

Uterine (Endometrial) Cancer

Cancer of the uterus is the most common cancer of the female reproductive tract, with an annual rate of 21 per 100,000 women (Greenlee RT et al 2001). The majority of uterine (endometrial) cancer cases occur around or after menopause between the ages of 60 and 75 years. In the United States, 2 percent to 3 percent of women will develop cancer of the uterus during their lifetimes (McCann SE et al 2000).

The primary symptom of uterine cancer is abnormal vaginal bleeding. Obesity and a diet high in animal fats and low in fruits and vegetables are associated with the development of uterine cancer (Hu FB 2003; Schapira DV 1992). The relationship between unopposed estrogen exposure and uterine cancer is well established (Berstein L et al 2002; Doherty JA et al 2005; Persson I et al 1989). The incidence of uterine cancer has increased in the past 50 years because of longer female life expectancy and an increase in the use of unopposed estrogen therapy. However, enhanced methods of diagnosis have improved detection rates (Emons G et al 2004).

Fortunately, most uterine cancers are detected at an early stage, leading to successful cure rates. The usual treatment for uterine cancer is a complete hysterectomy (removal of the uterus) (Chen LM et al 1999). Depending on the severity and spread of the cancer, radiation therapy is sometimes recommended (McMeekin DS et al 2003). A healthy diet and lifestyle together with hormonal and dietary supplements may impede the development of uterine cancer and stop its spread in those who already have it (Hill HA, Austin H et al 1996; Pike MC et al 2004).

WHAT IS UTERINE CANCER?

The uterus (or womb) is a thick-walled, hollow, muscular organ, shaped like an inverted pear in the female pelvis (Stenchever MA et al 2002). The uterus is where a fetus grows. The innermost layer of the uterus (the endometrium) is shed during menstruation. Cancer of the uterus is a disease in which malignant (cancer) cells form in the tissues of the endometrium (*metra* is Greek for womb). Therefore, uterine cancer is often also referred to as endometrial cancer (Montgomery BE et al 2004).

Uterine cancer can spread outward through the layers of the uterus (Lutz MH et al 1978). Cancerous cells may invade nearby structures such as the cervix, fallopian tubes, and vagina (Chen LM et al 1999; Morrow CP et al 1991). Untreated uterine cancer cells can spread via the lymphatic system to nearby lymph nodes (Noumoff JS et al 1993). If left untreated and allowed to progress, uterine cancer can spread via the bloodstream, which may result in the spread of cancer to the lungs, liver, bone, and brain (McMeekin DS et al 2003).

SYMPTOMS OF UTERINE CANCER

The primary symptoms of uterine cancer are abnormal vaginal bleeding and pelvic pain (Juretzka MM et al 2005). This commonly occurs in postmenopausal women but may also occur in menstruating women who experience irregular bouts of bleeding. It is imperative that any abnormal bleeding or discharge from the vagina be evaluated by a physician (Chen LM et al 1999).

UNCONTROLLABLE RISK FACTORS FOR UTERINE CANCER

Getting older

In 95 percent of cases, uterine cancer occurs around or after menopause, usually between the ages of 60 and 75 years (Purdie DM et al 2001). It also occurs more often in obese postmenopausal women (Terry P et al 1999) who have had no or very few pregnancies (Goodman MT, Hankin JH et al 1997).

Ethnicity

Caucasian women have a 2.88 percent lifetime risk of developing uterine cancer compared with the 1.69 percent risk for African-American women (Greenlee RT et al 2001). However, mortality rates are nearly twice as high in the latter group (Hill HA, Eley JW et al 1996), who have more aggressive tumors and more accompanying illnesses and complications (Connell PP et al 1999).

Genes

Most cases of uterine cancer appear sporadically. However, approximately 10 percent of cases are thought to be hereditary

(Munstedt K et al 2004). There may be two forms of inherited uterine cancer—the first involving a genetic tendency for inheriting uterine cancer alone and the second involving a family cancer syndrome called Lynch syndrome type II, or hereditary nonpolyposis colorectal cancer (Banno K et al 2004). There is a 40 percent to 60 percent lifetime risk of developing uterine cancer in an individual who has Lynch syndrome type II (Banno K et al 2004). Genetic blood testing is available to identify individuals who carry this syndrome (Lipton LR et al 2004).

CAUSES OF UTERINE CANCER

Unopposed estrogen

When estrogen is taken without the counterbalancing effects of progesterone, it is referred to as unopposed estrogen (Persson I et al 1989). Increased exposure to unopposed estrogen from supplemental hormone replacement therapy (HRT) or through excessive estrogen generated in the body (Berstein L et al 2002; Chen LM et al 1999; Key TJ et al 1988) is the most common risk factor for uterine cancer. Women who take unopposed estrogen replacement therapy (ERT) may be at risk of uterine cancer (Sevelda P et al 1998) even after discontinuing the ERT (Grady D et al 1995).

Women using unopposed estrogen for more than 2 years have a 2- to 3-fold increased risk of uterine cancer (Emons G et al 2004), whereas women receiving progestin in conjunction with estrogen have no increased risk (Grady D et al 1995). The addition of progestin to HRT reduces the risk of uterine cancer by lowering the exposure of the endometrium to unopposed estrogen (Dai D et al 2005). For further information on hormone supplementation, see Female Hormone Replacement.

Endometrial cell growth is finely sensitive to the effects of estrogen that are unopposed by progesterone (Key TJ et al 1988). A possible precursor lesion for uterine cancer may be endometrial hyperplasia (abnormal growth) (Sivridis E et al 2001). Endometrial hyperplasia occurs when uterine lining cells become overstimulated, dense, and thickened. In most cases, endometrial hyperplasia is caused by estrogen stimulation (Abulafia O et al 1995; Bergeron C 2002; Montgomery BE et al 2004). This tissue may consist of normal cells or abnormal cells, and only 2 percent of cases of hyperplasia of normal cells will develop into uterine cancer. In contrast, between 25 percent and 100 percent of abnormal cell hyperplasia will progress into uterine cancer, indicating that abnormal cell hyperplasia is probably a precursor to uterine cancer (Dietl J 2002; Sivridis E et al 2004).

Obesity

Obesity is associated with a significantly increased risk of endometrial cancer in both premenopausal (Cancer and Steroid Hormone Study 1987; Henderson BE et al 1983) and postmenopausal women (Pike MC 1987). Fat cells produce 10 percent to 15 percent of estrogens. Estrogens are formed when androgens (male hormones) are converted to estrogens via aromatization (conversion) outside of the ovaries (Hu FB 2003; Longcope C et al 1978). In obese females, elevated levels of estrogens from fat can stimulate the endometrial lining of the uterus and increase the risk of uterine cancer (Calle EE et al 2004; Goodman MT, Hankin JH et al 1997). See the chapter on "Obesity," which outlines an integrative approach to counteracting obesity.

Ovulation problems

Ovulation problems and hormone imbalances in which excess androgens are produced, such as polycystic ovary syndrome (ovaries with many abnormal cysts), may result in excessive production of estrogens (Gallup DG et al 1984). This hormonal imbalance places women at increased risk of uterine cancer (Chubak J et al 2004; Hardiman P et al 2003).

No pregnancies

During pregnancy, the hormonal balance shifts toward more progesterone and less estrogen (Spencer TE et al 2002). If a woman does not go through a pregnancy, she does not benefit from this hormonal shift (more progesterone and a lower estradiol level), which provides protection against uterine cancer (Chubak J et al 2004). Women who have never been pregnant or have gone through only one pregnancy are more likely to develop uterine cancer than women who have had multiple pregnancies (Soliman PT et al 2005).

Late menopause

The average age for a woman to stop menstruating is 51 years old (Ouzounian S et al 2005). Women who experience menopause at a much later age will produce hormones (including estrogen) for a longer time (Purdie DM et al 2001). This increased exposure to estrogen is associated with uterine cancer (Chubak J et al 2004).

Tamoxifen

Tamoxifen is a medication that is often prescribed to breast cancer survivors. Unfortunately, tamoxifen users have a 2- to 3-fold

increased risk of uterine cancer (Mourits MJ et al 2001). Women taking tamoxifen should be monitored closely by their physician (Swerdlow AJ et al 2005). See the chapter on “Breast Cancer” for more information.

Western diet

The rates of uterine cancer increase in first and second generation Japanese women born in the United States (Liao CK et al 2003), suggesting that the Western diet, high in animal fat, may be a risk factor for uterine cancer (Potischman N et al 1993). The intake of animal protein and fat increases the risk of myoma, a benign (noncancerous) fibroid (Chiaffarino F et al 1999). It also increases the risk of uterine cancer. Conversely, eating fresh fruits and vegetables (Levi F et al 1993) and more fiber decreases the risk (Goodman MT, Hankin JH et al 1997). The chapter on “Uterine Fibroids” describes nutritional supplements that support healthy uterine structure and function.

What You Have Learned So Far

- Uterine cancer is a disease in which malignant (cancer) cells form, typically in the lining of the uterus (endometrium).
- Uterine cancer is highly curable by removal of the uterus (hysterectomy) if surgery is performed before the spread of the cancer.
- Taking tamoxifen and increased exposure to estrogens, whether from unopposed estrogen therapy or excess body fat, are the most common risk factors for developing uterine cancer (Armstrong B 1982; Bernstein L et al 1992).
- Possible signs of uterine cancer include unusual vaginal discharge or bleeding.
- The risk of uterine cancer can be reduced by lowering and balancing levels of estrogens in the body (Deslypere JP 1995; Hershcopf RJ et al 1987; Jensen H 1986), for example, by correcting obesity or adding progestin (Hu FB 2003; Longcope C et al 1978).
- It is important to make lifestyle and dietary changes, and to balance hormones, if you are at increased risk of uterine cancer.

DIAGNOSING UTERINE CANCER

The following are some of the tools used to diagnose uterine cancer

Biopsy

Although somewhat uncomfortable, a biopsy of the endometrial lining is a useful tool for the diagnosis of uterine cancer (Hofmeister FJ 1974; Minagawa Y et al 2005). Physicians do not usually recommend a biopsy as a general screening tool but it is the procedure of choice for high-risk individuals (Minagawa Y et al 2005). If the biopsy test result is positive for uterine cancer, the physician will discuss all treatment options.

Dilation and curettage (D&C)

If the biopsy test result is negative but the patient is at high risk of uterine cancer, the patient may need to have a D&C (Berek JS et al 2000). In this procedure, the physician dilates the woman's cervix and removes a sample of uterine tissue. The physician or a technician examines the tissue sample under a microscope for the presence of cancerous cells. A D&C is more accurate at diagnosing uterine cancer than is an endometrial biopsy (Lotfallah H et al 2005).

Pap Test

The Pap (short for Papanicolaou) test detects cervical cancer but is not a good test for detecting uterine cancer. A Pap test will fail to diagnose uterine cancer about 87 percent of the time (Nassar A et al 2003). Occasionally, uterine cells shed and appear on a Pap test. When this occurs in a postmenopausal woman, further evaluation is required. About 25 percent of postmenopausal women with *abnormal* uterine cells on their Pap tests will have uterine cancer (Berek JS et al 2000). However, about 6 percent of postmenopausal women whose Pap test results show *normal* uterine cells actually have uterine cancer (Ng AB et al 1974).

PREDICTING THE PROGNOSIS

Once uterine cancer has been diagnosed, magnetic resonance imaging (MRI) is often performed to evaluate the extent of disease. MRI is particularly useful in determining the depth of cancer invasion within the uterus (Robert Y et al 2002). Patients thought to have more advanced disease may be referred to a gynecologic cancer center for extensive surgery and treatment (Berek JS et al 2000; Purdie DM et al 2001).

UNDERSTANDING THE STAGING SYSTEM

Approximately 75 percent of women with uterine cancer have stage I (mild) disease. Of these women, almost 90 percent have no sign of cancer 5 years after surgery (Juretzka MM et al 2005). The possibility of curing the disease decreases as the cancer becomes more advanced (Juretzka MM et al 2005). Advanced disease has a poor prognosis; the 5-year survival rate for stage III is 29 percent and declines to 10 percent for stage IV (Magrina JF et al 2004).

Table. International Federation of Gynecologists and Obstetricians (FIGO) Uterine Cancer Staging System

Stage I (mild)	Cancer found only in uterus
Stage II	Cancer in uterus and cervix, but not outside uterus
Stage III	Cancer in uterus and beyond, but not outside pelvis
Stage IV (most advanced stage)	Cancer beyond pelvis, in bladder, bowel, or other areas of the body

(Berek JS et al 2000)

Decoding the Pathology Report

After the surgeon removes the uterine cancer tissue, it is sent to the pathology laboratory for analysis. A technician examines the tissue for the absence or presence of hormone receptors (places where hormones can attach) within the tumor (Martin R et al 1993). Most uterine cancer cells possess receptors for estrogen or progesterone, or for both (Gurpide E 1981; Kedzia W 1996). This is why uterine cancer is often classified as a hormonally responsive cancer.

Patients who have tumors that test positive for progesterone and/or estrogen receptors typically have longer survival rates than patients whose tumors lack these hormone receptors (Creasman WT 1993; Friberg LG et al 1993). However, progesterone receptors appear to be a stronger predictor of long-term survival than estrogen receptors (Dai D et al 2002). Tumors with progesterone receptors have a much greater response to progestin therapy than do tumors without progesterone receptors (Dai D et al 2005; Ehrlich CE et al 1988).

If the cancerous tissue contains estrogen and/or progesterone receptors, it may be responsive to hormonal therapy, particularly if the cancer recurs (Ayoub J et al 1988; Bokhman I et al 1987; Lotze W et al 1982; Martin R et al 1993). Therefore, it is recommended that the cancerous tissue be analyzed for the presence of estrogen and/or progesterone receptors at the time of surgery (Ayoub J et al 1988; Bokhman I et al 1987; Martin R et al 1993; Thurzo L 1990).

MEDICAL TREATMENT

The following surgeries and therapies are used to treat uterine cancer.

Surgery

Removing the cancer in an operation is the most common treatment of uterine cancer. During surgery, the physician evaluates the extent of the cancer and uses a staging guide to assess each patient's cancer stage. The following surgical procedures may be used:

- **Radical hysterectomy** —The primary treatment of uterine cancer is a hysterectomy in which the uterus, fallopian tubes, cervix, ovaries, surrounding tissue, and lymph glands are removed. A radical hysterectomy is usually done through the abdomen.
- **Total hysterectomy** —This type of hysterectomy involves removal of just the uterus and cervix. It can be done through the abdomen or through the vagina. Sometimes a total vaginal hysterectomy can be done with the aid of a laparoscope (a viewing instrument passed through a small incision in the abdomen).
- **Bilateral salpingo-oophorectomy** —A bilateral salpingo-oophorectomy is the removal of both ovaries and both fallopian tubes via surgery. It is used in conjunction with a hysterectomy.

Radiation

If the cancer is confined to the uterine lining, usually no additional treatment after surgery is needed. However, if the cancer has spread further, then radiation treatment after surgery may be indicated (McMeekin DS et al 2003).

Depending on the results of the surgical staging and the existence of high-risk factors, radiation may be recommended immediately after surgery (postoperative) to minimize the possibility of the cancer returning (Kao MS 2004). Radiation has been shown to

decrease the incidence of both pelvic and vaginal cancer recurrences (Berek JS et al 2000). Radiation appears to benefit women who have cancer in their para-aortic lymph nodes (Kao MS 2004; Morrow CP et al 1991) and improves 5-year survival rate by nearly 40 percent (Murphy KT et al 2003). Brachytherapy is a one-time intravaginal radiation treatment that produces a high dose of radiation close to the cancer and a lesser dosage in healthy tissues, thus producing fewer adverse effects.

Treatment of recurrent cancer

The likelihood that uterine cancer may recur depends on the extent of the disease and the success of the initial treatment (Kao MS 2004). Approximately 34 percent of all recurrences are detected within 1 year and 76 percent within 3 years of primary treatment. The cancer usually recurs in the pelvis (i.e., locally), not in distant parts of the body (Mariani A et al 2004).

Chemotherapy and hormonal therapy are not recommended as standard treatment when uterine cancer is initially diagnosed (Lewis GC Jr et al 1974; Mariani A et al 2004; Yahata H et al 2004). However, they are sometimes recommended if the cancer recurs after surgery and radiation (Kao MS 2004; Yahata H et al 2004).

Hormonal therapy

Endometrial cancer is a hormone-dependent disease. Therefore, hormonal therapy added to standard treatments may improve the outcome in the early stages of the disease (Li CZ et al 2003; Montz FJ et al 2002; Piver MS 1988; Urbanski K et al 1993). Hormonal therapy is not usually recommended as standard treatment when uterine cancer is diagnosed; however, it has been used after hysterectomy with some success (Bokhman I et al 1987; Li CZ et al 2003). Hormonal therapy has also been demonstrated to be useful in treating selected patients who have widespread uterine cancer that has returned after treatment; it is used primarily to relieve symptoms (Kao MS 2004; La Vecchia C et al 1986).

Uterine cancer with progesterone receptors is more responsive to progestin therapy than if progesterone receptors are lacking (Ehrlich CE et al 1988). Therefore, future therapeutic regimens targeted at enhancing progesterone receptor expression have the potential to improve outcomes in women with uterine cancer (Dai D et al 2005; Gurpide E 1981). Progestin therapy is most commonly prescribed in pill form, but intramuscular injection of medroxyprogesterone acetate (MPA; a synthetic progestin) and intravaginal forms are also available (Li CZ et al 2003; Thurzo L 1990). Adverse effects of progestins are usually minor and include weight gain, edema (swelling), and headache; however, blood clots can occur (Benagiano G et al 2004; Neumann F 1978; Warren MP et al 1999). Unlike synthetic progestins (such as MPA), micronized progesterone has been reported to cause only fatigue and sleepiness.

Heading Toward Hormones

Therapy with one of a number of progestational agents has been the conventional approach to the management of endometrial carcinoma in cases where surgery or radiation therapy is not recommended, particularly in obese women. Progestins such as MPA in particular are considered useful in treating uterine cancer (Urbanski K et al 1993). MPA has been widely used both intramuscularly and orally in a variety of doses and schedules.

While the role of MPA in the palliative treatment of advanced disease is well accepted, opinion is divided on its role in the adjuvant setting (treatment given after surgery to increase the chances of a cure). The commonly used progestational agents megestrol acetate, hydroxyprogesterone, and MPA all produce similar response rates, and the antiestrogen tamoxifen produces responses in 10 percent to 25 percent of patients in the final phase of medical treatment.

Natural progesterone is obtained primarily from plant sources and is currently available in oral and injectable forms and in topical gels. An oral micronized progesterone preparation is also available. It has improved bioavailability and fewer reported adverse effects when compared with synthetic progestins (Apgar BS et al 2000). Natural progesterone is used to prevent uterine cancer. However, currently there is little evidence that progesterone can be used to treat uterine cancer once it has been diagnosed (Apgar BS et al 2000).

LIFE AFTER TREATMENT: NUTRITIONAL SUPPORT AND DIETARY RECOMMENDATIONS

Nutritional factors have been estimated to contribute to 20 percent to 60 percent of cancers and to almost one third of deaths from cancer in Western countries.

Low-fat diet

A diet high in animal fat, particularly red meat, may be associated with a small to moderately increased risk of uterine cancer (Potischman N et al 1993; Terry P et al 2002). This is probably because high-fat (and sugar) diets cause increased body fat content, which in turn results in high levels of estrogens. Estrogens are known for their proliferative effects on estrogen-sensitive tissues, resulting in tumor development. There is a stronger association between dietary fat and uterine cancer in women who have high circulating levels of estrogen, such as women with a higher body mass index (BMI) and users of unopposed estrogens (Littman AJ et al 2001). A low-fat diet may be linked to lower estrogen levels and thereby protect against uterine cancer (Hill HA et al 1996).

Fish and flaxseed

Oily fish such as salmon, herring, mackerel, bluefin tuna, and sardines contain high levels of essential omega-3 polyunsaturated fatty acids. Omega-3 fatty acids reduce the risk of certain hormone-dependent cancers by exerting favorable effects on estrogen metabolism, such as decreasing estrogen stimulation of these tumors and competitive inhibition of omega-6 fatty acids, which are associated with cancer development (Lord RS et al 2002).

The American Heart Association recommends two servings of fatty fish per week to obtain cardiovascular benefits from omega-3 fatty acids (Kris-Etherton PM et al 2002). Two to three servings of fatty fish per week are also suggested to prevent uterine cancer (Lord RS et al 2002; Terry P et al 1999).

Other primary sources of dietary alpha-linolenic acid (which can be converted into omega-3 fatty acids) are ground flaxseed, soybeans, pumpkin seeds, and walnuts (Kris-Etherton PM et al 2002). Ground flaxseed is a good source of omega-3 fatty acids (Brooks JD et al 2004; Lucas EA et al 2002) and is "as effective as oral estrogen-progesterone to improve mild menopausal symptoms" and to lower glucose and insulin levels (Lemay A et al 2002).

Fruits and vegetables

Significant protection against uterine cancer (a 40 percent to 60 percent reduction) was found to be conferred by elevated intake of most fresh vegetables and fruits and whole-grain foods (Levi F et al 1993). Therefore, a diet rich in fruits, vegetables, whole grains, and fiber most likely will help protect against uterine cancer (Doll R 1992; La Vecchia C et al 1986; McCullough ML et al 2004; Willett WC 2005).

Various nutrients found in fruits and vegetables seem to have the ability to detoxify certain carcinogens (cancer-causing agents) (Steinmetz KA et al 1991). For example, the risk of uterine cancer is inversely related to intake of beta-carotene and fiber (La Vecchia C et al 1986). Fruits and vegetables that contain high amounts of vitamin A (Schapira DV 1992), beta-carotene (Levi F et al 1993), and vitamin C (Berstein L et al 2002) may decrease the risk of uterine cancer.

In addition, cruciferous vegetables may have favorable effects on estrogen metabolism (Terry P et al 2002) and thus reduce the risk of developing uterine cancer (Kobayashi Y et al 2003). Examples of cruciferous vegetables include cabbage, Brussels sprouts, bok choy, kale, kohlrabi, broccoli, and watercress.

Vegetables from the allium group (*allium* is Latin for garlic) also may reduce the risk of uterine cancer by interrupting cancer cells' reproduction cycle (Shu XO et al 1993; Tanaka S et al 2004). Examples of allium vegetables include garlic, onions, scallions, leeks, chives, and shallots.

Whole grains and high-fiber foods

A diet rich in whole grains and high-fiber foods has been closely correlated with reduced uterine cancer risk (Jacobs DR Jr et al 2004; La Vecchia C et al 1986; Schapira DV 1992). These foods are rich in antioxidants, which are important in cancer prevention (Nishino H et al 2004; Potischman N et al 1993). Low levels of antioxidants within the uterus and surrounding pelvic organs may allow proliferating free radicals to cause damage and prevent optimal functioning (Khorram O et al 2002). Many of these types of foods also contain plant estrogens (phytoestrogens), which exert protective hormonal effects against hormone-related cancers such as uterine, breast, and prostate cancer (Cassidy A 2003; Goodman MT, Wilkens LR et al 1997). Examples of whole grains include

brown rice, oatmeal, pearl barley, whole wheat, and whole rye. High-fiber foods include legumes, beans, seeds, and nuts.

Soy

Nutritional studies indicate that people in Asian countries consume approximately 10 times the amount of fermented soy as the average American. A diet rich in fermented soy reduces the risk of uterine cancer (Horn-Ross PL et al 2003; Xu WH et al 2004). The consumption of soy foods also provides high amounts of fiber, which is protective against uterine cancer (Cassidy A 2003; Goodman MT, Wilkens LR et al 1997).

Fermented soy foods include miso, tempeh, and natto. Soy milk, soy flour, and textured soy protein are used to make a variety of soy-based products including soy burgers (veggie burgers), soy cheese, and soy ice cream and yogurts. However, these processed nonfermented soy foods may not be recommended for people who already have cancer; fermented soy is the preferred source for them.

DIETARY SUPPLEMENTS

The following are some of the dietary supplements that have been found to prevent and, in some cases, treat uterine cancer.

Vitamin A and carotenoids

Carotenoids such as alpha-carotene, beta-carotene, lutein, and lycopene have been shown to be protective against uterine cancer (Hill HA et al 1996; La Vecchia C et al 1986; Levi F et al 1993; Nagpal S 2004; Nahum A et al 2001). Vitamin A inhibits uterine tumor growth (Nagpal S 2004; Petridou E et al 2002; Schapira DV 1992).

Vitamin A can be obtained from liver and yellow or orange vegetables. The Council for Responsible Nutrition (CRN) suggests taking 10,000 international units (IU) of vitamin A if you have a low dietary retinol intake or 5000 IU of vitamin A if you already have a high dietary retinol intake. The dosage for optimum health and for cancer prevention is not defined, but several cancer studies have shown benefits of 25,000 IU per day (Alberts DS et al 2004; Carter CA et al 1996; Kakizoe T 2003; Meyskens FL Jr et al 1995).

Vitamin C

Vitamin C is an important antioxidant and has been linked to reduced risk of uterine cancer (Berstein L et al 2002; Goodman MT, Hankin JH et al 1997; Levi F et al 1993; McCann SE et al 2000). It is believed that vitamin C works against cancer by enhancing the immune system and suppressing cancer cell growth (De Loecker W et al 1993; Lenton KJ et al 2003). In addition, vitamin C causes the formation of collagen (Golde DW 2003), which can wall off tumors (Alcain FJ et al 1994; De Loecker W et al 1993; Head KA 1998) and help block the spread of cancer (Block KI et al 2003; Tamayo C et al 2003). Vitamin C can be obtained by eating citrus fruits and dark green, leafy vegetables (Cameron E et al 1978; Gonzalez MJ et al 2005). Many people prefer to take vitamin C in the form of a dietary supplement. Clinical studies have used up to 10 grams (g) daily (10,000 milligrams [mg] per day) (Cameron E et al 1978; Gonzalez MJ et al 2005).

Melatonin

Melatonin is a hormone secreted by the pineal gland. It is responsible for sleep patterns and can enhance immunological activity (Simonneaux V et al 2003). Melatonin may help prevent cancer, especially cancers related to hormonal activity such as breast, prostate, and uterine cancers (Barrenetxe J et al 2004; Lissoni P, Chilelli M et al 2003; Lissoni P, Malugani F et al 2003; Reiter RJ 2004; Sanchez-Barcelo EJ et al 2005).

The melatonin dosage for insomnia is normally 3 to 6 mg at bedtime (Chase JE et al 1997; Dolberg OT et al 1998). However, the majority of clinical cancer studies have used much higher doses, up to 20 mg of melatonin at bedtime (Barrenetxe J et al 2004; Lissoni P, Chilelli M et al 2003; Lissoni P, Malugani F et al 2003; Sanchez-Barcelo EJ et al 2005).

Ginseng

Ginseng is an herb that has been used in Asian medicine for thousands of years. In experimental conditions, ginseng destroys cancerous tumors by attacking them at the cellular level (Bespalov VG et al 2001) and preventing cancer spread (Fujimoto J et al 2001). Moreover, Siberian ginseng but not Asian ginseng (*Panax ginseng*) or North American ginseng (*Panax quinquefolius*) has been shown to bind to estrogen receptors (Liu J et al 2001; Pearce PT et al 1982).

Preliminary clinical trials with panaxel and bio ginseng (*Panax ginseng from Siberia*) were carried out in patients with precancerous lesions of the endometrium. Bio ginseng caused regression of these precancerous lesions (adenomatous cystic hyperplasia) of the endometrium in some patients. Thus, bio ginseng appears to hold considerable promise for uterine cancer prevention (Bespalov VG

et al 2001).

A multicenter cancer-prevention study of hepatocellular carcinoma (a type of liver cancer) is underway in Korea where participants take 1 g of red ginseng powder per day for 5 years in an attempt to prevent this type of liver cancer (Ginseng- HCC Chemopreventive Study Osaka Group 2001; Manusirivithaya S et al 2004).

In a randomized, multicenter, double-blind study of symptomatic postmenopausal women, a standardized ginseng extract was found to improve quality of life and overall relief of symptoms without increasing thickening of the endometrium or raising estradiol levels (Wiklund IK et al 1999).

Adverse effects of ginseng are rare, but may include nervousness, insomnia, blood-clotting problems, high blood pressure, diarrhea, and, rarely, breast tenderness and irregular menstruation in women (Yuan CS et al 2004).

Allicin

Allicin is the major ingredient in fresh crushed garlic. Allicin is also found in onions, scallions, leeks, chives, and shallots. These vegetables have been shown to reduce the risk of uterine cancer by interrupting the reproductive cycle of the cancer cells (Hirsch K et al 2000; Shu XO et al 1993; Tanaka S et al 2004).

Selenium

Because selenium is a trace mineral found in soil, the amount of selenium in plant foods relates to the quality of the soil the plants are grown in. Therefore, diet is not the best method of obtaining reliable amounts of selenium (Sundstrom H 1985).

A low concentration of selenium in the body may be a contributing factor in uterine carcinogenesis (Sundstrom H et al 1986, 1984). Selenium works against cancer cells through antioxidant activity (Zhao L et al 2001), preventing or slowing tumor growth (Lou H et al 1995). Selenium is linked to a decreased risk of developing various types of gynecological cancers (Cunzhi H et al 2003; Drozd M et al 1989; Sundstrom H et al 1986; Sundstrom H et al 1989).

A dosage of 400 micrograms (mcg) has been proposed as a safe daily dietary selenium intake (Yang G et al 1994). High doses (more than 910 mcg/day) can result in a rare condition called selenosis, is characterized by gastrointestinal upset, hair loss, white blotchy nails, fatigue, and irritability (Kaur R et al 2003; Sundstrom H 1985).

Calcium

Daily use of calcium supplements appears to lower endometrial cancer risk (Salazar-Martinez E et al 2005), especially in women whose calcium intake is low because they do not eat dairy products (La Vecchia C et al 1986; Terry P et al 2002).

The amount of calcium supplementation varies, depending on how much calcium is consumed in the diet (Schaafsma G 1992). However, the American College of Obstetricians and Gynecologists recommends that women take 1000 mg/day of calcium if they are younger than age 50 and 1500 mg/day of calcium if they are age 50 and above (American College of Obstetricians and Gynecologists 1998; Power ML et al 1999).

For More Information

The complications of uterine cancer are related to the natural progression of the disease, or to the adverse effects of surgery, chemotherapy, or radiation. Thromboembolic disease (a tendency toward blood clots) has long been associated with uterine cancer.

Most of the adverse effects of chemotherapeutic agents are predictable and can be lessened with adjuvant medications or by taking nutritional supplements because poor nutrition is a risk factor.

The complications related to radiation can be acute (such as low blood cell counts) and chronic (gastrointestinal, genitourinary, and pulmonary). Gastrointestinal symptoms are controlled with supportive therapy such as eating a glutamine-rich diet, drinking enough water, and avoiding high-fiber foods while symptoms persist. For further information on some of the topics outlined in this chapter, read the following chapters:

- Cancer Surgery
- Cancer Radiation
- Cancer Chemotherapy
- Obesity

- Female Hormone Replacement
- Breast Cancer

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Women who have uterine cancer should consult their physician before taking any nutritional supplements, especially if they are receiving conventional medical treatment. The Life Extension Foundation suggests:

- **Apple pectin**—2.8 grams (g) daily, with water
- **Calcium**—1000 to 1500 milligrams (mg) daily
- **Essential fatty acids**—4.8 g of eicosapentaenoic acid (EPA) and 2.4 g of docosahexaenoic acid (DHA) daily
- **Ground flaxseed**—3 tablespoons (25 to 40 g) daily, with water
- **Garlic**—1200 mg daily
- **Melatonin**—6 to 20 mg, 1 to 2 hours before sleeping (nighttime)
- **Panax ginseng (Siberian)**—200 to 1000 mg daily
- **Soy extract containing 50 mg of isoflavones**—twice daily
- **Vegetable extract** —daily
- **Vitamin A**—25,000 IU daily
- **Vitamin C**—2.5 to 5 g daily
- **Multivitamin/multimineral supplement** (without copper) containing 20 mg of beta-carotene, 15 mg of lycopene, and 200 mcg of selenium daily.

UTERINE 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:

Calcium

- Do not take calcium if you have hypercalcemia.
- Do not take calcium if you form calcium-containing kidney stones.
- Ingesting calcium without food can increase the risk of kidney stones in women and possibly men.
- Calcium can cause gastrointestinal symptoms such as constipation, bloating, gas, and flatulence.
- Large doses of calcium carbonate (12 grams or more daily or 5 grams or more of elemental calcium daily) can cause milk-alkali syndrome, nephrocalcinosis, or renal insufficiency.

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Flaxseed

- Flaxseed has blood-thinning, anticlotting properties.
- Discontinue using flaxseed before any surgical procedure.
- Consult your doctor before taking flaxseed if you have hemophilia or if you take warfarin (Coumadin).
- Flaxseed can cause gastrointestinal symptoms such as nausea and diarrhea.

Garlic

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

Ginseng

- Consult your doctor before taking ginseng if you have high blood pressure. Overuse of ginseng can increase blood pressure.
- Consult your doctor before taking ginseng if you take nonsteroidal anti-inflammatory drugs (NSAIDs) and/or warfarin (Coumadin). Taking NSAIDs or warfarin with ginseng can increase the risk of bleeding.
- Consult your doctor before taking ginseng if you have diabetes. Taking ginseng can cause an extreme drop in your blood glucose level.
- Ginseng can cause breast pain, vaginal bleeding after menopause, insomnia, headaches, and nosebleeds.

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.

Pectin

- Do not take pectin if you have a gastrointestinal obstruction.
- Pectin can cause gastrointestinal symptoms such as flatulence, cramps, gas, and diarrhea.

Soy

- Do not take soy if you have an estrogen receptor-positive tumor.
- Soy has been associated with hypothyroidism.

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 A

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans-retinoic acid, bexarotene, etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.
- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

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.

For more information see the Safety Appendix

Product Availability

All the nutrients and supplements in this chapter are available through the Life Extension Foundation. For ordering information, call 1-800-544-4440 , or visit us online at www.lef.org.

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