

Cervical Dysplasia Reversing the Road to Cervical Cancer

Cervical dysplasia is characterized by abnormal (dysplastic) cells in the cervix. Extending into the vagina, the cervix is the lowest part of the uterus. Although cervical dysplasia does not produce symptoms itself, it is potentially dangerous because it can progress to cervical cancer, the second-most-common type of cancer in women, especially among younger women (Nicol AF et al 2005; Marshall K 2003; Rock CL et al 2000).

Since the introduction of the Pap smear in 1941, the death rate from cervical cancer has dropped significantly because of early detection of cervical dysplasia. In developing countries, where Pap smears are not as common as in industrialized countries, cervical cancer is reported to be the leading cause of cancer in women (Potischman N et al 1996). Worldwide, cervical cancer accounts for 11.6 percent of cancers in women (Giuliano AR et al 1998; Rock CL et al 2000).

In more than 99 percent of cases, cervical cancer and cervical dysplasia are caused by the human papillomavirus (HPV), the virus that causes genital warts (Yeo AS et al 2000). HPV is very common: the lifetime risk of a woman contracting genital HPV is estimated to be 80 percent (Bekkers RL et al 2004). It is transmitted through sexual intercourse. The virus may be present without symptoms, making it possible for carriers to transmit it unknowingly.

The vast majority of women with HPV will not develop cervical dysplasia or cancer (Marshall K 2003; Giuliano AR et al 1998). There are many variations of the virus, and some forms carry a higher risk for the development of cancer than others, especially HPV16 and HPV18 (Liu T et al 1993). HPV is often difficult to detect because it only rarely causes symptoms. Only about 1 percent of women with HPV have visible genital warts (Wright TC et al 2004), which adds to the importance of regular Pap smears.

The goal of cervical dysplasia treatment is reducing the risk of its progression to cervical cancer. This risk reduction may be accomplished through dietary modification and supplementation and possibly by chemoprevention through the use of medical or chemical modifiers (Rock CL et al 2000; Pereira DB et al 2004; Maissi E et al 2004). Fortunately, there is hope on the horizon: because of lifestyle changes, the prevalence of Pap smears, and exciting research into HPV vaccines, cervical cancer rates are expected to continue dropping in the industrialized world.

CLASSIFICATION AND SCREENING FOR CERVICAL DYSPLASIA

Cervical dysplasia is commonly referred to as cervical intraepithelial neoplasia (CIN). It is often classified by the degree of penetration of abnormal cells into the tissue lining (epithelium):

- CIN I describes the involvement of the basal third of the epithelium.
- CIN II involves the basal two thirds of the epithelium.
- CIN III involves more than two thirds of the epithelium.

A diagnosis of cervical dysplasia does not necessarily mean that cervical cancer will develop. In fact, up to 74 percent of women with mild CIN will naturally regress to normal within five years (Holowaty P et al 1999). Of those cases that do progress, only a minority of women will actually develop cancer.

- Only 1 percent of women with CIN I who experience progression will progress to severe dysplasia or worse (Holowaty P et al 1999).
- Among patients with CIN II, 16 percent will advance to severe dysplasia within two years and 25 percent within five years.
- An overall progression rate of severe dysplasia (CIN III) to cervical cancer has been observed in 12 percent to 32 percent of patients (Arends MJ et al 1998; McIndoe WA et al 1984).

Pap smears are the standard tool used to screen women for cervical dysplasia or cancer. During a Pap smear, cells are scraped from the cervix, then evaluated microscopically. About 5 percent to 7 percent of Pap smears yield abnormal findings (Jones BA et al 2000).

One major problem with screening is poor follow-up testing among women with abnormal Pap smears. In most cases, an abnormal Pap smear requires a follow-up test in a few months. However, an estimated 10 percent to 61 percent of women with abnormal Pap smears do not undergo follow-up testing (Shinn E et al 2004). Factors associated with noncompliance include only an elementary

education, prior surgery, additional diseases, consumption of medications for chronic conditions, and family illness (Bornstein J et al 2004).

In general, according to the American Cancer Society's 2002 screening guidelines:

- Women should begin cervical cancer screening no later than three years after beginning vaginal intercourse but no later than 21 years of age.
- Cervical cancer screening should be performed annually with regular Pap tests or every two years with liquid-based Pap tests.
- A woman 30 years of age or older with three consecutive normal Pap smears may elect to be screened every two to three years.
- Women who have undergone hysterectomy can elect to discontinue Pap smears if the surgery was not performed to treat cervical cancer or precancer. Women with an intact cervix posthysterectomy should undergo screening until at least age 70.
- A woman older than age 70 may choose to discontinue Pap smear screening after three prior normal Pap smears and no abnormal results in the preceding 10 years.

RISK FACTORS FOR PROGRESSION

While it may take years for cervical dysplasia to progress to cancer, the cancer can quickly spread throughout the body once established. If left untreated, cervical cancer has a relatively high mortality rate, although the survival rate for properly treated early-stage cervical dysplasia and cervical cancer is high.

Early symptoms of cervical cancer, such as altered vaginal discharge and abnormal vaginal bleeding, are rare. Advanced cervical cancer may present with pelvic, back, or leg pain, leaking of urine or feces from the vagina, loss of appetite, weight loss, and bone fracture.

Not all cases of cervical dysplasia progress into cancer (Marshall K 2003). Rather, it appears that certain factors may hasten the progression from cervical dysplasia to cervical cancer:

- **Decreased methylation.** DNA hypomethylation is significantly associated with grade of CIN (Fowler BM et al 1998; Goodman MT et al 2001).
- **Multiple HPV types.** One study showed a significantly increased risk of CIN in women with several HPV subtypes (Ho GY et al 1998).
- **Viral load.** A high level of the virus is a significant risk factor for CIN (Li SM et al 2004; Schlecht NF et al 2003; Dalstein V et al 2003; Ylitalo N et al 2000; Josefsson AM et al 2000; Ho GY et al 1998; Romney SL 1997; Flores R et al 2005).
- **High-risk HPV variants.** Certain virus strains are an independent risk factor for cervical dysplasia (Thomson et al 2000; Liu T et al 1995).
- **Persistence of HPV infection.** Persistent infection with HPV increases the risk of cervical cancer (Giuliano AR et al 1997; Romney SL et al 1997).
- **Smoking.** Smoking is a serious independent risk factor for advanced cervical dysplasia (Palan PR et al 1991). Passive cigarette smoking via a spouse also has been associated with a higher incidence of high-grade squamous intraepithelial lesions (Tay SK et al 2004). Women with abnormal Pap smears absolutely should avoid smoking.
- **Obesity.** In one large study, fewer overweight and obese women (78 percent in each group) underwent cervical cancer screening with Pap smears (Wee CC et al 2000). Because this group of women have a higher mortality rate for cervical cancer compared with women of normal weight, special attention should be paid to increasing screening among overweight and obese women.
- **Number of sexual partners.** The number of sexual partners increases the risk of cervical dysplasia (Thomson SW et al 2000), perhaps by increasing the chances of encounter with HPV strains.
- **Multiple pregnancies.** Multiple pregnancies have been cited as a possible risk factor for cervical dysplasia (Munoz N et al 2002; Liu T et al 1993; Thomson SW et al 2000).
- **Lower socioeconomic status and lack of Pap smears.** Women with a lower educational level may avoid follow-up Pap smears (Bornstein J et al 2004). Additionally, those with lower socioeconomic status may lack access to appropriate health care.
- **Diethylstilbestrol (DES).** DES was given to expectant mothers from the late 1930s until 1970 to prevent early delivery. However, many mothers were unaware that the drug was being administered to them; sometimes it was given with a vitamin supplement. Unfortunately, it resulted in increased cervical cancer in female offspring. Current research regarding the use of DES focuses on the effects of the drug in granddaughters and grandsons of those who received it (Centers for Disease Control 2005).
- **Compromised immune function.** Women with medical conditions that affect the immune system are at greater risk for cervical dysplasia. These conditions include HIV, systemic lupus erythematosus, and transplanted organs (Duerr A et al

2001; Robinson WR et al 2002; Bernatsky S et al 2004; Malouf MA et al 2004; Ozsaran AA et al 1999).

- **Other sexually transmitted diseases.** One study concluded that the presence of other sexually transmitted diseases, such as Herpes simplex virus and Chlamydia trachomatis, can cause dysplasia to progress to cervical cancer (Smith JS et al 2002a; Smith JS et al 2002b). However, other studies failed to show an association between these sexually transmitted diseases and cervical cancer progression (Castle PE et al 2003; Tran-Thanh D et al 2003).

CONVENTIONAL TREATMENT OF CERVICAL DYSPLASIA AND CANCER

Cervical Dysplasia

The success rate of treating early-stage cervical dysplasia is extremely high. During treatment, a physician will attempt to remove the abnormal cells through a variety of methods, including cryotherapy, or freezing the cells to destroy them.

Alternatively, a procedure called loop electrosurgical excision may be performed. During this procedure, a thin wire loop with an electrical current is used to remove a cone-shaped piece of tissue. Women treated with loop excision are likely to convert to HPV-negative status, which eliminates the risk for HPV-related cervical dysplasia and cancer (Aschkenazi-Steinberg SO et al 2005). If a larger area of the cervix contains abnormal cells, a gynecologist may perform a surgical procedure called cervical conization to remove all the abnormal cells.

In case of high-grade CIN, or if previous surgeries left too little cervical tissue, a hysterectomy may be recommended (Das N et al 2005). In rare advanced cases, all the organs of the pelvis can be removed in a procedure called pelvic exenteration. Except for hysterectomy or pelvic exenteration, the surgical choices typically allow a woman to carry a child in future pregnancies.

Cervical Cancer

Sometimes radiation or chemotherapy is required in addition to surgery for cancers that are recurrent or have spread beyond the pelvis. Survival rates depend on the stage of the cancer. With treatment, five-year survival rates are 80 percent to 85 percent for cervical and uterine tumors, 60 percent to 80 percent for tumors involving the upper part of the vagina, 30 percent to 50 percent for tumors still retained in the pelvis, and 14 percent when cancer has invaded the bladder or rectum or metastasized outside the pelvis.

Vaccines and Antivirals: Hope for the Future?

Recently, media attention has focused on possible vaccines for cervical cancer. Although these vaccines are still in the development stage, a vaccine for low-grade dysplasia will likely be available soon (Stanley M 2003a).

Large-scale trials have shown that developmental vaccines have reduced the rate of HPV infection and CIN (Villa LL 2005; Torrens I et al 2005). One factor that may complicate a successful vaccination program is a lack of vaccine in developing countries (where vaccines are most needed); another is a lack of vaccines that are specific to certain types of HPV (Maclean J et al 2005).

However, given their early record, it appears that vaccines may soon offer hope of dramatically reducing the rate of HPV infection and in turn, the rates of cervical dysplasia and cervical cancer.

What You Have Learned So Far

- Cervical dysplasia is a proliferation of abnormal cells in the lining of the cervix.
- Cervical dysplasia left untreated may develop into cervical cancer.
- Cervical cancer is the second-most-common type of cancer in women.
- Early detection and treatment of cervical cancer are highly effective. The mortality rate for untreated cervical cancer is 95 percent within two years.
- The survival rate for properly treated early-stage cervical cancers is between 70 percent and 100 percent.
- Virtually 100 percent of cases of cervical dysplasia and cervical cancer are the result of HPV.
- The lifetime risk of contracting a genital HPV infection is about 80 percent in women.
- Not all women with HPV will develop dysplasia or cancer of the cervix.
- Only 1 percent of women with HPV develop external warts.
- Dysplasia does not cause symptoms.
- The lack of symptoms in dysplasia, infrequent screening, and various risk factors sometimes allow cervical dysplasia to develop into cervical cancer.
- The Pap smear is the standard screening tool to detect dysplasia.

NUTRIENT SUPPORT FOR A HEALTHY CERVIX

Since as far back as 1981, statistically significant differences in levels of vitamins A and C and beta carotene have been noted between women with cervical dysplasia and healthy controls (Romney SL et al 1981; Wassertheil-Smoller S et al 1981). Other nutrients studied in cervical dysplasia include folate, zinc, and vitamins B6, B12, and E. Changes in diet and nutritional supplementation can reduce the odds of developing cervical cancer (Marshall K 2003; Gagandeep et al 2003; Friedman M et al 2005).

Vitamin A. Vitamin A deficiency has been observed in women with various grades of CIN, and higher levels of vitamin A have been shown to help reduce the risk of progression to cervical cancer (Kwasniewska A et al 1996a; Yeo AS et al 2000; Liu T et al 1993; Shannon J et al 2002; Volz J et al 1995). Vitamin A deficiencies have been linked to CIN among Southwestern American Indian women (Yeo AS et al 2000) and HIV-positive women (French AL et al 2000). Vitamin A also may have a protective effect for black women in the early stages of CIN (Kanetsky PA et al 1998b).

In two studies of women with CIN, a 3-fold to 4.5-fold higher risk of cervical cancer development was seen in those with a low level of vitamin A (Nagata C et al 1999; Wylie-Rosett JA et al 1984). More severe stages of cervical dysplasia were associated with an even lower level of vitamin A (Kwasniewska A et al 1996a). Conversely, high levels of vitamin A were associated with cervical dysplasia regression, particularly in those who were HPV16 positive (Liu T et al 1995).

B vitamins. Numerous studies have also shown vitamin B deficiencies among women with cervical dysplasia.

Vitamin B1. In women with high- and low-grade squamous intraepithelial lesions of the cervix, the level of vitamin B1 was decreased in those with CIN. Progression of cervical dysplasia was associated with reduced levels of vitamin B1 (Hernandez BY 2003)

Vitamin B2. Low levels of vitamin B2 have been associated with an increased risk of low-grade and high-grade CIN (Liu T et al 1993; Hernandez BY et al 2003). Interestingly, vitamin B2 deficiency has been associated with oral contraceptive use.

Vitamin B6. Cervical squamous intraepithelial lesions have been associated with a deficiency of vitamin B6 (Ramaswamy PJ et al 1984).

Vitamin B12. Low levels of vitamin B12 have been associated with both low-grade and high-grade squamous cervical lesions, as well as with HPV persistence (Hernandez BY et al 2003; Sedjo RL et al 2002; Goodman MT et al 2001). However, another study did not show an association between vitamin B12 and women who were either positive or negative for HPV (Sedjo RL et al 2003).

Folic Acid. Insufficient intake of folate is associated with increased risk for cervical dysplasia (Liu T et al 1993; Kwanbunjan K et al 2004; Buckley DI et al 1992; Griro R et al 1993; Kwasniewska A et al 1997; Weinstein SJ et al 2001; Butterworth CE et al 1992; Ziegler RG 1986; Hernandez BY et al 2003; Goodman MT et al 2001). Interestingly, folate deficiency can even be misdiagnosed as cervical dysplasia because their characteristics are similar (Zarcone R et al 1996; Butterworth CE et al 1982).

Other theories to explain the connection between folate deficiency and cervical dysplasia include the increased demand for folate associated with pregnancy and oral contraceptive use (Potischman N et al 1991; Butterworth CE et al 1982). This increased demand results in a folate deficiency in the cervical tissue, which could increase the risk of CIN (Piyathilake CJ et al 2000).

One study suggests that folate deficiency could cause chromosomal damage, such as that seen in cervical cancer, as a result of impaired DNA synthesis or repair (Christensen B 1996). Additional studies state that folate status may be involved in early stages of CIN but not in advanced disease (Potischman N et al 1996; Butterworth CE et al 1992).

Vitamin C. An increased incidence of cervical dysplasia has been found with low levels of vitamin C (ascorbic acid) in several studies (Romney SL et al 1985; Liu T et al 1993; Potischman N et al 1996; Palan PR et al 1996; Kwasniewska A et al 1998; Buckley DI et al 1992; de Vet HC et al 1991; Kwasniewska A et al 1996b; Lee GJ et al 2005).

Antioxidants. In general, antioxidant status has been closely linked to cervical dysplasia. Many studies have found low levels of antioxidants in women with various grades of cervical dysplasia. These antioxidants include alpha-tocopherol, gamma-tocopherol, beta-carotene, lutein, lycopene, canthaxanthin, alpha- and beta-cryptoxanthin, coenzyme Q10, and glutathione (Palan PR et al 2003; Palan PR et al 2004; Palan PR et al 1991; Palan PR et al 1996; Giuliano AR et al 1997; Kim SY et al 2003; Ho GY et al

1998; Goodman MT et al 1998). However, the relationship between reduced antioxidant levels and cervical dysplasia is poorly understood. It could be that lower antioxidant levels contribute to development of the condition, or conversely, the disease might cause reduced antioxidant levels as the body seeks to fight the disease. In either case, patients with cervical dysplasia should consider supplementing with a robust antioxidant program.

Minerals. Cervical dysplasia patients have also been found to have abnormal levels of minerals, including copper, selenium, and zinc. Studies have shown that patients with cervical dysplasia and invasive cancers have lower levels of selenium and zinc and a higher level of copper (Kim SY et al 2003; Grail A et al 1986; Rybnikov VI 1985; Liu T et al 1995). Ferritin, an iron-storing protein, has been shown to have a protective effect against cervical dysplasia (Amburgey CF et al 1993).

Cumin. Finally, the spice cumin has been demonstrated in animal studies to reduce the likelihood of developing cervical cancer (Gagandeep et al 2003).

Melatonin

Melatonin may help suppress rapid cell growth and mutation, but this association is still being studied, and some studies have found no effect of melatonin on certain cancer lines (Anisimov VN et al 2000; Panzer A et al 1998). Nevertheless, melatonin is commonly used by patients with cervical dysplasia (Greenlee H et al 2004). One study found that melatonin inhibits the growth of cervical cancer cells in laboratory culture after 48 hours of treatment (Chen LD et al 1995).

Researchers are also looking at variations in melatonin levels among patients with cervical dysplasia. One study revealed lowered melatonin secretion in endometrial cancer patients but not in those with squamous cervical cancer (Karasek M et al 2000).

WORKING TO FIGHT OFF CERVICAL CANCER

It is fortunate that most cases of cervical dysplasia will not progress to cancer, and if detected, cervical dysplasia is relatively easily treated. If cervical dysplasia progresses to cervical cancer, the treatment options are similar: freezing the cancer or loop electrosurgical excision. If they are treated early enough, it is possible for many women with early-stage cervical cancer to bear children. Advanced cancer that has spread beyond the cervix can require hysterectomy, radiation treatment, or chemotherapy.

While an abnormal Pap smear is reason to carefully adhere to any regimen of follow-up testing and treatment under the care of a physician, studies show certain nutrients also have an ability to fight cervical cancer. Research on cervical cancer has focused on agents that have low toxicity and display activity against HPV-positive cell lines (Vlastos AT et al 2003). The following chemical compounds are under investigation:

Indole-3-carbinol. Indole-3-carbinol, a plant compound from cruciferous vegetables like broccoli and cauliflower, has been studied in connection with the management of CIN. The effectiveness of this plant compound has been documented in small clinical trials (Stanley M 2003b; Bell MC et al 2000). Indole-3-carbinol reduces the formation of 16 alpha-hydroxyestrone, a suspected carcinogen, which in high levels is associated with a greater risk of cervical cancer (Sepkovic DW et al 2001).

Vitamin A. Retinoids, the natural and synthetic forms of vitamin A, inhibit the growth of epithelial cells through transforming growth factor beta (Comerci JT Jr et al 1997). Additionally, retinoids have been reported to support the differentiation of cells (thereby preventing abnormal cervical cancer cells), as well as to affect the immune response of cells (Ahn WS et al 1997; Darwiche N et al 1994).

Coenzyme Q10. Coenzyme Q10 is used by cells for growth and maintenance and as an antioxidant. Some studies have suggested coenzyme Q10 stimulates the immune system. Low levels have been found in certain cancers. Studies suggest the usefulness of coenzyme Q10 in adjuvant therapy in cervical cancer, especially in conjunction with alpha and gamma tocopherols (Palan PR et al 2003).

Green tea. A study of 51 patients showed a reduction of 69 percent of cervical dysplasia lesions in patients who received green tea extracts as either an ointment or capsule (Ahn WS et al 2003).

Melatonin. In animal studies, this hormone is reported to prevent the proliferation of errant cells as well as to help prevent mutation of cells and the breakage of chromosomes (Anisimov VN et al 2000). In lab studies, growth of cervical cancer cells diminished within 48 hours of administration of melatonin (Chen LD et al 1995).

Turmeric (curcumin). Turmeric is effective in regulating cell development, cell division, and programmed cell death (Nagai S et al 2005; Chen A et al 2005; Ramachandran C et al 2005; Sharma RA et al 2005; Seo WG et al 2005; Fang J et al 2005; Weber WM et al 2005; Karunagaran D et al 2005; Furness MS et al 2005; Tilak JC et al 2004; Surh YJ 1999). With regard to cervical cancer, turmeric affects the transcription of the high-risk variant HPV18 as well as other cellular transcription responses (Prusty BK et al

2005). Finally, turmeric with the chemotherapeutic agent vinblastine is effective against resistant cervical cancer (Limtrakul P et al 2004; Chearwae W et al 2004).

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Regular Pap smear testing for women older than age 30 and careful adherence to any follow-up testing is critical. Poor follow-up on testing after abnormal Pap smears can have potentially devastating consequences if cervical dysplasia is left untreated and allowed to progress to more serious forms of dysplasia or cervical cancer.

Life Extension's recommendations are designed with the goal of helping women prevent CIN from developing or progressing into cervical cancer. It is very important that women with any stage of cervical cancer work closely with a qualified physician to manage their disease before it spreads from the cervix into the rest of the body. Close supervision by a qualified physician is critical.

For women with cervical dysplasia or abnormal Pap smears, the following nutrients may be helpful:

- **Life Extension multivitamin/mineral mix**—follow label directions; this mix includes
 - Vitamin A
 - Vitamin C
 - Beta carotene
 - Folic acid
 - Vitamin B6
 - Vitamin B12
 - Selenium
 - Zinc
- **Melatonin**—3 to 10 milligrams (mg) nightly
- **Curcumin**—800 mg once or twice daily

For women whose condition has progressed to CIN or who have overt cancer, the following nutrients should be considered, in consultation with a qualified physician

- **Indole-3-carbinol**—follow directions on label because this product is weight specific
- **Coenzyme Q10**—100 to 200 mg daily with food
- **MSM**—1000 mg daily
- **Ginseng**—follow label directions
- **Green tea extract**—725 mg daily

CERVICAL DYSPLASIA 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:

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.

Curcumin

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.

- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

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.

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.

MSM

- MSM can cause headache or gastrointestinal symptoms such as nausea and diarrhea.

For more information see the Safety Appendix

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