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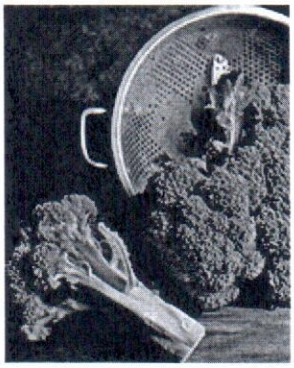
REPORT

I3C & DIM

Natural, Dual-Action Protection Against Deadly Cancers

By Dale Kiefer



With the increasing toxicity of our natural environment, guarding against cancer is an essential part of the quest for a longer, healthier life. Despite the expenditure of hundreds of billions of research dollars, the war on cancer has yet to produce a significant cure for most forms of this deadly disease. As a result, all health-conscious adults are advised to adopt an aggressive strategy of cancer prevention.

Fortunately, scientists have identified and isolated remarkable chemicals in cruciferous vegetables such as broccoli, cabbage, and watercress that can protect against cellular changes that lead to colon, breast, thyroid, and other cancers.[1-12] Many studies have demonstrated that specific compounds isolated from these vegetables—including diindolylmethane (DIM) and its precursor, indole-3-carbinol (I3C)—have unique cancer-fighting benefits. These compounds have been found to alter estrogen metabolism in both men and women, thus protecting against hormone-dependent cancers such as those of the breast, cervix, and prostate.

According to the American Cancer Society, diet and lack of adequate exercise are implicated in about one third of all cancer cases among adults.[13] Given that more than 1.3 million new cases were expected to be diagnosed in 2005, improved dietary and exercise habits could help prevent more than 400,000 Americans from developing cancer in just one year alone.

Colon cancer, for example, is among the cancers believed to be directly inhibited by compounds in cruciferous vegetables. The American Cancer Society estimates that in 2005, more than 100,000 new cases of colon cancer were diagnosed and more than 56,000 Americans died of this dreaded disease.[14] Prostate cancer, which studies show is also thwarted by compounds in cruciferous vegetables,[1,2,11,15] is the second leading cause of cancer-related deaths among US men. More than 200,000 new prostate cancer cases and 30,000 deaths from the disease were expected in 2005. Among women, breast cancer is comparably devastating, with about 212,000 new cases expected in 2005 and more than 40,000 women expected to die of the disease.[14] Clearly, there is a need for increased protection against these and other cancers. If cancer-fighting compounds in cruciferous vegetable could have prevented just one third of those breast cancer cases, perhaps 13,000 or more lives could have been saved.

Given the status of current research, it is a safe bet that increased consumption of cruciferous vegetables would save lives. Epidemiological evidence suggests that abundant consumption of cruciferous vegetables correlates with lower breast cancer risk. For example, a recent study in China concluded that greater cruciferous vegetable consumption "was associated with significantly reduced breast cancer risk among Chinese women."[16]

HEALTH-PROMOTING CHEMICAL CONVERSIONS

Not everyone consistently eats the cruciferous vegetables that have been shown to reduce cancer risk. Moreover, there is also natural variability in the anti-cancer phytonutrient content of these vegetables.

Scientists have long sought to extract the beneficial compounds of cruciferous vegetables. One group of bioactive nutrients responsible for cancer protection in cruciferous vegetables is known as glucosinolates. When consumed by humans, glucosinolates are converted to highly beneficial compounds including isothiocyanates such as sulforaphane and indoles such as I3C. These compounds are believed to inhibit cancer by various mechanisms within the body.[17]

The conversion of glucosinolates to isothiocyanates occurs naturally in several ways. One method is through the presence of

myrosinase, an enzyme found in the cells of cruciferous vegetables. However, the process of cooking cruciferous vegetables destroys much of the naturally available myrosinase. Glucosinolates obtained from cooked cruciferous vegetables can still be converted to isothiocyanates inside the body, albeit much less efficiently than when myrosinase is available. This conversion can occur in the colon, where native gut bacteria hydrolyze the glucosinolates.[18,19] Among the most powerful, abundant, and important glucosinolate derivatives is I3C.

REMARKABLE EFFECTS OF I3C

While cruciferous vegetables supply numerous beneficial compounds, I3C is the real reason that "eat your broccoli" has always been good nutritional advice. According to a recent article in *The Journal of Nutritional Biochemistry*, "Mounting preclinical and clinical evidence indicate[s] that indole-3-carbinol (I3C), a key bio-active food component in cruciferous vegetables, has multiple anticarcinogenic and antitumorigenic properties."[6] Although it may seem obvious that a substance consumed by millions worldwide over thousands of years is inherently safe, scientists have now taken a closer look at this important phytonutrient. Numerous cell culture, animal, and human studies have demonstrated I3C's safety and tolerability,[20-22] along with its targeted ability to suppress cancer growth and induce programmed cell death in a variety of tumors, including those associated with breast, prostate, endometrial, leukemia, and colon cancers.[1]

Many scientists consider I3C to be especially valuable in protecting against hormone-dependent cancers—such as certain breast, cervical, and prostate cancers—due to its ability to favorably influence the human body's balance of estrogens.[1,22-26] For example, I3C halts cancer cell growth by interfering with the production of proteins involved in abnormal cellular reproduction, and by promoting the production of tumor-suppressor proteins.[1,27,28]

As one researcher recently noted, "I3C . . . regulate[s] many genes that are important for the control of cell cycle, cell proliferation, signal transduction, and other cellular processes, suggesting the [multiple beneficial] effects of I3C.[2]

I3C has also been shown to induce apoptosis (programmed cell death) in cancer cells by interfering with the production of cellular products that cancer ordinarily marshals to resist apoptosis.[1,29]

In the liver and intestinal lining, I3C is believed to enhance the functioning of critical enzyme systems that are responsible for detoxifying the body of harmful, potentially cancer-causing chemicals. Such toxic substances may be ingested in food or drink, or be absorbed through environmental contact. These enzyme systems, technically known as Phase I and Phase II enzymes, alter the chemical structure of unwelcome compounds in order to detoxify them.[21,30,31]

Newly published research suggests that I3C may also work to prevent cancer by interfering with angiogenesis, a process critical to the body's defense against cancer. Angiogenesis—the formation of new blood vessels that tumors rely on for nutrients and oxygen—has long been regarded as a major potential target in the battle against cancer.[1,32] In addition, research shows that I3C also induces breast cancer cells to become more responsive to interferon gamma, an important immune system chemical associated with protecting the body from disease.[33]

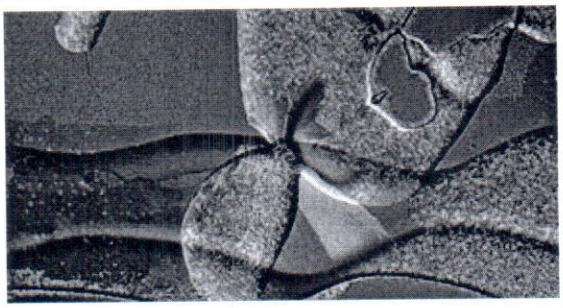
HOW DIM COMPLEMENTS I3C

Many scientists believe that I3C's beneficial effects are partly driven by one of its principal byproducts, diindolylmethane, or DIM.[34,35] For instance, DIM has recently been shown to promote production of beneficial interferon gamma by breast cancer cells. According to scientists at the University of California, Berkeley, "This novel effect may provide important clues to explain the anti-cancer effects of DIM because it is well known that [interferon gamma] plays an important role in preventing the development of primary and transplanted tumors."[36] Recently, scientists working with cell cultures also showed that DIM activates cellular stress response pathways in breast, prostate, and cervical cancer cells. This response mimics the reaction of cells deprived of adequate nutrition, further enhancing the cells' susceptibility to destruction.[37] In other studies, researchers have shown that both DIM and I3C induce cell death in prostate cancer cells.[15,29]

Scientists at Wayne State University School of Medicine recently noted that "I3C and DIM affected the expression of a large number of genes that are related to the control of carcinogenesis, cell survival, and physiologic behaviors."[15]

Like I3C, DIM also stops the growth of new blood vessels that tumors require for their survival and metastasis. This newly discovered anti-cancer activity (anti-angiogenesis) is significant. In research at the University of California, Berkeley, in both cell culture assays and live animal models of cancer, small amounts of DIM dramatically reduced biochemical markers of angiogenesis and significantly impeded the rate of new vessel growth. "This is the first study," the scientists noted, "to show that DIM can strongly inhibit the development of human breast tumor in [an animal] model and to provide evidence for the antiangiogenic properties of this dietary indole."[8]

TAMING THE ESTROGEN CONNECTION



Photomicrograph of estradiol crystals. Estradiol, the most potent of the natural estrogens, is used in its natural or semisynthetic form to treat menopausal symptoms.

Perhaps the single most important mechanism of action of I3C and DIM is modulating estrogen metabolism. This is because estrogen receptors are present on the surface of virtually every type of tissue in the bodies of both men and women, and are associated with several hormone-dependent cancers.[38] The body modifies, or metabolizes, estrogens through two mutually exclusive pathways, which lead to compounds with dramatically different biological activities. Estradiol is the primary estrogen in circulation, and one of the most active. It is metabolized to a number of other chemicals, all with some degree of estrogenic activity.

The enzymes 2-hydroxylase and 16-alpha-hydroxylase help metabolize estrogens. Several years ago, scientists hypothesized that a preference towards the 2-hydroxylase pathway, which generates 2-hydroxyestrone (2-OHE1), results in less toxic estrogen in the circulation, which should result in a reduction of breast cancer. On the other hand, they reasoned, women in whom a preponderance of estrogens tend to be metabolized via the 16-alpha-hydroxylase pathway—leading to greater amounts of a more biologically potent form of estrogen, 16-alpha-hydroxyestrone (16a-OHE1)—should experience a greater risk of breast cancer.

In 2000, in a study known as ORDET, scientists analyzed data gathered on more than 10,000 Italian women over more than five years, examining diet and other factors associated with breast cancer risk.[39]

The researchers found that a higher ratio of "good" 2-OHE1 to "bad" 16a-OHE1 at the beginning of the study was significantly associated with a reduced risk of breast cancer. Subsequent studies of different populations have lent support to this finding.[16] The ratio of these two estrogen metabolites is now widely regarded as an indicator for the risk of breast and other hormone-associated cancers, with a higher 2-OHE1:16a-OHE1 ratio considered desirable.[16,35,40,41]

In a subsequent study, scientists examined the association between the 2-OHE1:16a-OHE1 ratio and prostate cancer risk. Although the study results failed to achieve statistical significance, elevated 2-OHE1 levels in urine suggested a reduced risk of prostate cancer, while elevated 16a-OHE1 urinary levels were associated with an increased risk of prostate cancer. Men with the highest values of 16a-OHE1 were twice as likely to have prostate cancer as men with the highest levels of 2-OHE1.[42]

I3C appears to be effective in shifting the metabolism of estradiol from the dangerous 16-alpha-hydroxylase pathway to the 2-hydroxylase pathway.43-46 As a result, consumption of I3C boosts the ratio of 2-OHE1:16a-OHE1, which correlates with reduced risk of breast and other cancers, including cervical, prostate, and even head and neck cancers.[16,38,47-53]

Another estrogen of note is 4-hydroxyestrone, a relatively potent estrogen with growth-promoting effects. DIM does not appear to increase 4-hydroxyestrone levels, and the available research does not clearly indicate that I3C significantly increases 4-hydroxyestrone levels in humans. For example, in a dose-ranging study of I3C in human volunteers, 4-hydroxyestrogens increased following supplementation with 400 mg of I3C daily, but this increase was not significant.[43]

Other studies actually show that I3C inhibits the formation of 4-hydroxyestrone. For example, a quantitative study evaluating DIM levels in urine after I3C supplementation in humans showed that I3C supplementation decreased 4-hydroxyestrone levels.[54]

Clearly, while more research is needed to assess I3C's effect on 4-hydroxyestrogens, a preponderance of the available scientific data consistently supports I3C's cancer-fighting effects.

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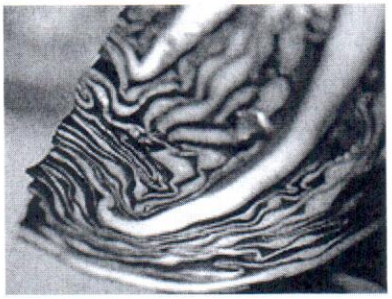
CANCER-FIGHTING WATERCRESS AND BROCCOLI

An often overlooked member of the cruciferous vegetable family, watercress is an "exceptionally rich source"[59] of potent cancer-fighting isothiocyanates, including a much-studied compound known as phenethyl isothiocyanate, or PEITC.

Recently published research indicates that an extract of the cruciferous vegetables watercress and broccoli suppresses an enzyme closely associated with the invasive potential of breast cancer.60 Scientists working with breast cancer cell cultures observed that a broccoli-watercress extract effectively lowers the expression of metalloproteinase-9, an enzyme associated with breast cancer's invasiveness. The same team simultaneously published research indicating that isothiocyanate compounds in watercress suppress production of pro-inflammatory compounds in laboratory models of cellular activity. "Overproduction of both nitric oxide (NO) and prostaglandins (PGE) has been associated with numerous pathological conditions, including chronic inflammation and cancer," the researchers noted. They speculated that this effect may contribute to the anti-cancer activity of cruciferous vegetables.[61]

For men, PEITC has particular value in preventing prostate cancer. Noting that epidemiological evidence shows a strong association between greater intake of cruciferous vegetables and reduced risk of prostate cancer, scientists in New York sought to identify the specific compounds responsible for cancer prevention. They found that a conjugate of PEITC, which is abundant in watercress, inhibited proliferation and tumorigenesis of prostate cancer cells growing in culture.[62]



Oncology researchers and physicians are becoming interested in watercress's potential use against deadly lung cancer.[63] Research shows that watercress-derived PEITC is a protective agent against lung cancer in laboratory rodents.[64,65] Subsequent research continues to confirm and expand on these findings.[66,67]

Remarkably, research shows that even after isothiocyanates such as PEITC are modified for efficient removal from the body in urine, they remain active against cancer. Urine containing conjugated isothiocyanates, which are stored in the bladder while awaiting removal, acts on the tissue lining the bladder to prevent carcinoma. This is precisely the site where most bladder tumors arise. "Development of effective preventive strategies for bladder cancer is of critical importance," one research team recently noted, concluding that isothiocyanates such as those in watercress "may be especially useful for the prevention of bladder cancer."[68]

Adding another piece to the puzzle, scientists at the University of Arizona determined in 2003 that PEITC inhibits cancer cell proliferation with surprising rapidity. This is significant, they noted, because PEITC and other dietary isothiocyanates from cruciferous vegetables tend to be cleared from the body through urinary excretion. Working with human leukemia cells, they discovered that isothiocyanates, including PEITC, were able to limit cancer cell proliferation.[69] After only three hours of exposure to PEITC and other cruciferous isothiocyanates, the cancer cells experienced the full spectrum of PEITC's anti-cancer effects.

French scientists recently discovered that compounds in watercress are adept at inducing both phase I and phase II enzymes, an effect that may explain its ability to inhibit chemically induced DNA damage from a wide variety of compounds. DNA damage can lead to carcinogenesis.[70]

PROTECTING AGAINST HORMONE-INDUCED BREAST CANCER

Breast cancer is the most common cancer, and the second leading cause of cancer-related death, in women. Many factors such as age, genetics, alcohol intake, and level of physical activity influence breast cancer risk.[55]

Hormones also play a crucial role in influencing breast cancer risk. After noting that women who experience early menarche (onset of menstruation) or late menopause have an increased risk of breast cancer, scientists have proposed that a woman's cumulative lifetime exposure to hormones helps determine her risk of developing breast cancer. Furthermore, the long-term use of hormone replacement therapy with conjugated equine estrogens combined with synthetic progestins is also known to increase breast cancer risk.[55]

One of the most important applications of I3C and DIM may be in protecting against hormone-induced breast cancer. Epidemiological, laboratory, and animal studies indicate that dietary intake of I3C prevents the development of estrogen-enhanced cancers, including breast, endometrial, and cervical cancers. While estrogen increases the growth and survival of tumors, I3C has been found to cause growth arrest and increased apoptosis (programmed cell death).[56]

Both I3C and DIM help promote healthy metabolism of estrogen by influencing the ratio of beneficial 2-hydroxyestrone to unfavorable 16-alpha-hydroxyestrone.[48,50] An increased ratio of these estrogen metabolites is associated with a decreased risk of breast and other cancers.[39,47-53] A placebo-controlled, double-blind study of women at increased risk for breast cancer found that four weeks of supplementation with I3C promoted favorable changes in the urinary estrogen metabolite

ratio of 2-hydroxy-estrone to 16-alpha-hydroxyestrone.[50]

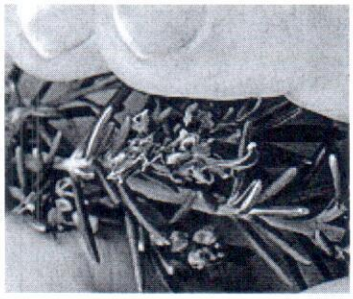
A recent pilot study examined DIM's effects on estrogen metabolites in postmenopausal women with a history of early-stage breast cancer. After one month of supplementation with DIM, the participants demonstrated a significant increase in levels of beneficial 2-hydroxyestrone and an insignificant increase in the ratio of 2-hydroxyestrone to 16-alpha-hydroxy-estrone. These results suggest that DIM may play a role in preventing breast cancer reoccurrence by promoting healthy estrogen metabolism.[48]

A clinical trial assessing I3C's role in preventing cancer in healthy individuals is currently under way.[57] Several clinical trials investigating DIM's cancer-preventive and therapeutic potential are also in progress.[58]

CARNOSIC ACID AND VITAMIN D

Cancer researchers have been paying a lot of attention to vitamin D. Scientists know that vitamin D functions as a hormone, affecting immune response and acting in various ways to protect against cancer.[71-74] Vitamin D is available in foods and supplements, as well as through its naturally occurring activation in the skin following exposure to ultraviolet light (sunlight). Vitamin D thus appears to be very important to the body's innate ability to fight cancer.[75,76]

To complement vitamin's D anti-cancer role, a compound derived from the culinary herb rosemary (Rosmarinus officinalis) acts to enhance vitamin D's biochemical activity. Carnosic acid and carnosol, found in rosemary, are antioxidant polyphenols that have been shown to aid vitamin D's efforts to thwart cancer. Rather than killing cancer cells outright as many chemotherapeutic agents do, vitamin D halts cancer by forcing precancerous cells to differentiate or become, in essence, more mature cells.[77,78] Because cancer is characterized by less mature cells, a process that compels these cells to become more mature is beneficial to fighting cancer. Scientists therefore are keenly interested in using supplemental vitamin D for differentiation therapy to prevent and possibly treat cancer.



Beyond this promising partnership with natural vitamin D, researchers have identified other mechanisms by which carnosic acid and carnosol work to protect and enhance the immune system.[79] These powerful natural antioxidants exhibit antibacterial activity, even against problematic bacteria that have developed resistance to standard antibiotics.[80] Carnosol has demonstrated activity against the HIV virus, at concentrations that were not harmful to healthy cells.81 Much like I3C and DIM, rosemary compounds have also been shown to reduce the carcinogenic potential of natural estrogens by enhancing their metabolism in the liver. When treated with a diet containing 2% rosemary for three weeks, female mice increased their beneficial 2-hydroxylation of estrogens by approximately 150% while inhibiting the detrimental 16-alpha-hydroxylation of estradiol by approximately 50%.[82]

Glucosinolates and their derivatives from cruciferous vegetables, along with the powerful cancer-fighting compound carnosic acid from rosemary, have thus been shown to be powerful weapons in the battle against cancer.

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