article, summarizing the current state of knowledge related to acupuncture use in cancer care, concluded that research has yielded promising evidence for the role of acupuncture in the management of several challenging symptoms for which existing standard options remain limited. These symptoms include pain, fatigue, hot flashes, nausea/vomiting, and xerostomia.[74] To evaluate the effectiveness of acupuncture as a potential treatment modality in symptomatic lung cancer patients, a cancer center in Canada conducted a prospective observational study. Researchers combined acupuncture with the conventional best care for that center and observed statistically significant improvement in pain, appetite, nausea, anxiety, and well-being. These effects were obtained with a minimum of six acupuncture sessions. The researchers concluded that acupuncture may be an effective approach for improving symptoms, especially pain and well-being, in lung cancer patients.[75]

Since then, additional studies have emerged suggesting that acupuncture might have a beneficial effect in other situations in cancer care. In a small randomized, double-blind, placebo-controlled pilot trial that aimed to evaluate the clinical effect of acupuncture on cancer-related fatigue in lung cancer patients, researchers found that Brief Fatigue Inventory scores were significantly reduced in participants who received active acupuncture compared with those receiving the placebo.[76]

In another study that investigated acupuncture for the relief of breathlessness in lung cancer, researchers performed a single-center, randomized phase II study of 173 patients with NSCLC or mesothelioma with a dyspnea score of >4 on the visual analog scale. In that study, patients were randomized to receive acupuncture alone, morphine alone, or both. Acupuncture was found to be effective in relieving dyspnea, and the changes in visual analog scale scores were not significantly different between treatment arms. In addition, acupuncture, alone and combined with morphine, reduced anxiety, with a significant improvement in visual analog scale relaxation scores. Morphine alone increased anxiety. The effects of acupuncture were evident at 90 min and maximal at 4 h, but the effects were sustained for up to 2 weeks.[77]

### *Homeopathy*

Homeopathy is a health system of care that is commonly practiced in Europe, Asia, and South America, mostly for minor ailments. Homeopathic remedies have appeared to be safe and free of adverse effects in multiple clinical trials.[73,78–81] However, it is unclear if homeopathy has any clinical effect in cancer patients, and until recently, homeopathy has not received attention as a possible option for care.

In a survey of 123 cancer centers across Europe, 47.5% of the centers provided CIM treatments. The leading CIM treatments in those centers were acupuncture (55.3%) and homeopathy (40.4%).[73] In another cross-sectional survey across eight European countries that specifically targeted lung cancer patients who use CIM, researchers found that homeopathy was also one of the leading CIM treatments.[5]

Data from multiple research disciplines, ranging from studies evaluating the effect of homeopathic remedies on

cancer cell lines to scientifically valid animal and clinical studies, suggest that homeopathy may have a role in improving quality of life in selected cancer patients.[78] In a recent study of an integrative oncology service in a large comprehensive cancer center in Israel, homeopathy was found to be successfully incorporated as a supportive care modality. Review of 124 files of cancer patients who received homeopathy for symptom relief revealed that nearly three-quarters of these patients reported a beneficial effect when they used homeopathic treatment for symptom relief.[79]

In another pragmatic randomized controlled trial in a comprehensive cancer center in Austria, with 410 cancer patients who were randomized to receive or not receive classic homeopathic adjunctive therapy in addition to standard therapy, researchers found that the subjective well-being of these patients improved significantly when they received adjunct classic homeopathic treatment in addition to conventional therapy.[80]

Some might argue that the intensive homeopathic interview conducted at baseline may have influenced the findings.

Most researchers seem to agree that given its low toxicity, homeopathy is a possible option for symptom management and supportive care. Whether these remedies have direct effects on the tumor or survival is a more complex issue. In Austria, researchers from the Medical University of Vienna collected survival data on 538 patients with fatal disease and poor prognosis who used homeopathy in addition to conventional cancer care. The study included patients with glioblastoma, lung cancer (both SCLC and NSCLC), metastatic renal cell carcinoma, and others.[82] Median overall survival was compared with experts' predictions of survival outcomes by specific cancer type. The researchers found that patients who received homeopathy survived longer than the expected prognosis, across all observed cancer types. Patients with SCLC and metastatic renal cell carcinoma had the best results. The expected median overall survival was 11.3 months for SCLC and 26.4 months for metastatic renal cell carcinoma, but the observed median overall survival was 47 months for patients with SCLC who received homeopathy and 61.4 months for patients with metastatic renal cell carcinoma who received homeopathy. Although these results were promising, the authors stressed the need for further study of homeopathic care in cancer patients.[82] These European studies suggest that there is an urgent need for homeopathic clinical trials in lung cancer.



## Summary

Most patients with lung cancer are diagnosed late in their disease process and thus have a poor prognosis and increased distress. As a result, a large percentage of these patients tend to use CIM. Patients use CIM therapies to reduce symptoms, lower the toxicity of conventional therapies, improve their ability to heal, and increase their sense of autonomy and control. Communicating openly with these patients and their families about the use of CIM is important for improving patients' quality of life and empowering them during the disease trajectory. A growing number of studies support the use of CIM interventions such as nutrition and dietary supplements, exercise, acupuncture, homeopathy, and mind–body approaches. These interventions reduce the severity of symptoms that relate to the disease and its treatment, increase well-being, improve quality of life, and may even improve the survival of these patients.

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Address for correspondence:
*Moshe Frenkel, MD*
*Department of Family Medicine*
*The University of Texas Medical Branch at Galveston*
*Hashoftim 1 B*
*Zichron Yaacov 30900 Israel*
*Galveston, TX*

*E-mail:* frenkelm@netvision.net.il