

Lung Cancer

Each year, an estimated 93,000 men and 82,000 women in the United States will be diagnosed with lung cancer, with a median age of 70 years of age (Jemal A et al 2006; Gloeckler Ries LA et al 2003). To date the prognosis is grim for most forms of lung cancer as the five-year overall survival rate of only 14 percent has hardly changed in the past 50 years (Sugimura H et al 2006). Cigarette smoking is the main cause of lung cancer; however, nonsmokers also develop the disease due to genetics, secondhand smoke, and exposure to toxins and radon gas (Toh CK et al 2006; Vukovic B et al 2005).

Novel approaches are urgently needed that reverse, suppress, or prevent lung cancer development (van Zandwijk N 2005). Early detection offers the best chance for long-term survival (Saba NF et al 2005). The conventional choices of treatment include surgery, chemotherapy, and radiotherapy and depend on the type and stage of the cancer (European Lung Cancer Working Party 2006). Irrespective of the treatment method used, complementary therapy, such as nutritional supplementation and the use of bioresponse modifiers, is an important addition to traditional treatment that could help control symptoms, enhance quality of life, and improve overall survival (Jatoi A et al 2005b).

WHAT IS LUNG CANCER?

Lung cancer is a disease in which cells in the lungs begin to grow out of control and interfere with normal lung functions such as breathing. The vast majority of lung cancer cases fall into one of two categories: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

NSCLC. NSCLC is the most common type of lung cancer, making up nearly 80 percent of all cases. This type of lung cancer grows and spreads more slowly than the other major type and is therefore more treatable. NSCLC is divided into three subtypes: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The five-year survival rate for patients with NSCLC is less than 25 percent (Jemal A et al 2006).

SCLC. SCLC accounts for 20 percent of all lung cancer cases. Its small cells can rapidly reproduce to form large tumors that quickly spread to the lymph nodes and other parts of the body. This type of lung cancer is almost always caused by smoking or secondhand smoke. SCLC responds well to chemotherapy and radiotherapy treatment initially. However, less than 5 percent of SCLC patients survive five years past diagnosis; a patient with untreated SCLC has an average survival time of two to three months (Toyooka S et al 2001).

Mesothelioma. Mesothelioma is diagnosed when cancer cells are found in pleural fluid or tissue. It is associated with asbestos exposure (70 percent of cases), and asbestos workers have a lifetime risk of 8 percent; tumors arise 20 to 40 years after asbestos exposure. Mesothelioma has a poor prognosis, with 75 percent of patients dying within one year and five-year survival being about 5 percent. Long-term survival has been reported in 50 percent of patients who receive a combination of surgical removal of cancer followed by chemotherapy during surgery and intraperitoneal chemotherapy soon after surgery.

WHAT CAUSES LUNG CANCER?

Lung cancer is a multistep process that involves cancer-causing agents (environmental carcinogens), inherited genes, and tumor promoters (e.g., inflammatory mediators) (Miller YE 2005; Philip M et al 2004; Tokuhata GK et al 1963). Cigarette smoking may cause as many as 90 percent of male and 79 percent of female lung cancers (Ozlu T et al 2005).

Smoking. Cigarette smoke contains potent cancer-causing derivatives of nicotine, and nicotine itself is directly involved in lung cancer development (Minna JD 2003). Smoking cessation is difficult because nicotine is highly addictive; however, nicotine replacement therapy combined with Zyban® (bupropion) enables a higher smoking cessation rate (L F et al 2005). Medicinal herbal tea made from cloves and milk vetch reduces smoking withdrawal symptoms and increases the rate of smoking cessation (Lee HJ et al 2005). In 2006, the Food and Drug Administration approved a new smoking cessation drug called Chantix™ (varenicline). This new drug is the first prescription medication approved for smoking cessation in almost a decade. It works by partially activating the nicotine receptors in the brain, thus reducing the craving for nicotine and reducing withdrawal symptoms. It also reduces the satisfaction gained by smoking, which may lessen addiction.

Nonsmokers get lung cancer too. Nonsmokers make up 10 to 15 percent of all lung cancer cases (Vastag B 2006). Many nonsmokers who develop lung cancer appear to carry a genetic tendency (Gorlova OY et al 2006).

Some cancer risk is inherited. A two- to threefold increase in lung cancer risk is associated with having a relative with lung cancer (Matakidou A et al 2005). Adults with retinoblastomas (inherited mutations in the retinoblastoma-1 (RB1) gene) and those with Li-Fraumeni syndrome (inherited mutations in the tumor suppressor p53 gene) may develop lung cancer (typically bronchial cancers) at a higher rate than the general population, suggesting a family association (Kleinerman RA et al 2000; Zalcman G et al 1994). The p53 and RB1 genes are both mutated in more than 90 percent of SCLCs, while p53 is mutated in more than 50 percent and RB1 in 20 percent of NSCLCs (Campling BG et al 2003; Horowitz JM et al 1990).

Some lung cancer is caused by exposure to toxins and viruses. Indoor exposure to secondhand smoke, radon gas, asbestos, and heavy metals (e.g., arsenic, nickel, chromium, iron oxide) and exposure to petrochemicals, polycyclic aromatic hydrocarbons, and human papillomavirus all cause lung cancer (Miller YE 2005; Vukovic B et al 2005; Chen YC et al 2004; Minna JD et al 2002; Hertz-Picciotto I et al 1993).

UNDERSTANDING AND REDUCING YOUR RISK

Smoking and secondhand smoke. More than 90 percent of lung cancers are unquestionably caused by tobacco and the 4000 cancer-causing substances in cigarette smoke (van Zandwijk N et al 2000). The risk of developing lung cancer increases 20- to 40-fold for lifelong smokers and 1.5-fold for people with long-term passive exposure to cigarette smoke. Population studies show that approximately 15 percent of heavy smokers will ultimately develop lung cancer but that, interestingly, 85 percent of heavy smokers will not develop lung cancer because of innate differences in cancer susceptibility, or in other words, genetics. If a family member has lung cancer, chances are your genes render you susceptible to cancer, and you should stop smoking.

The lung cancer death rate is related to the total number of cigarettes smoked, and the risk for a man smoking two packs daily for 20 years is 60- to 70-fold the risk run by a nonsmoker. Among individuals who smoke 15 or more cigarettes per day, reducing smoking by 50 percent significantly reduces the danger of lung cancer (Godtfredsen NS et al 2005). In addition, stopping smoking may prolong survival of cancer patients (Ozlu T et al 2005).

To reduce risk:

- Stop smoking. Use nicotine replacement therapy, Zyban®, counseling, and herbal tea made of cloves and milk vetch (Lee HJ et al 2005). A smoking cessation drug, Chantix™ (varenicline), is available by prescription.
- Increase intake of citrus fruits and tomatoes, which are high in beta-cryptoxanthin, lycopene, alpha-carotene, and lutein (Mannisto S et al 2004; Yuan JM et al 2001; Knekt P et al 1999; Le ML et al 1993).
- With the approval of your physician, take aspirin regularly (Moysich KB et al 2002).
- Take folate and vitamin B12, which improve abnormal bronchial cell growth in smokers (Heimbürger DC et al 1988).
- Consume green tea, whose polyphenols prevent DNA damage in lung cells exposed to oxidants from cigarette smoke.
- Test your home for radon gas.

Dietary factors. A low intake of fruits and vegetables and consumption of red meat and preserved and fatty foods increase risk (Kubik A et al 2004; Wang J et al 2004). Therefore, your diet should consist mostly of vegetables, fruits, raw foods, and fresh fish (Takezaki T et al 2003; Gao CM et al 1993). However, the genes one inherits play an important role in individual susceptibility to lung cancer (Lam WK et al 2004).

- The overall risk of lung cancer decreases by one half among those with a high intake of lettuce and cabbage, even among current smokers (Gao CM et al 1993).
- Chinese leek (*Allium tuberosum Rottler*), also known as Chinese chives, reduced lung cancer metastasis (spread) in mice by 40 percent and prevented cancer cell growth in experimental conditions (Shao J et al 2001).

See the section below titled “Preventing Lung Cancer” for more recommendations.

Genetics. Especially among nonsmokers, a genetic predisposition increases an individual’s susceptibility to cancer-causing agents (carcinogens) in the environment. Nonsmokers with a close family member stricken by cancer might reduce their lung cancer risk by about 25 to 50 percent by taking the following steps:

- Increasing intake of darkly colored vegetables and fruits
- Consuming carotene-containing fruits and vegetables—spinach, kale, carrots, cantaloupes, and sweet potatoes (Fabricius P et al 2003; Fontham ET 1990).

Lung disease. Lung diseases such as chronic obstructive pulmonary disease and infections such as tuberculosis, human papilloma virus, and *Microsporum canis* (skin fungus) are linked with a proinflammatory state and a high risk of lung cancer (Lam WK et al 2004; Biesalski HK et al 1998). Although most of these conditions are easily diagnosed and fairly well managed, smoking

cessation is a must.

Environmental carcinogens. Certain elements in the environment further increase one's risk of developing lung cancer. See the discussion under "Some lung cancer is caused by exposure to toxins and viruses" above.

HOW IS LUNG CANCER DIAGNOSED?

Approximately 5 to 15 percent of lung cancers are discovered in the course of a routine chest x-ray of people with no symptoms. However, more than 50 percent of new lung cancer cases will be diagnosed by the presence of symptoms that indicate cancer spread (metastasis).

Symptoms. Lung cancer symptoms are caused by tumor growth in the lungs, invasion or obstruction of nearby structures, and tumor growth in lymph nodes and in distant sites after cancer spreads through the blood. Symptoms include worsening or chronic cough, shortness of breath, wheezing, coughing up blood, back pain, and weight loss.

Screening. Screening methods include examination of a sputum (spit) sample, chest x-ray, and low-dose spiral computed tomography (CT) lung scanning. A biopsy of the tumor tissue is necessary to confirm a diagnosis of lung cancer. Physical examination, bone scans, brain CT, and bone marrow examination are performed when SCLC is suspected. Positron emission tomography scans are also useful in detecting cancer spread.

WHAT IF LUNG CANCER IS DETECTED?

Blood tests. Blood tests should measure levels of electrolytes (sodium, potassium, calcium, magnesium, phosphorus, chloride, and bicarbonate), indicators of liver function (aspartate aminotransferase, alanine aminotransferase, prothrombin time, bilirubin, and alkaline phosphatase), and level of lactate dehydrogenase.

A complete blood count will determine most of these values. However, the prothrombin time is a separate test that measures how quickly the blood clots. A prolonged prothrombin time, in the absence of vitamin K deficiency, and an elevated D-dimer level are associated with a poor outcome after surgery for lung cancer (Ferrigno D et al 2001; Kostecka IA et al 2000). An elevated alkaline phosphatase level suggests cancer spread to the bone. Blood tests can be performed via National Diagnostics: <http://www.lef.org/bloodtest/>.

What You Have Learned So Far

- Smoking is the major cause of lung cancer; thus, most lung cancers are preventable.
- Genetics, secondhand smoke, human papillomavirus infection, an unhealthy diet, and exposure to chemicals, heavy metals, and radon gas cause lung cancer in nonsmokers.
- All these risk factors are modifiable.
- Symptoms include worsening or chronic cough, shortness of breath, wheezing, coughing up blood, back pain, and weight loss.
- Tests for lung cancer include sputum sample, chest x-ray, and computed tomography lung scanning, but a biopsy is needed for diagnosis.
- In the past 50 years, the five-year survival rate for lung cancer has not improved significantly.
- A healthy lifestyle and diet (citrus fruits, tomatoes, spinach, carrots, cantaloupes, and sweet potatoes), in addition to supplementation with folate and vitamin B12, may help prevent lung cancer.

HOW ADVANCED IS THE CANCER?

How extensive or advanced a cancer is can be determined by "staging," which is important in determining the proper treatment approach. NSCLC is staged according to tumor size, whether lymph nodes are affected, and whether the cancer has spread (metastasized). NSCLC has five stages, numbered 0 through IV, with 0 being the earliest stage and having the best chance of cure and IV being the most advanced.

SCLC is divided into two stages: limited disease (25 to 30 percent of cases), in which the cancer is limited to the chest and nearby lymph nodes, and extensive disease (70 to 75 percent of cases), in which the cancer extends beyond the chest.

WHAT IS THE PROGNOSIS?

Lung cancer generally has a grim prognosis, which can be defined by means of the blood tests mentioned above as well as the

following tests:

Tumor markers. Tumor markers are substances produced by cancer cells. They reflect the presence or absence of cancer, and indicate whether a cancer returns (recurs) after treatment. Measuring the following six tumor markers is essential to daily lung cancer management. They are measured either by blood testing or by testing the tumor biopsy sample:

- *Carcinoembryonic antigen:* High carcinoembryonic antigen (CEA) levels in the blood (>10 ng/mL before and after surgery) are linked with poor survival (Tomita M et al 2005).
- *Neuron-specific enolase:* Neuron-specific enolase (NSE) in the tumor biopsy sample is a significant predictor of survival (Komagata H et al 2004; Ferrigno D et al 2003).
- *Sialyl Lewis X-i antigen:* Sialyl Lewis X-i antigen (SLX) identifies the presence of lung metastasis (Sato H et al 1998).
- *Serum cytokeratin fragment 21.1:* Serum cytokeratin fragment 21.1 (CYFRA) diagnoses NSCLC, especially squamous cell and adenocarcinoma (Chantapet P et al 2000).
- *Squamous cell carcinoma antigen:* Some 85 percent of patients with squamous cell carcinoma antigen (SCC) levels higher than 2 ng/mL have squamous tumors (Molina R et al 2003).
- *Pro-gastrin-releasing peptide:* High levels of pro-gastrin-releasing peptide (ProGRP) are found in SCLC patients, and this test is more specific than NSE for SCLC (Molina R et al 2004).

Cyclooxygenase-2. Cyclooxygenase-2 (COX-2) is associated with a worsening prognosis in lung cancer. Therefore, COX-2 inhibitors, taken as either prescription medication or nutritional supplements, may be beneficial in addition to standard treatments and in the prevention of lung cancer (Scagliotti GV et al 2003). COX-2 inhibitors enhance the cancer-killing effects of chemotherapy and radiation therapy in lung cancer cell lines with high levels of COX-2 (Saha, P et al 2005).

Advanced lung cancer patients who took Celebrex® (celecoxib; 200 mg twice daily), medroxyprogesterone (500 mg twice daily), and oral food supplementation for six weeks had stable weight (± 1 percent) or gained weight and had significant appetite improvement and relief from nausea and fatigue (Cerchietti LC et al 2004). Consequently, clinical trials are currently assessing Celebrex® alone for preventing lung cancer in heavy smokers and Celebrex® in combination with chemotherapy or after radiation therapy in lung cancer treatment. More information on ongoing clinical trials may be found at www.clinicaltrials.gov.

The following may also inhibit the effects of COX-2:

- Eicosapentaenoic acid (EPA) from fish oil (Yang P et al 2004), alpha-tocopheryl succinate (Lee E et al 2006); and a tea made from clove (Banerjee S et al 2006) hinder COX-2 in lung cancer cells.
- Aspirin also slows down COX-2 activity in lung cancer cells and may prevent tobacco carcinogenesis (Harris RE et al 2005).

Gene abnormalities. Mutations in K-ras genes are associated with a poor prognosis in NSCLC (Mascaux C et al 2005; Slebos RJ et al 1990), while tumor amplification of c-myc is associated with a poor prognosis in SCLC (Zajac-Kaye M 2001) and shorter survival in NSCLC (Yakut T et al 2003). The p16/CDKN2 gene is abnormal in 10 percent of SCLCs and in more than 50 percent of NSCLCs, and its detection may improve early diagnosis (Su C et al 2002).

Detection of K-ras mutations may help predict treatment outcome. For example, tumors in patients with a mutant ras gene are more difficult to kill with radiation than are tumors in people without the mutation. K-ras mutations can be detected in blood, sputum, lavage fluids, stool sample (Minamoto T et al 2000), and the tumor itself. Testing can be performed through the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics Laboratory for Molecular Medicine (<http://www.hpcgg.org/LMM/tests.jsp?name=LMM&subname=geneticstests#Cancer>). Several gene therapies are under investigation:

- Perillyl alcohol, found in lavender, cherries, and mint, slowed down ras activity and prevented lung cancer in experimental studies. Because it stimulated lung cancer cell death, it is being tested in clinical trials as an anticancer agent (Xu M et al 2004; Lantry LE et al 1997).
- Theaflavins and epigallocatechin gallate (EGCG), black tea components, alter c-myc levels, resulting in a decreased occurrence and delayed onset of preinvasive lung cancers (Saha P et al 2005; Lin JK 2002).
- Grape seed proanthocyanidins alter c-myc activity and protect against tobacco-induced death of healthy cells (Bagchi D et al 2002).

HOW IS LUNG CANCER TREATED?

Treatment methods depend on the type of lung cancer. SCLCs are treated with chemotherapy with or without radiotherapy, as surgery is unlikely to control the cancer in most cases. NSCLCs, if contained within the lung area, may be cured with either surgery or radiotherapy. Alternatively, certain chemotherapy agents are beneficial in specific cases.

Surgery. The goal of surgery is to remove as much of the cancer as possible in order to prevent a recurrence, to increase the effectiveness of chemotherapy and radiotherapy if they are needed, and to use the cancer cells to make a vaccine if required.

SCLC: Approximately 25 percent of SCLC patients with a single lung nodule (i.e., limited disease) can be cured with surgery (Chandra V et al 2006; Raez L et al 2005). The five-year survival rate of stage I patients with a peripherally located tumor who undergo cancer surgery is 44.9 percent, compared with 11.3 percent for conventionally treated patients (i.e., those treated with chemotherapy or chemoradiotherapy) (Rostad H et al 2004). However, studies show surgery will not benefit most SCLC patients (Waddell TK et al 2004).

Complete lung (pulmonary) function tests should be performed before surgery because part of a lung lobe or an entire lung may be removed. The chapter titled Cancer Surgery provides information on nutritional supplementation in preparation for surgery and for recuperation afterwards.

NSCLC: Fewer than 25 percent of patients with NSCLC are diagnosed with early-stage disease and are best treated by surgery (Scagliotti GV et al 2003). The five-year survival rate of NSCLC patients who undergo complete removal of cancer via surgery is 33 percent (Nesbitt JC et al 1995).

The combined effects of the season in which surgery is performed and recent vitamin D intake are associated with the survival of early-stage NSCLC patients. Some 56 percent of NSCLC patients who have surgery during summer and have the highest vitamin D intake (from sunlight) have remissions lasting more than five years, compared with 23 percent of patients who have surgery during winter and have the lowest vitamin D intake (Zhou W et al 2005). Therefore, if regular exposure of the skin to sunlight (which makes vitamin D in the body) is not possible before cancer surgery, then increased vitamin D intake or supplementation is suggested as an alternative.

Surgical removal of lung cancer causes a significant reduction of total plasma antioxidant capacity in lung cancer patients during the first postoperative day (Erhola M et al 1998). An antioxidant-rich diet is therefore recommended after surgery.

If cancer returns after surgery, it usually occurs within two years and involves cancer spread to the brain, bones, and liver. Treatments after surgery, such as chemotherapy or radiotherapy (or both), have been tested, but unfortunately they generally do not improve survival rates for most advanced lung cancer patients (Scagliotti GV et al 2003).

Radiation therapy (radiotherapy). The goal of radiotherapy is to kill any cancer cells remaining after surgery and to cure patients with early-stage lung cancer if they are not suitable for surgery or if they refuse it. It is also used to relieve symptoms in advanced cancer patients (Silvano G 2006).

In the past, radiotherapy after surgery had an unfavorable effect on survival. A meta-analysis found that the risk of death increased by 21 percent and the two-year survival rate fell seven points (from 55 to 48 percent) with radiation therapy after surgery (PORT Meta-analysis Trialists Group 1998). However, in those studies most of the patients were treated with older technology (cobalt-60) (Machtay M et al 2001). The newer radiotherapy technologies, such as intensity modulated radiotherapy, four-dimensional proton beam therapy, image guided radiotherapy, three-dimensional conformal radiotherapy, and radiation seeds (brachytherapy), reduce lung and heart damage (e.g., pneumonitis and fibrosis) significantly and, when combined with nutritional supplements, improve overall survival (Chang JY et al 2006; Engelsman M et al 2006; Fanta J et al 2006; Keall P et al 2006; Nagata Y et al 2006; Silvano G 2006; Mehta V 2005).

SCLC: Radiation therapy to the chest area is used to treat SCLC that has spread to bone and the central nervous system, and it improves survival in patients with limited-stage disease but not those with widespread disease. Whole-brain radiation therapy decreases the occurrence of cancer spread to the central nervous system but does not affect survival (Wagner H Jr 1997).

NSCLC: Radiation therapy combined with alpha-tocopherol (a type of vitamin E) and pentoxifylline (Trental®) improves survival in stage IIIB NSCLC (Engelsman M et al 2006; Misirlioglu CH et al 2006; Silvano G 2006): 66 patients were treated with alpha-tocopherol (300 mg twice daily) and Trental® (400 mg three times daily) during radiotherapy, followed by 300 mg alpha-tocopherol and 400 mg Trental® daily for three months after radiotherapy. In patients who received Trental® and alpha-tocopherol, one- and two-year overall survival rates were 55 percent and 30 percent, respectively, and most patients survived at least 18 months. In patients treated with radiotherapy alone, one- and two-year overall survival rates were significantly lower, 40 percent and 14 percent,

respectively, with a median survival of 10 months (Misirlioglu CH et al 2006). Trental® is safe and effective in preventing lung damage caused by radiotherapy (Mehta V 2005).

Several nutritional supplements may also mitigate the effects of radiotherapy.

- Coenzyme Q10 and vitamin E have protective effects against heart damage (cardiotoxicity) caused by radiation (Wang SQ 1991).
- Wobe-Mugos enzymes were given systemically to 44 patients with lung cancer undergoing radiation treatment (and polychemotherapy). It prevented lung damage, specifically fibrosis (Smolanka II 2000).

See the chapter titled Cancer Radiation Therapy for information on other nutritional supplements (taurine, L-arginine, and vitamin A) that help radiotherapy kill cancer cells without damaging normal, healthy cells or causing heart or lung damage or other side effects, thus improving the success of radiotherapy for lung cancer. Cancer Radiation Therapy also provides a list of proton beam therapy centers in North America.

Chemotherapy. The goal of chemotherapy is to treat lung cancer with drugs that have a specific toxic effect on cancer cells and result in direct cancer death. It is sometimes used before surgery to shrink inoperable tumors to make them operable. In these cases the response rates vary from 50 to 60 percent.

Unfortunately, chemotherapy cannot selectively destroy cancer cells; it damages healthy cells too, resulting in many serious and often life-threatening side effects (such as low blood cell counts, immunosuppression, and heart damage). The chapter titled Cancer Chemotherapy outlines nutritional supplements and prescription drugs that mitigate the well-known adverse effects of specific chemotherapy drugs.

NSCLC: In patients with early-stage NSCLC completely removed by surgery, cisplatin plus Navelbine therapy after surgery (without radiotherapy) significantly prolonged survival (94 versus 73 months) compared with surgery alone, but not without severe toxicities (low white blood cell counts, nausea, vomiting, and fatigue) and two deaths among 242 patients. The five-year survival rates were 69 percent and 54 percent, respectively (Winton T et al 2005). By contrast, chemotherapy with alkylating agents (mainly cyclophosphamide or nitrosourea in combination with methotrexate) after surgery is detrimental to survival (producing a 15 percent increased risk of death) and should not be used to treat NSCLC after surgery. Furthermore, the use of radiotherapy in combination with chemotherapy after surgery is not recommended as a treatment for patients with completely removed NSCLC (Alam N et al 2006).

SCLC: A customized chemotherapy approach including chemosensitivity testing (see the Cancer Chemotherapy chapter) is critical to determine which chemotherapy combinations will be effective in killing these cancers, particularly in early-stage SCLC. Tailoring chemotherapy to the unique characteristics of patients and their tumor should improve treatment outcome, provided that patients are in fairly good health (Huang CL et al 2006). The chemotherapy drugs cisplatin and etoposide, or oral topotecan (Hycamtin®) with intravenous cisplatin, are used to treat SCLC, resulting in one- and two-year survival rates of 31 percent and 5 to 20 percent, respectively, depending on the stage of the cancer (Eckardt JR et al 2006).

The following supplements may optimize the effects of chemotherapy:

- Polysaccharopeptide (PSP), from the mushroom *Coriolus versicolor*, helps lessen symptoms and prevents decline in immune status of lung cancer patients who are undergoing chemotherapy or radiotherapy (Ng TB 1998).
- Low molecular weight heparin, an anticoagulant, improves survival in patients with SCLC undergoing chemotherapy with Cytoxan®, Ellence® (epirubicin), and Oncovin® (vincristine). Median overall survival was eight months with chemotherapy alone and 13 months when low molecular weight heparin was added to chemotherapy (Altinbas M et al 2004).
- *Scutellaria baicalensis* is used in traditional Chinese medicine and increases blood cell production during chemotherapy (when it is typically reduced, resulting in side effects). It also intensifies bone-marrow activity (erythro- and granulocytopoiesis) and the numbers of circulating red and white blood cell precursors (Udut EV et al 2005; Gol'dberg VE et al 1997). Lung cancer patients who took *Scutellaria baicalensis* extract during chemotherapy had a beneficial increase in the number of immunoglobulins and maintained their relative number of T cells (Gol'dberg VE et al 1997).
- Coenzyme Q10 protects the heart from damage typically caused by doxorubicin, cytoxan, and 5-fluorouracil (Wang SQ 1991).
- A clinical study tested the efficacy of high-dose multiple antioxidants (ascorbic acid, 6100 mg daily; dl-alpha-tocopherol (vitamin E), 1050 mg daily; and beta-carotene, 60 mg daily) in addition to chemotherapy (Taxol® and carboplatin) in 136 advanced NSCLC patients. The overall survival rates at one year in the chemotherapy-alone group were 32.9 percent and in the antioxidants-plus-chemotherapy group, 39.1 percent. At two years, the two groups' survival rates were 11.1 percent and 15.6 percent, respectively (Pathak AK et al 2005).

Hormones and chemotherapy. Advanced stage NSCLC patients who have had no previous surgery or chemoradiotherapy may

benefit from a combination of hormones and oral chemotherapy. Treatment with melatonin, vitamin D, retinoids, somatostatin, bromocriptine, and the chemotherapy drug Cytoxan® improved survival and quality of life (relieved cough, shortness of breath, pain, fatigue, and insomnia) in NSCLC patients. Median survival time was 12.9 months (range, 1.5–33.5 months), and the overall survival rates at one and two years were 51.2 percent and 21.1 percent, respectively (Norsa A et al 2006).

Customizing Chemotherapy to the Patient

The concept of customized chemotherapy involves predicting how well proposed chemotherapy drugs will kill a patient's cancer or lower the patient's risk of adverse effects (Von Hoff DD 1990) before they are given to the patient. It is critical to extending survival time (Thunnissen FB et al 2006). Molecular markers in patients' tumors can help predict response to specific chemotherapy drugs.

- Iressa® treatment is linked with favorable survival in NSCLC patients whose tumors have low levels of ribonucleotide reductase (Huang CL et al 2006; Kwon WS et al 2006).
- The ability of 5-fluorouracil to kill lung cancer cells depends on the activity of dihydropyrimidine dehydrogenase and thymidylate synthase in patients' tumors (Ploylearmsaeng SA et al 2006; Takizawa M et al 2006).
- The responsiveness of NSCLC to Iressa® and Tarceva® depends on the presence of epidermal growth factor receptor (EGFR) mutations in the tumor (Tokumo M et al 2006).
- The response to Taxol® and Navelbine® depends on tubulin III and stathmin mRNA levels in tumor cells. High levels of tubulin III are associated with a poor response to chemotherapy and a shorter progression-free survival (Seve P et al 2005).
- If the tumor shows BRCA1 and ERCC1 (genes involved in DNA repair pathways), then cisplatin, carboplatin, and taxanes will not be effective in killing the tumor, resulting in poor survival (Rosell R et al 2006; Santarpi M et al 2006).

For more details, see *Cancer Chemotherapy: Evaluating the Molecular Biology of the Tumor Cell Population and Chemosensitivity Testing*.

INTEGRATIVE CANCER THERAPY

Hormones. Estrogens and peptide hormones play important roles in the development and progression of lung cancer, whereas melatonin and thyroid hormones are pivotal in the stabilization and inhibition of lung cancer in men (Zhou XD et al 2002; Bhatavdekar JM et al 1994).

Estrogens: Whether produced in the body or obtained through hormone replacement therapy, estrogens may be involved in lung cancer development and progression (Inoue M et al 2006; Liu Y et al 2005). Lung cancer tissue contains an abundance of estrogen receptors, which are not found in normal lung tissue, thus opening up a possibility of antiestrogen therapy for patients with advanced lung cancer displaying estrogen receptors in their tumors (Canver CC et al 1994).

If a patient's lung cancer displays estrogen receptors, then reducing estrogen levels in the body (because estrogen stimulates cancer growth), in addition to standard treatments, is potentially beneficial. Because body fat is a source of estrogen, it is important to establish and maintain a healthy weight (Siiteri PK 1987). In addition, the following nutritional supplements with natural antiestrogen properties show promise:

- Melatonin has multiple antiestrogen actions and decreases estradiol levels in the body (Sanchez-Barcelo EJ et al 2005; Rato AG et al 1999).
- Vitamin K2 (menaquinone), known for its blood coagulation effects, decreases the ratio of estradiol to estrone, slowing down estrogen activity (Otsuka M et al 2005).

Furthermore, estrogen levels in the body can be lowered by counteracting obesity (see the Obesity chapter) and keeping a low-fat diet (Deslypere JP 1995; Alavanja MC et al 1994; Kolonel LN 1993).

Peptide hormones: Peptide hormones act as growth factors and increase lung cancer growth (Moody TW 2006). For example, SCLC and NSCLC both produce gastrin-releasing peptide (GRP), neurotensin and adrenomedullin, which are growth factors, and as the name suggests, they increase lung cancer growth (Moody TW 2006). However, growth factor antagonists prevent SCLC growth in vitro and have been studied in Phase III clinical trials (Moody TW et al 2001). These growth factor antagonists may provide new treatments for SCLC patients in the future.

Melatonin: The most widely investigated anticancer hormone is melatonin (Lissoni P et al 2001). It has been used both alone and in combination with most standard cancer treatments because it improves both survival and quality of life (Lynch E 2005). Advanced lung cancer patients show a progressive reduction in melatonin levels (Mazzoccoli G et al 1999), and their daily sleep-wake patterns are disrupted (Levin RD et al 2005; Lissoni P et al 1998). However, even in patients for whom no other standard treatment is offered, melatonin with aloe vera extract stabilizes the cancer growth and improves survival (Lissoni P et al 1998).

In a study of 100 lung cancer patients who were randomized to receive either chemotherapy alone or chemotherapy with melatonin (20 mg/day orally), the five-year survival rates were significantly higher for the group of patients who received melatonin. In addition, no patient treated with chemotherapy alone was alive after two years, whereas five-year survival was achieved in three of 49 patients (6 percent) treated with chemotherapy and melatonin. Furthermore, lung cancer patients treated with melatonin tolerate chemotherapy better and have less-serious side effects (Lissoni P et al 1999, 2003a,b).

Thyroid hormones: Thyroid stimulating hormone (TSH) controls 25 percent of the body's metabolism, thereby affecting how quickly cells (including cancer cells) grow and die. Therefore, making the thyroid underactive (a condition known as hypothyroidism) by reducing TSH levels in the body may slow down cancer growth. Hypothyroidism can be achieved artificially with the prescription drugs propylthiouracil (PTU) or Tapazole®.

When All Else Fails: Increase Survival with Hypothyroidism

A case in point: A patient originally diagnosed with metastatic lung cancer (i.e., lung cancer that had spread throughout the body) was admitted to the hospital because of a rare complication of underactive thyroid disease (i.e., hypothyroidism) called myxedema coma. This rare clinical condition can be caused by insufficient thyroid hormone (T4) replacement, infection, cold exposure, trauma, or the drug amiodarone (which causes thyroid hormone abnormalities) (Hondeghem LM 1987). The myxedema coma occurred just two months after the patient was diagnosed with metastatic lung cancer. On examination for myxedema coma, the patient was found to have no evidence of remaining cancer, and five years later the lung cancer had still not returned (i.e., he remained in remission). It was concluded that spontaneous remission (complete permanent disappearance) of the lung cancer had occurred due to a severe deficiency of thyroid hormone; in other words, thyroid hormone deprivation had induced total tumor cell death (Herbergs A 1993, 1999).

If a lung cancer patient also has hypothyroidism or subclinical hypothyroidism, it may be wise to avoid taking too much thyroid hormone to correct this condition. By contrast, if a lung cancer patient has an overactive thyroid (hyperthyroidism), it is essential to reduce the levels of the thyroid hormones triiodothyronine (T3) and T4 to normal (or lower) as quickly as possible (typically with PTU or Tapazole®) because hypothyroidism or inadequate thyroid hormone replacement prolongs survival of lung cancer patients and in some cases causes spontaneous remission of the lung cancer (Garfield D 2002). TSH, T3, and T4 can be measured by a simple blood test.

COMPLEMENTARY ALTERNATIVE THERAPIES

Vitamin and mineral supplementation is associated with longer survival and quality of life in NSCLC patients. Median survival is 4.3 years for NSCLC patients who supplement with vitamins and minerals versus 2.0 years for those who do not use such supplements (Jatoi A et al 2005a). As the statistics on conventional treatment outcomes for lung cancer remain disappointing, vitamin and mineral supplementation combined with complementary alternative therapies should be considered to help control lung cancer, maintain quality of life, and prolong survival (van Zandwijk N et al 2000). It is particularly important for advanced lung cancer patients to incorporate novel and integrative nutritional supplementation into their treatment regimens.

Vitamin D. As previously outlined in the "Surgery" section, vitamin D improves survival in early-stage NSCLC patients (Zhou W et al 2005). Therefore, vitamin D supplementation is recommended for lung cancer patients planning to undergo surgery, particularly during the winter season, and especially for those with darker skin, and for vegans who have limited sun exposure. Experimental studies show that vitamin D protects against lung cancer progression by preventing cancer spread (metastases) (Wiers KM et al 2000). Sources of vitamin D include sunlight, milk, and darkly colored fish.

Adenosine triphosphate. Adenosine triphosphate (ATP) is produced in the body and provides energy to cells. In nonrandomized studies involving advanced NSCLC patients, ATP infusions slowed weight loss and deterioration of quality of life (Haskell CM et al 1998). A randomized trial showed that ATP infusions (20–75 mg/kg per minute for 30 hours at two- to four-week intervals) have beneficial effects on weight, muscle strength, energy levels, and quality of life in patients with advanced NSCLC (Agteresch HJ et al 2003).

Intravenous ATP infusions work by restoring liver energy levels in patients with advanced lung cancer (Leij-Halfwerk S et al 2002) and by counteracting tissue loss (Agteresch HJ et al 2002). ATP is taken up by red blood cells and reaches levels 50 to 70 percent above baseline concentrations at approximately 24 hours (Agteresch HJ et al 2000). In addition, preclinical studies showed that ATP administration may improve the anticancer effects of chemotherapy (Maymon R et al 1994) and radiotherapy (Estrela JM et al 1995) and may also have protective effects against tissue damage caused by radiation (Senagore AJ et al 1992).

Green tea. A phase I clinical trial in advanced NSCLC patients determined that high doses of green tea extract (3 g/m² daily) are well tolerated and stabilize cancer in some patients (Laurie SA et al 2005). Based on their results, the researchers proposed that green tea extract might be useful in preventing cancer progression in those at high risk for lung cancer relapse (following completion of treatment for early-stage lung cancer) or in those at high risk of developing a second cancer. In addition, green tea extract could be considered in combination with standard chemotherapy agents in advanced lung cancer (Laurie SA et al 2005).

Green tea extract can be taken safely for at least six months at an oral dose of seven to eight Japanese cups (120 mL) three times daily (Pisters KM et al 2001). The side effects of green tea extract are caffeine related. However, preclinical studies found that caffeine contributes to the prevention of tumor growth (Lu YP et al 2000; Xu Y et al 1992). Therefore, decaffeinated green tea extract may be less effective.

Alpha-tocopherol. High levels of alpha-tocopherol (50 mg), if taken during the early critical stages of lung cancer initiation, may prevent lung cancer development (Woodson K et al 1999). Alpha-tocopheryl succinate hinders the initiation and progression of lung cancer by preventing COX activity and by blocking inflammatory responses mediated by prostaglandin E2 (Lee E et al 2006).

Selenium. Selenium protects against lung cancer, especially in populations in which average selenium intakes are low (Rayman MP 2005; Zhuo H et al 2004; Reid ME et al 2002;). Family members of lung cancer patients were found to have selenium levels significantly lower than those of healthy controls (Miyamoto H et al 1987). At pharmacological doses, selenium may act as an adjuvant treatment for lung cancer (Neve J 2002). A phase III multicenter clinical trial is investigating whether daily selenium supplementation is effective in preventing the growth of new tumors in NSCLC patients whose tumors were surgically removed; details are available at www.clinicaltrials.gov.

Novel nutritional supplements. The following nutritional supplements have been investigated in lung cancer patients and found to be without adverse effects; however, optimum doses have not yet been established:

- N-acetylcysteine (Maasilta P et al 1992; Jepsen S et al 1989)
- R-lipoic acid (Mantovani G et al 2003)
- Zinc (Evans WK et al 1987)
- Magnesium (Takeda Y et al 2005)
- *Scutellaria baicalensis* (Udut EV et al 2005; Gol'dberg VE et al 1997)

The following nutritional supplements have shown promising effects against lung cancer in experimental studies, although clinical studies have not yet been carried out:

- Curcumin (Lee J et al 2005)
- Ginseng (Panwar M et al 2005)
- Garlic (Wu XJ et al 2005)
- Lycopene (Arab L et al 2002)
- GLA (de Bravo MG et al 1995)
- Silibinin (Chen PN et al 2005)
- Grape seed proanthocyanidins (Bagchi D et al 2002)
- Black tea polyphenols (Lin JK 2002)
- Genistein from soy (Lei W et al 1998, 1999)

Lung cancer patients may want to call Life Extension at 1-800-544-4440 for updated information on optimal dosages of the above nutrients.

PREVENTING LUNG CANCER

To lower the risk of lung cancer, the following interventions are recommended:

Stop smoking. Smokers should stop smoking (by using nicotine replacement therapy, Zyban®, and counseling) because at present there are no known dietary changes that can guarantee prevention or lower the occurrence of lung cancer in smokers. Medicinal herbal tea made from cloves and milk vetch reduces smoking withdrawal symptoms and increases the rate of smoking cessation (Lee HJ et al 2005).

Test your home for radon. Read the section above titled "What Causes Lung Cancer?" to learn why this is important and to find important sources for more information.

Take aspirin. Take aspirin regularly if your physician approves (Moysich KB et al 2002).

Monitor your diet. Smokers, ex-smokers, and people who have never smoked should all consume five or more servings of colorful vegetables (including raw, darkly colored, and root vegetables) and fruits daily to achieve serum levels of micronutrients associated with the lowest risk of lung cancer. A diet rich in tomatoes, tomato-based products (containing lycopene), citrus fruits, and carotenoids (lutein, zeaxanthin, beta-cryptoxanthin, and retinol) reduces the risk of lung cancer (Holick CN et al 2002). Egg yolk is a bioavailable source of lutein and zeaxanthin (Johnson EJ 2002). Good food sources of carotenoids are spinach, kale, carrots, cantaloupes, cherries, and sweet potatoes.

Phytoestrogens (plant estrogens) from food sources are associated with a decrease in the risk of lung cancer in both current

smokers and people who never smoked, but less so in former smokers. Food phytoestrogens include isoflavones, phytosterols, and lignans. High intake of the lignans enterolactone and enterodiol and use of hormone therapy are associated with a 50 percent reduction in the risk of lung cancer (Schabath MB et al 2005). The soy isoflavone genistein significantly prevented lung tumor formation and cancer metastasis in mice (Menon LG et al 1998). Phytoestrogens are also available as nutritional supplements.

Consider antioxidants. Studies examining the role of antioxidants in lung cancer have gained significant attention. In the 1990s, a study was launched to determine if alpha-tocopherol and beta-carotene could reduce the risk of cancer, particularly lung cancer. The study, however, indicated that lung cancer incidence increased among people who took beta-carotene. These results were later replicated in a study that tested a combination of beta-carotene and vitamin A. Additional studies found that beta-carotene raised the risk of lung cancer among smokers (Albanes D et al 1996).

However, newer studies have examined the role that dosage plays and found that low-dose antioxidants, including beta-carotene, in combination with additional antioxidants may reduce the incidence of lung cancer. One study tested the effectiveness of daily, low-dose antioxidant supplementation with vitamins (vitamin C, 120 mg; vitamin E, 30 mg; and beta-carotene, 6 mg) and minerals (selenium, 100 mcg; and zinc, 20 mg) in reducing the frequency of cancers. After 7.5 years of supplementation, this low-dose antioxidant regimen lowered total cancer occurrences and deaths in men but not in women (Galan P et al 2005). Based on these study results, Life Extension recommends that people at high risk for lung cancer avoid high doses of beta-carotene but supplement with low-dose antioxidants to reduce their risk of lung cancer.

Add folate and vitamin B12. Folate and vitamin B12 reduce abnormal bronchial cell growth in smokers (Heimbürger DC et al 1988).

Take alpha-tocopherol. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, higher serum alpha-tocopherol status was associated with lower lung cancer risk. Alpha-tocopherol supplementation may reduce the risk of lung cancer associated with increasing smoking exposure for some people more than for others, depending on hereditary factors (Ratnasinghe D et al 2001).

Drink green tea. Consumption of green tea by nonsmoking women is associated with a reduced risk of lung cancer, and the risks decrease with increasing consumption (Zhong L et al 2001). Experimental studies consistently show that green tea and its polyphenols (e.g. EGCG) can slow the growth of, and kill, lung cancer cells (Clark J et al 2006).

For More Information...

The complications related to lung cancer treatment can be acute (such as low blood cell counts) and chronic (heart and lung damage). For more information, please refer to the following chapters:

- Cancer Surgery
- Cancer Chemotherapy
- Cancer Vaccines and Immunotherapy
- Blood Disorders
- Heavy Metal Detoxification

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

For optimal results, nutritional supplements or dietary changes should be introduced before starting lung cancer treatment.

Life Extension suggests:

- **Beta-carotene**—6 milligrams (mg) daily
- **Coenzyme Q10**—100 to 400 mg daily
- **Folate**—800 to 1600 micrograms (mcg) daily
- **Green tea extract**—up to 5.7 grams (g) daily
- **Melatonin**—20 mg nightly
- **Multivitamin-multimineral supplement** (without copper)—daily
- **N-acetylcysteine**—1200 mg daily
- **Perillyl alcohol**—2050 mg four times daily
- **PSP** (from the mushroom *Coriolus versicolor*)—2 g daily
- **R-lipoic acid**—300 mg daily
- **Selenium**—200 to 400 mcg daily

- **Vitamin B12**—500 to 1000 mcg daily
- **Vitamin C**—2500 mg daily
- **Vitamin D**—800 IU daily
- **Vitamin E**—800 mg daily of d-alpha tocopheryl succinate
- **Vitamin K2**—10 mg daily
- **Wobenzym N**—3 tablets, two times daily, at least 45 minutes before meals
- **Zinc**—20 mg daily

INNOVATIVE DRUG STRATEGIES

ATP intravenous infusion—20 to 75 milligrams/kilograms (mg/kg) per minute for 30 hours at two-to-four-week intervals (must be performed by a qualified physician)

Celebrex®—200 mg twice daily

Medroxyprogesterone—500 mg twice daily

Trental® (pentoxifylline)—400 mg three times daily

PTU or Tapazole®, low molecular weight heparin, nicotine replacement therapy (e.g., Zyban®), and aspirin: appropriate dosages of these pharmaceutical drugs should be discussed with your treating physician.

PRODUCT AVAILABILITY

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444.

PSP can be purchased from JHS Natural Products and can be ordered online

(<http://www.jhsnp.com/store/pspcoriolusversicolor.html>) or by calling 1-888-330-4691 (toll-free in the United States only) or 1-541-344-1396 for international callers.

LUNG CANCER SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Beta-Carotene

- Do not take beta-carotene if you smoke. Daily intake of 20 milligrams or more has been associated with a higher incidence of lung cancer in smokers.
- Taking 30 milligrams or more daily for prolonged periods can cause carotenoderma, a yellowish skin discoloration (carotenoderma can be distinguished from jaundice because the whites of the eyes are not discolored in carotenoderma).

Coenzyme Q10

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

Folic acid

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

Green Tea

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache,

muscle tension, sleep disturbances, and rapid heartbeat.

Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a “heavy head,” or gastrointestinal symptoms such as nausea and diarrhea.

NAC

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

Lipoic Acid

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

Vitamin B12 (cyanocobalamin)

- Do not take cyanocobalamin if you have Leber's optic atrophy.

Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

Vitamin D

- Do not take vitamin D if you have hypercalcemia.
- Consult your doctor before taking vitamin D if you are taking digoxin or any cardiac glycoside.
- Only take large doses of vitamin D (2000 international units or 50 micrograms or more daily) if prescribed by your doctor.
- See your doctor frequently if you take vitamin D and thiazides or if you take large doses of vitamin D. You may develop hypercalcemia.
- Chronic large doses (95 micrograms or 3800 international units or more daily) of vitamin D can cause hypercalcemia.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic

stroke, or hemophilia.

- Discontinue using vitamin E 1 month before any surgical procedure.

Vitamin K

- Do not take vitamin K if you are taking warfarin sodium unless, the vitamin K is specifically prescribed by your physician.

Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system.

For more information see the Safety Appendix

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