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Dietary Indoles: Chemopreventive Agents © VR

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In recent years, considerable attention has been paid to cancer prevention from cruciferous vegetables and active components present in these vegetables, such as indole-3-carbinol (I3C) and its metabolite di-indolyl-methane (DIM), and isothiocyanates.

Indole-3-carbinol is found in high amounts in the cruciferous vegetables (broccoli, cauliflower, Brussels sprouts, and cabbage). It is the natural precursor to DIM, which is formed from a "condensation reaction" in which two molecules of I3C molecules are combined to create a "di-indole." The formation of DIM is facilitated by the action of gastric acid on I3C released during digestion.

DIM in its pure crystalline form is insoluble in water, and requires an absorption-enhancing delivery system for use in dietary supplements. One such formulation in the market contains micro-particles of DIM associated with a soluble matrix, which enhances its absorption.

Several epidemiological studies suggest that consumption of vegetables may be particularly effective in reducing cancer risk of the stomach, esophagus, lung, oral cavity and pharynx, pancreas, and colon. The types of vegetables or fruit that most often appear to be protective against cancer are allium vegetables (e.g., onion), followed by carrots, cruciferous vegetables, and tomatoes.

Carcinogenesis
Carcinogenesis is a multi-step process that converts normal cells into malignant cells. Once transformed, malignant cells acquire the ability to invade and metastasize, leading to cancer. During this transformation from normal to malignant cells, carcinogenic steps can be suppressed or reversed through the use of specific natural or synthetic chemical agents before the onset of invasive cancer.

Research studies have consistently shown that the chemo-preventive agents derived from the cruciferous vegetables

influence carcinogenesis during initiation, promotion, and progression phases of cancer development.

In a recent study, I3C was shown to exhibit anti-cancer activities by suppressing breast tumor cell growth and metastatic spread, which is the most devastating problem in breast cancer.

Breast Cancer
The American Cancer Society estimates that more than 200,000 women will be diagnosed with breast cancer this year. Epidemiological studies suggest that estrogen metabolites produced by enzymatic oxidation of estrone and estradiol play an important role in breast cancer.

The concentration of the protective metabolite 2-hydroxy-estrone has been modulated by a variety of agents, including I3C and DIM. DIM increases the beneficial estrogen metabolites 2-hydroxy-estradiol and 2-hydroxy-estrone (2-OHE), and decreases the 16-alpha-hydroxy-estrone (16-alpha-OHE) and 4-hydroxy-estrone metabolites.

Research has shown that 2-OHE metabolites are protective against breast cancer, whereas the metabolite 16-alpha-OHE and the minor metabolite 4-hydroxy-estrone are potent carcinogens. This ratio of 2-hydroxy-estrogens to 16-alpha-hydroxy-estrone has been shown to be a predictor of breast cancer.

The oxidative metabolism of estrogens in humans is mediated primarily by a class of iso-enzymes known as cytochrome P450, many of which are inducible by dietary and pharmacological agents. Cytochrome P450 is also involved in the oxidative metabolism of a large number of drugs. One major cytochrome P450-mediated oxidative pathway is hydroxylation of estradiol and estrone to yield 16-alpha-OHE and 2-OHE products.

The effects of acute and chronic oral treatments with I3C on the cytochrome P450 catalyzed metabolism of estradiol and estrone by the liver and mammary gland were examined in female Sprague-Dawley rats. Both acute and chronic treatments with I3C increased cytochrome P450 content approximately two-fold.

The ability of I3C to raise the levels of good 2-OHE metabolites has been demonstrated in two studies. In the first study, seven men received I3C (6-7 mg per kg daily) for one week; in the second study, 10 women received I3C (6-7 mg per kg daily) for two months. Analysis of estrogen metabolites

in the urine of both men and women revealed a significant increase in the 2-hydroxy-estrogens and a decrease in the levels of estradiol, estrone, and 16-alpha-OHE.

I3C has also been shown in rodent models to induce a metabolic pathway competing with 16-alpha-OHE, which increases 2-OHE, and thereby reduces substrate available for the 16-alpha-OHE pathway. These findings indicate that I3C induces the formation of 2-OHE and decreases the concentrations of other metabolites known to activate estrogen receptor, and hence may have chemo-protective activity against breast cancer in women.

In an earlier study, I3C administered to Sprague-Dawley rats, treated with the chemical dimethyl-benzanthracene (DMBA) to induce tumors, was shown to prevent chemically induced mammary tumors during the initiation and promotion phases. This study also suggested that I3C might be a good candidate for chemo-prevention of breast cancer in women. I3C was also found to increase the ratio of 2-OHE to 16-alpha-OHE in MCF breast cells treated with DMBA.

In a dose-dependent, placebo-controlled, double-blind study, 60 women at increased risk for breast cancer received either a placebo or I3C at a low-dose (50 to 200 mg) or a high-dose (300 and 400 mg) daily for four weeks. The urinary estrogen metabolite ratio of 2-OHE to 16-alpha-OHE in the high-dose women group was significantly greater than that for women in the control and low-dose group. The study suggested that 300 mg per day is the minimum effective dose of I3C as a chemo-preventive agent for breast cancer.

In another study, both DIM and I3C have been shown to increase the 2-hydroxy- to 16-alpha-hydroxy-estrone ratio. In a prospective study of 5,000 Italian women, the risk of developing breast cancer over a four-year period was reduced in the pre-menopausal women who had the highest 2-OHE to 16-alpha-OHE ratio.

Dietary I3C can also raise the estrogen metabolite ratio 2-Hydroxy-estrone to estriol (another estrogen metabolite). The long-term responses of women to I3C was examined in a three-month randomized clinical trial. The female subjects were divided into three groups of 20; the first group received 400 mg of I3C daily, the second group received 20 g of dietary fiber and the third group received a placebo.

The urinary ratio of 2-OHE to estriol was measured monthly, and only the I3C group showed a substantial increase in this ratio. That increase was maintained over the three-month time

period, indicating the ability of I3C to increase this ratio in a sustained manner without detectable side effects.

Prostate Cancer
Prostate cancer is the second leading cause of cancer-related death among men in the United States. A diet rich in fruits and vegetables provides phyto-chemicals, particularly I3C, which may be responsible for the prevention of many types of cancer, including hormone-related cancers such as prostate.

A recent study (2000) showed that men who consumed three or more servings of cruciferous vegetables a week reduced their prostate cancer risk by almost half.

In another recent study (2001), I3C was found to inhibit the growth of prostate cancer cells by regulating the expression of apoptosis-related genes. This finding suggests that I3C may be an effective chemo-preventive or therapeutic agent against prostate cancer.

Summary
The cruciferous indoles: indole-3-carbinol (I3C) and di-indolyl-methane (DIM), promote healthy estrogen. Supplementation wit I3C is effective in adjusting the pathways of estrogen metabolism to favor the production of 2-hydroxy estrogen metabolites, which are associated with the reduction of estrogen-dependent cancer risk. ***VR***

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