Cancer Surgery

The surgical removal of the primary tumor has been the cornerstone of treatment for most types of cancer. The rationale for this approach is straightforward -- if you can get rid of the cancer by removing it from the body, then a cure can likely be achieved. Unfortunately, this approach does not take into account that following surgery, the cancer will frequently metastasize (spread to different organs). Quite often the metastatic recurrence is far more serious than the original tumor. In fact, for many cancers it is the metastatic recurrence, and not the primary tumor that ultimately proves to be fatal (Bird 2006).

A growing body of scientific evidence has revealed that cancer surgery can increase the risk of metastasis (van der Bij 2009). Even though this contradicts conventional medical thinking, the facts are undeniable.

A complicated sequence of events must occur in order for cancer to metastasize (van der Bij 2009). Isolated cancer cells that break away from the primary tumor must first breach the connective tissue immediately surrounding the cancer. Once this occurs, the cancer cell enters a blood or lymphatic vessel. To gain entry, the cancer cell must secrete enzymes that degrade the basement membrane of the blood vessel (Wagennar-Miller 2004). This is vitally important for the metastatic cancer cell as it uses the bloodstream for transport to other vital organs of the body (i.e., the liver, brain, or lungs) where it can form a new deadly tumor.

Traveling within the bloodstream can be a hazardous journey for cancer cells. Turbulence from the fast moving blood can damage and destroy the cancer cell. Furthermore, cancer cells must avoid detection and destruction from white blood cells circulating in the blood stream.

To complete its voyage, the cancer cell must adhere to the lining of the blood vessel where it degrades through and exits the basement membrane of the blood vessel. Its final task is to burrow through the surrounding connective tissue to arrive at its final destination, the organ. Now the cancer cell can multiply and form a growing colony, serving as the foundation for a new metastatic cancer.

We now see that cancer metastasis is a complicated and difficult process. Fraught with peril, very few free-standing cancer cells survive this arduous journey (van der Bij 2009).

In a groundbreaking study, researchers reported that cancer surgery itself can greatly lessen the cancer cell’s obstacles to metastasis (van der Bij 2009). Cancer surgery can produce an alternate route of metastasis that bypasses natural barriers. During cancer surgery, the removal of the tumor almost always disrupts the structural integrity of the tumor and/or blood vessels feeding the tumor. This can lead to either an unobstructed dispersal of cancer cells into the bloodstream or seeding of these cancer cells directly into the chest or abdomen (Ben-Eliyahu 2003; Yamaguchi 2000; Da Costa 1998; Shakhar 2003).This surgery-induced “alternate route” can greatly simplify the path to metastasis.

To illustrate, a study compared the survival of women with breast cancer who had surgery to that of women with breast cancer who did not have surgery. As expected, surgery substantially improved survival in the early years. However, further analysis of the data revealed that the surgery group had a spike in their risk of death at eight years that was not evident in the non-surgery group (Demicheli 2001).

Given these findings, a worthwhile strategy to protect against the increased risk of metastasis would be to examine all of the mechanisms by which surgery promotes metastasis, and then create a comprehensive plan that counteracts each and every one of these mechanisms.

What You Need to Know: Cancer Surgery

- Surgical removal of cancer typically provides the best chance of disease-free survival.
- Since metastatic disease is often deadlier than the original tumor, it is important to utilize preventive strategies to prevent cancer metastasis.
- A growing body of evidence suggests that cancer surgery itself may increase the risk of metastasis (spread to other areas) via numerous mechanisms including increasing cancer cell adhesion, suppressing immune function, promoting angiogenesis (growth of new blood vessels from pre-existing vessels), and stimulating inflammation.
- Choose surgeons and anesthesiologists who utilize advanced techniques that may reduce metastatic risk.
- Certain nutrients and drugs are associated with reduced risk of metastasis.

Surgery Increases Cancer Cell Adhesion

One mechanism by which surgery increases the risk of metastasis is by enhancing cancer cell adhesion (Dowdall 2002). Cancer cells that break away from the primary tumor utilize adhesion to boost their ability to form metastases in distant organs. These cancer cells must be able to clump together and form colonies that can expand and grow. It is unlikely that a single cancer cell will form a metastatic tumor. Cancer cells use adhesion molecules (which are present on the surface of cancer cells), such as galectin-3, to facilitate their ability to clump together (Raz 1987). Cancer cells circulating in the bloodstream also make use of galectin-3 surface adhesion molecules to latch onto the lining of blood vessels (Yu 2007). The adherence of circulating tumor cells (CTCs) to the blood vessel walls is an essential step for the process of metastasis. A cancer cell that cannot adhere to the blood vessel wall will just continue to wander through the blood stream incapable of forming metastases. Eventually, white blood cells circulating in the bloodstream will target and destroy the CTCs. If the CTCs successfully bind to the blood vessel wall and burrow their way through the basement membrane, they will then utilize galectin-3 adhesion molecules to adhere to the organ to form a new metastatic cancer (Raz 1987).

Combating Cancer Cell Adhesion

Research has shown that cancer surgery increases tumor cell adhesion. In one experiment that mimicked surgical conditions, scientists reported that the binding of cancer cells to the blood vessel walls was increased by 250%, compared to cancer cells not exposed to surgical conditions (ten Kate 2004). A natural supplement called modified citrus pectin (MCP) can help neutralize the surgery-induced increase in cancer cell adhesion. Citrus pectin—a type of dietary fiber—is not absorbed into the intestine. However, modified citrus pectin has been altered so that it can be absorbed into the blood and exert its anti-cancer effects. Modified citrus pectin inhibits cancer cell adhesion by binding to galectin-3 adhesion molecules on the surface of cancer cells, thereby preventing cancer cells from sticking together and forming a cluster (Nangia-Makker 2002). Modified citrus pectin can also inhibit circulating tumor cells from latching onto the lining of blood vessels. This was demonstrated by an experiment in which modified citrus pectin blocked the adhesion of galectin-3 to the lining of blood vessels by 95%. Modified citrus pectin also substantially decreased the adhesion of breast cancer cells to the blood vessel walls (Nangia-Makker 2002).

In one study, rats were injected with prostate cancer cells. One group received the modified citrus pectin while the other (control group) did not. Lung metastasis was noted in 50% of the modified citrus pectin group versus 93% in the control group. Even more noteworthy was that the modified citrus pectin group had an 89% reduction in the size of the metastatic colonies compared to the control group (Pienta 1995). In a similar experiment, mice injected with melanoma cancer cells that were fed modified citrus pectin experienced a greater than 90% reduction in lung metastasis compared to the control group (Platt 1992).

In a human trial, 10 men with recurrent prostate cancer received 14.4 g daily of modified citrus pectin. After one year, a considerable improvement in cancer progression was noted as determined by a rate reduction in the prostate-specific antigen (PSA) level (Guess 2003). This was followed by a study in which 49 men with various types of prostate cancer were given

modified citrus pectin for a four-week cycle. After two treatment cycles, 22% of the men experienced a stabilization of their disease or improved quality of life; 12% remained stable for more than 24 weeks. The authors of the study concluded that "MCP seems to have positive impacts especially regarding clinical benefit and life quality for patients with far advanced solid tumor" (Azemar 2007).

Cimetidine, commonly known as Tagamet®, is a drug historically used to alleviate heartburn. A growing body of scientific evidence has revealed that cimetidine also possesses potent anti-cancer activity. Cimetidine inhibits cancer cell adhesion by blocking the expression of an adhesive (cancer cells latch on) molecule called E-selectin on the surface of cells lining blood vessels (Platt 1992). By preventing the expression of E-selectin, cimetidine significantly limits the ability of cancer cell adherence to the blood vessel walls.

In a study supporting the potential anti-cancer effects of cimetidine, 64 colon cancer patients received chemotherapy with or without cimetidine (800 mg per day) for one year. The 10-year survival rate for the cimetidine group was almost 90% versus 49.8% for the control group. For those patients with a more aggressive form of colon cancer, the 10-year survival was 85% in those treated with cimetidine compared to 23% in the control group (Matsumoto 2002). The authors of the study concluded that "taken together, these results suggested a mechanism underlying the beneficial effect of cimetidine on colorectal cancer patients, presumably by blocking the expression of E-selectin on vascular endothelial [lining of blood vessels] cells and inhibiting the adhesion of cancer cells." These findings were supported by another study with colorectal cancer patients wherein cimetidine given for just seven days at the time of surgery increased three-year survival rate from 59% to 93% (Adams 1994).

This combination regimen of 14g of modified citrus pectin and 800mg of cimetidine, taken at least five days before surgery, may be followed for a year or longer to reduce metastatic risk.

Preventing Surgery-Induced Immune Suppression

The immune system is essential in combating cancer. Natural killer (NK) cells are a type of white blood cell which seeks out and destroys cancer cells. Research has shown that NK cells can spontaneously recognize and kill a variety of cancer cells (Herberman 1981).

In a study examining NK cell activity in women shortly after surgery for breast cancer, it was reported that low levels of NK cell activity were associated with an increased risk of death from breast cancer (Mccoy 2000). In fact, reduced NK cell activity was a better predictor of survival than the actual stage of the cancer itself. In another study, colon cancer patients with a reduced NK cell activity before surgery had a 350% increased risk of metastasis during the following 31 months (Koda 1997).

The likelihood of surgery-induced metastasis requires the immune system to be highly active and vigilant in seeking out and destroying renegade cancer cells during the perioperative period (the time immediately before, during, and after surgery). Numerous studies have documented that cancer surgery results in a substantial reduction in NK cell activity (Da Costa 1998; Shakhar 2003; McCulloch 1993; Rosenne 2007). In an investigation, NK cell activity in women having surgery for breast cancer was reduced by over 50% on the first day after surgery (McCulloch 1993). A group of researchers stated that "we therefore believe that shortly after surgery, even transitory immune dysfunction might permit neoplasms [cancer] to enter the next stage of development and eventually form sizable metastases" (Shakhar 2003).

The surgical procedure itself reduces NK activity. In other words, NK cell activity becomes impaired when it is most needed to fight metastasis. With that said, the perioperative period presents a window of opportunity to actively strengthen immune function by enhancing NK cell activity. Fortunately, numerous nutraceutical (e.g., dietary supplements, herbal products), pharmaceutical, and medical interventions known to enhance NK cell activity are available to the person undergoing cancer surgery.

One prominent natural supplement that can increase NK cell activity is an enzymatically modified rice bran extract. This

specialized rice bran extract has been termed a “biological response modifier” because of its ability to enhance several aspects of immune function (Ghoneum 2011). Studies show that enzymatically modified rice bran extract activates natural killer cells, T cells, macrophages, and monocytes (Ghoneum 2011; Ghoneum 2004). This specialized compound can increase the ability of paclitaxel to kill both metastatic and non-metastatic breast cancer cells. In fact, one study found that enzymatically modified rice bran extract increased by more than 100-fold the suceptiabilty of breast cancer cells to paclitaxel. The extract worked in synergy with paclitaxel in this study, causing DNA damage, enhancing apoptosis, and inhibiting proliferation of metastatic breast cancer cells (Ghoneum 2014). A similar laboratory study showed that the specially modified rice bran extract increased the ability of the chemotherapeutic agent daunorubicin to kill breast cancer cells (Gollapudi 2008). Another preclinical model showed that enzymatically modified rice bran extract promoted apoptosis in leukemia cells (Ghoneum 2003).

Enzymatically modified rice bran extract has also been shown to complement conventional treatment of liver cancer. In a randomized, blinded, controlled clinical trial involving 68 liver cancer patients, enzymatically modified rice bran extract was shown to improve the efficacy of common treatment approaches including chemoembolization, ethanol injection, cryoablation, and radiofrequency ablation (collectively termed “interventional therapy”). Thirty-eight subjects underwent interventional therapy and received 1 g of the rice bran extract daily for three years, while 30 underwent interventional therapy only. Compared with interventional therapy alone, enzymatically modified rice bran extract in combination with interventional therapy led to reduced rates of disease recurrence (31% vs. 46%), improved survival rate after two years (6% vs. 35%), and a significant reduction in tumor volume (Bang 2010). Moreover, adverse side effects were more common in the group of subjects who only underwent interventional therapy.

Other nutraceuticals that have been documented to increase NK cell activity are garlic, glutamine, IP6 (inositol hexaphosphate), and lactoferrin (Ishikawa 2006; Baten 1989; Kuhara 2006; Klimberg 1996; Matsui 2002). One experiment in mice with breast cancer found that glutamine supplementation resulted in a 40% decrease in tumor growth paired with a 2.5-fold increase in NK cell activity (Klimberg 1996).

Scientists in Germany explored the effects of mistletoe extract on NK cell activity in 62 patients undergoing surgery for colon cancer. The participants were randomized to receive either an intravenous infusion of mistletoe extract immediately before general anesthesia or general anesthesia alone. Measurements of NK cell activity were taken before and 24 hours after surgery. The group receiving anesthesia alone experienced a 44% reduction in NK cell activity 24 hours after surgery. The scientists reported that the group receiving mistletoe did not experience a significant decrease in NK cell activity after surgery. They went on to conclude that “perioperative infusion of mistletoe extracts can prevent a suppression of NK cell activity in cancer patients” (Schink 2007).

Pharmaceuticals used to increase NK cell activity include interferon-alpha and granulocyte-macrophage colony-stimulating factor. These drugs were shown to prevent surgery-induced immune suppression when given perioperatively (Mels 2001; Bhandarkar 2007). Another immune boosting drug to consider in the perioperative setting is interleukin-2 (Brivio 2002).

Tinospora cordifolia (*T. cordifolia*), long associated with adaptogenic and disease preventive activity, has been used in the traditional Indian Ayurvedic System of medicine to increase immune response against diseases (eg, malaria), infection, and liver toxicity, and reduce immune response in cases of inflammation, allergies, arthritis, fever, and diabetes (Thawani 2006; Sharma 2012; Upadhyay 2010; Wadood 1992; Sharma 2010).

In a human trial of 30 patients undergoing surgical intervention for malignant obstructive jaundice, pretreatment with oral *T. cordifolia* (16 mg/kg/day) prevented septicemia (a life-threatening infection of the blood), normalized debris removal and killing capacity of the immune system’s white blood cells, and resulted in a postoperative survival rate of 92.4% in the treatment group versus 40% in the control group. Researchers concluded that strengthening of the immune system by extracts of *T. cordifolia* may be responsible for considerable improvement in post-surgical outcome (Rege 1993).

In a laboratory study, a novel extract of *T. cordifolia* was found to powerfully activate different types of lymphocytes, which are important immune factors. The researchers found that it increased NK cell activity by 331%, T-cell activity by

102%, and B-cell activity by 39%, all of which demonstrate increased immune activity. These observations prompted the study authors to categorize *T. cordifolia* as “exhibiting unique immune stimulating properties” (Nair 2004).

Heightening Immune Surveillance with Cancer Vaccines

Using vaccines for cancer is the same as using vaccines for infectious diseases, except that tumor vaccines target cancer cells instead of a virus. Another distinguishing feature of tumor vaccines is that they are autologous, that is, they are produced from a person’s own cancer cells and removed during surgery. This is a critical distinction since there can be considerable genetic differences between cancers. This highly individualized cancer vaccine greatly amplifies the ability of the immune system to identify and target any residual cancer cells present in the body. Cancer vaccines provide the immune system with the specific identifying markers of the cancer that can then be used to mount a successful attack against metastatic cancer cells.

Autologous cancer vaccines have been studied extensively, with the most encouraging results noted in randomized, controlled clinical trials including more than 1,300 colorectal cancer patients in which tumor vaccines were given after surgery. These trials reported reduced recurrence rates and improved survival (Mosolits 2005). Unlike chemotherapy, which can cause severe side effects and toxicity, cancer vaccines are a gentle therapy with proven long-term safety (Choudhury 2006).

In a landmark study reported in 2003, 567 individuals with colon cancer were randomized to receive either surgery alone or surgery combined with vaccines derived from their own cancer cells. The median survival for the cancer vaccine group was over 7 years (66.5% 5-year survival rate) compared to 4.5 years (45.6% 5-year survival rate) for the group receiving surgery alone (Liang 2003). This difference in five-year survival rates clearly displays the power of individually-tailored cancer vaccines to greatly focus a person’s own immunity to target and attack residual metastatic cancer cells.

Cancer Surgery, Angiogenesis, and Metastasis

Angiogenesis (the formation of new blood vessels) is a normal and necessary process for childhood growth and development as well as wound healing. Unfortunately, cancers use this otherwise normal process in order to increase blood supply to the tumor. Because tumors cannot grow beyond the size of a pinhead (i.e., 1-2mm) without expanding their blood supply, the formation of new blood vessels supplying the tumor is a requirement for successful metastasis (Ribatti 2009; Rege 2005).

The primary tumor produces anti-angiogenic factors which serve to limit the growth of metastatic cancer elsewhere in the body (Baum 2005; Folkman 2003; Pinsolle 2000; Raymond 1998) by inhibiting the formation of new blood vessels to potential sites of metastasis. Unfortunately, the surgical removal of the primary cancer also results in the removal of these anti-angiogenic factors, and the growth of metastasis is no longer inhibited. With these restrictions lifted, it is now easier for small sites of metastatic cancer to attract new blood vessels that promote their growth (Goldfarb 2006-2007). Indeed, these concerns were voiced by researchers who declared that “removal of the primary tumor might eliminate a safeguard against angiogenesis and thus awaken dormant micrometastasis [small sites of metastatic cancer]” (Shakhar 2003).

As it turns out, the surgery causes another angiogenic effect. After surgery, levels of vascular endothelial growth factor (VEGF) (factors that increase angiogenesis) are significantly elevated. This can result in an increased formation of new blood vessels supplying areas of metastatic cancer. A group of scientists asserted that “after surgery, the angiogenic balance of pro- and antiangiogenic factors is shifted in favor of angiogenesis to facilitate wound healing. Especially levels of vascular endothelial growth factor (VEGF) are persistently elevated. This may not only benefit tumor recurrence and the formation of metastatic disease, but also result in activation of dormant micrometastases” (van der Bij 2009).

Various nutrients have been shown to inhibit VEGF. These include soy isoflavones (genistein), silibinin (a component of milk thistle), epigallocatechin gallate (EGCG) from green tea, and curcumin (Zhu 2007; Yoysungnoen 2006; Binion 2008; Guo 2007; Buchler 2004; Yang 2003).

In one experiment, EGCG, the active constituent of green tea, was administered to mice with stomach cancer. EGCG reduced the tumor mass by 60% and the concentration of blood vessels feeding the tumor by 38%. In addition, EGCG decreased the expression of VEGF in cancer cells by 80%. The authors of the study concluded that "EGCG inhibits the growth of gastric cancer by reducing VEGF production and angiogenesis, and is a promising candidate for anti-angiogenic treatment of gastric cancer" (Zhu 2007).

In a survey of curcumin's anti-angiogenic effects, researchers noted that "Curcumin is a direct inhibitor of angiogenesis and also downregulates various proangiogenic proteins like vascular endothelial growth factor." Additionally, they remarked that "cell adhesion molecules are upregulated in active angiogenesis and curcumin can block this effect, adding further dimensions to curcumin's antiangiogenic effect." In conclusion, they commented that "Curcumin's effect on the overall process of angiogenesis compounds its enormous potential as an antiangiogenic drug" (Bhandarkar 2007).

The Choice of Surgical Anesthesia Can Influence Metastasis

The traditional protocol for anesthesia use is general anesthesia during surgery followed by intravenous morphine (for pain control) after surgery. However, this may not be the optimal approach for preventing surgery-induced metastasis. At a time when immune function is already suppressed, morphine further weakens the immune system by diminishing NK cell activity (Vallejo 2004). Surgical anesthesia has also been shown to weaken NK cell activity (Melamed 2003). One study found that morphine increased angiogenesis and stimulated the growth of breast cancer in mice. The researchers concluded that "these results indicate that clinical use of morphine could potentially be harmful in patients with angiogenesis-dependent cancers" (Gupta 2002).

Given the inherent problems associated with the use of morphine and anesthesia, researchers have explored other approaches to surgical anesthesia and pain control. One approach is the use of conventional general anesthesia combined with regional anesthesia (anesthesia that affects a specific part of the body). The benefits achieved with this approach are two-fold --1) the use of regional anesthesia reduces the amount of general anesthesia required during surgery, and 2) it decreasing the amount of morphine needed after surgery for pain control (Goldfarb 2006-2007).

In one experiment, mice with cancer received surgery with either general anesthesia alone or combined with regional anesthesia. The scientists reported that the addition of regional anesthesia "markedly attenuates the promotion of metastasis by surgery." Regional anesthesia reduced 70% of the metastasis-promoting effects of general anesthesia alone (Bar-Yosef 2001).

In another study, doctors compared NK cell activity in patients receiving general or regional anesthesia for abdominal surgery. NK cell activity dropped substantially in the general anesthesia group, while it was preserved at pre-operative levels in the group receiving regional anesthesia (Koltun 1996). In a pioneering study, 50 women having breast cancer surgery with general and regional anesthesia were compared to 79 women having breast cancer surgery and receiving general anesthesia followed by morphine. The type of regional anesthesia used was called a paravertebral block, which involves the injection of a local anesthetic around the spinal nerves between the vertebral bones of the spine. After nearly three years, dramatic differences were noted between the two groups. Only 6% of patients who received regional anesthesia experienced a metastatic recurrence compared to 24% in the group that did not receive regional anesthesia. In other words, women who received regional and general anesthesia had a 75% decreased risk for metastatic cancer. These findings led researchers to proclaim that regional anesthesia for breast cancer surgery "markedly reduces the risk of recurrence of metastasis during the initial years following surgery" (Goldfarb 2006-2007).

In yet another study, surgeons concluded that regional anesthesia "can be used to perform major operations for breast cancer with minimal complications. Most importantly, by reducing nausea, vomiting, and surgical pain, paravertebral block [regional anesthesia] markedly improves the quality of operative recovery for patients who are treated for breast cancer" (Coveney 1998).

A group of researchers announced that “as regional techniques [anesthesia] are easy to implement, inexpensive, and do not pose a threat greater than general anesthesia, it would be easy for anesthesiologists to implement them, thus reducing the risk of disease recurrence and metastasis” (Goldfarb 2006-2007).

Those requiring medication for pain control after surgery can consider asking their doctor for tramadol instead of morphine. Unlike morphine, tramadol does not suppress immune function (Liu 2006). On the contrary, tramadol has been shown to stimulate NK cell activity. In one experiment, tramadol prevented the suppression of NK cell activity and blocked the formation of lung metastasis induced by surgery in rats (Gaspani 2002).

Less Invasive Surgery Reduces Risk of Metastasis

Surgery places an enormous physical stress upon the body. There is considerable scientific evidence supporting the belief that less invasive surgeries, and therefore less traumatic, pose a decreased risk of metastasis. Laparoscopic surgery, performed by making a small incision in the abdomen, is one type of minimally invasive surgery.

In a study comparing laparoscopic to open surgery in colon cancer patients receiving a partial colectomy (removal of the colon), the laparoscopic group had a 61% decreased risk of cancer recurrence coupled with a 62% decreased risk of death from colon cancer. The surgeons concluded that laparoscopic colectomy is more effective than open colectomy for treatment of colon cancer (Lacy 2002). A long-term (median time ~8 years) follow-up of these patients reported a 56% decreased risk of death from colon cancer following laparoscopic surgery as compared to traditional open surgery (Lacy 2008).

Minimally invasive surgery has produced substantial improvements in survival rates for lung cancer patients. Video-assisted thoracoscopic surgery (VATS) was compared to traditional open surgery for removing lung tumors (lobectomy). The five-year survival rate from lung cancer was 97% in the VATS group compared to 79% in the open surgery group (Kaseda 2000).

A group of surgeons commented that minimally invasive surgery for lung cancer “can be performed safely with proven advantages over conventional thoracotomy [chest surgery] for lobectomy: smaller incisions, decreased postoperative pain, decreased blood loss, better preservation of pulmonary function, and earlier return to normal activities. The evidence in the literature is mounting that VATS may offer reduced rates of complications and better survival” (Mahtabifard 2007).

Administering Chemo and Radiation Therapies Prior to Surgery

A group of doctors studied the use of combined radiation and chemotherapy prior to surgery for individuals with esophageal cancer. Twenty-six cancer patients received surgery alone, while 30 received radiation and chemotherapy followed up by surgery. The group receiving combined treatment had a five-year survival rate of 39% compared to 16% in the group treated with surgery alone (Tepper 2008).

In another study comparing treatment with surgery alone to treatment with chemotherapy (both directly before and after surgery) in patients with stomach or esophageal cancer, the five-year survival rate for the group receiving surgery and chemotherapy was 36% compared to 23% in the group receiving surgery alone (Cunningham 2006).

Research also supports the use of chemotherapy and radiation therapy during the critical perioperative period. In one study, 544 patients with stomach cancer received combined chemotherapy and radiation shortly after surgery. Survival comparisons were made with a similar group of 446 patients with stomach cancer treated with surgery alone. The group treated with surgery alone had a median survival of only 62.6 months compared to 95.3 months in the combination group (Kim 2005).

Inflammation and Metastasis

Cancer surgery causes an increased production of inflammatory chemicals such as interleukin-1 and interleukin-6 (Baigrie

1992; Wu 2003; Volk 2003). These chemicals are known to increase the activity of cyclooxygenase-2 (COX-2). A highly potent inflammatory enzyme, COX-2 plays a pivotal role in promoting cancer growth and metastasis by stimulating the formation of new blood vessels feeding the tumor (Tsujii 1998; Chu 2003). It also increases cancer cell adhesion to the blood vessel walls (Kakiuchi 2002), thereby enhancing the ability of cancer cells to metastasize.

This was evident in an article which reported levels of COX-2 in pancreatic cancer cells to be 60 times greater than in normal pancreatic cells (Tucker 1999). Levels of COX-2 were 150 times higher in cancer cells from individuals with head and neck cancers compared to normal tissue from healthy volunteers (Chan 1999). This was further supported when

Two hundred eighty-eight individuals undergoing surgery for colon cancer had their tumors examined for the presence of COX-2. With other factors being controlled, the group whose cancers tested positive for the presence of COX-2 had a 311% greater risk of death compared to the group whose cancers did not express COX-2 (Soumaoro 2004). A subsequent study in lung cancer patients found that those with high tumor levels of COX-2 had a median survival rate of 15 months compared to 40 months in those with low levels (Yuan 2005).

Given these findings, researchers began investigating the anti-cancer effects of COX-2 inhibitor drugs. Although initially used for inflammatory conditions (i.e., arthritis), COX-2 inhibitor drugs have been shown to possess powerful anti-cancer benefits. For example, 134 patients with advanced lung cancer were treated with chemotherapy alone or combined with Celebrex® (a COX-2 inhibitor). For those individuals with cancer expressing higher amounts of COX-2, treatment with Celebrex® dramatically prolonged survival (Edelman 2008). Treatment with Celebrex® also slowed cancer progression in men with recurrent prostate cancer (Pruthi 2006).

In a groundbreaking study, the incidence of bone metastases in breast cancer patients receiving COX-2 inhibitors for at least six months (following the initial diagnosis of breast cancer) was compared to the incidence in breast cancer patients not taking a COX-2 inhibitor. Those taking a COX-2 inhibitor were almost 80% less likely to develop bone metastases than those not taking a COX-2 inhibitor (Tester 2012).

Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, are COX-2 inhibitors. The widespread use of NSAIDs for pain and arthritis has created an ideal environment in which to examine whether these drugs can prevent cancer. Large-scale studies have documented a substantial reduction in cancer risk with the use of NSAIDs. A comprehensive review of 91 published studies reported that long-term use of NSAIDs (primarily aspirin) produced risk reductions of 63% for colon cancer, 39% for breast cancer, 36% for lung cancer, 39% for prostate cancer, 73% for esophageal cancer, 62% for stomach cancer, and 47% for ovarian cancer. The authors concluded that “this review provides compelling evidence that regular intake of NSAIDs that block COX-2 protects against the development of many types of cancer” (Harris 2005).

A number of nutritional and herbal supplements are known to inhibit COX-2. These include curcumin, resveratrol, vitamin E, soy isoflavones (genistein), green tea (EGCG), quercetin, fish oil, garlic, feverfew, and silymarin (milk thistle) (Binion 2008; Peng 2006; Subbaramaiah 1999; Subbaramaiah 1998; Horia 2007; O’Leary 2004; Hwang 1996; Ali 1995; Ramakrishnan 2008).

Scientists created an experimentally-induced increase in COX-2 activity in human breast cells, which was completely prevented by resveratrol. Resveratol blocked the production of COX-2 within the cell, as well as blocking COX-2 enzyme activity (Subbaramaiah 1998).

Life Extension Suggestions

Note: These products are to be used for cancer surgery recovery and preparation and are not intended to prevent, cure or treat cancer.

Begin taking the following supplements at least five days prior to surgery, discontinue taking the supplements the day of the surgery, and resume taking the supplements one day after surgery (unless otherwise directed by your

physician).

It is suggested to take these supplements for approximately one month after surgery.

- **Glutamine**: 3000 mg daily without food
- **IP6** (inositol hexaphosphate): 1 – 3 g daily
- **Lactoferrin**: 300 – 900 mg daily
- **Modified Rice Bran Extract**: 1 g daily
- **Cimetidine**: 800 mg before bedtime
- **Modified Citrus Pectin**: 14 – 30 g daily without food
- **Soy isoflavones** (genistein): 100 – 200 mg daily with food
- **Silibinin** (component of milk thistle): 500 – 600 mg daily
- **EGCG** (from Green Tea): 650 – 1000 mg daily
- **Curcumin**: BCM-95® extract: 400 mg daily with food or 2500 mg daily with food of a regular curcumin supplement. Different formulations of curcumin differ in their absorption and bioavailability. These differences in absorption can affect the suggested doses.
- **Resveratrol**: 20 – 25 mg before surgery; increase to 100 – 250 mg 2 weeks after surgery
- **Quercetin**: 500 – 1000 mg daily
- **Tinospora cordifolia extract** (std. to 20% polysaccharides [180 mg]): 900 mg daily

DUE TO THEIR BLOOD-THINNING EFFECTS, AVOID THE FOLLOWING SUPPLEMENTS FOR 2 WEEKS PRIOR TO SURGERY AND BEGIN TAKING 2 WEEKS AFTER SURGERY:

- **Garlic**: 1200 – 2400 mg daily with food
- **Fish oil**: 4000 mg daily with food
- **Vitamin E**: 400 – 800 IU daily with food
- **Feverfew**: 250 mg daily

PRESCRIPTION DRUGS:

Pharmaceuticals prescribed prior to surgery depend on the status of the individual cancer patient. Patients with low white blood count are typically treated with granulocyte colony-stimulating growth (GCF) factors such as Neupogen® (300-480 micrograms daily) or Neulasta® (6 mg), which lasts 3 weeks. Other pharmaceutical compounds which have shown benefits for cancer patients undergoing surgery are interferon alpha and Interleukin-2.

expressly disclaim responsibility for any error in literature.

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