

The Doctor's RESEARCH UPDATE

Natural Medicine for Men's Health

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Dr. Zeligs earned a Masters degree in stress-physiology from the University of California, Santa Barbara, completed a fellowship in Molecular Immunology, and received his M.D. from the University of California, Irvine, College of Medicine. Dr. Zeligs is a leading authority on diindolylmethane (DIM). He was awarded a patent for his microencapsulated formulation of absorbable DIM and has numerous issued and pending patents for novel uses of DIM in preventive medicine. As a physician-investigator, he has sponsored clinical trials for HPV, cervical dysplasia, uterine and prostate health. These clinical trials are underway in collaboration with Cornell University, the NYU School of Medicine, Cancer Research UK, Wayne State University, and New York Medical College. The National Cancer Institute, under a clinical trials agreement with Dr. Zeligs, has sponsored additional clinical trials investigating microencapsulated DIM as a natural preventive and therapeutic candidate for cancer.

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Prostate Health Promotion with Diindolylmethane (DIM)

Diindolylmethane (DIM) is the dominant dietary indole resulting from the digestion of cruciferous vegetables. Large epidemiologic studies have indicated that a greater intake of cruciferous vegetables is associated with reduced risk of a number of human cancers. A study of protective effects of specific vegetables for prostate health showed a reduced risk of prostate cancer with cruciferous vegetables that was not seen with other classes of dietary vegetables (1). One nutritionally related mechanism known to support prostate health is maintaining a favorable estrogen and testosterone metabolism. Epidemiologic studies of male populations have shown that healthy estrogen metabolism is a contributor to prostate health. A population study in Boston showed that increased 2-hydroxy metabolism of estrogen was associated with a reduced risk of prostate cancer (2). A study from South Carolina showed that men with greater 2-hydroxy estrogen production had lower Prostate Specific Antigen (PSA) levels compared to men with less favorable estrogen metabolism (3). DIM is known from laboratory studies to promote 2-hydroxy estrogen production. When tested in clinical trials, a microencapsulated formulation of DIM (BioResponse DIM®) was shown to benefit metabolism and

promoted a clear increase in estrogen 2-hydroxylation in both women (4) and men (5). When tested directly in human prostate tissue culture, the 2-hydroxy metabolites of estrogen promoted by DIM were shown to inhibit PSA production. Earlier research has established that men with under-active estrogen metabolism and higher circulating levels of active estrogen have larger prostate gland volumes (6). Aging and the development of prostate gland hypertrophy (enlargement) have been associated with the accumulation of un-metabolized estrogen in prostate gland tissue. Microencapsulated, absorbable DIM supplementation provides one way to stimulate healthy estrogen metabolism that favors prostate health.

A second nutritionally relevant mechanism by which DIM may act to promote prostate health is to reduce the activity of the Androgen Receptor (AR) in prostate gland cells. AR proteins concentrate Testosterone and related hormones from the circulation within prostate gland tissue. Overactive AR activity contributes to both prostate cell enlargement, cell multiplication, and to increased PSA production. DIM was shown to specifically reduce levels and activity of the AR in studies in prostate cancer cells (7).

A third mechanism by which DIM may benefit prostate health is by reducing the activity and levels of the related Estrogen Receptor (ER), also present in prostate tissue, which has recently been shown to interact with AR activity and also contribute to the development of prostate cancer (8).

More advanced laboratory studies have tested the use of microencapsulated DIM by feeding absorbable DIM to mice in which transplanted human prostate cancer tumors were growing. These studies showed that the prostate cancers ceased growing during ten weeks of receiving absorbable DIM orally (9). Results of these and other studies have led to the initiation of two clinical studies of absorbable, microencapsulated DIM in men with prostate cancer. One of these studies taking place at Wayne State University, Karmanos Cancer Center, involves giving absorbable DIM to men who have had a recurrence of treated prostate cancer associated with a rising PSA. The second study, based at the University of Wisconsin, involves men with prostate cancer who plan to have surgical removal of their prostate glands. These men are being given absorbable DIM for about 1 month prior to surgery to investigate effects of DIM on their abnormal prostate tissue.

These and other clinical studies using the established microencapsulated DIM formulation are ongoing in 2008. The clinical studies are ranked as formal Phase I and Phase II trials and are supported by the National Cancer Institute (NCI). This collaboration between NCI and BioResponse, LLC, will contribute greatly to further understanding of how DIM contributes to prostate health. Preliminary testing of absorbable, microencapsulated DIM in a pilot study has shown that 3 month use at 2 capsules (300 mg/day) has a lowering effect on PSA levels in men with an elevated PSA at the start of supplement use.

References:

1. Kirsh VA, Peters U, Mayne ST, Subar AF, Chatterjee N, Johnson CC, Hayes RB; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Prospective study of fruit and vegetable intake and risk of prostate cancer. *J Natl Cancer Inst.* 2007 Aug 1;99(15):1200-9.
2. Muti P, Westerlind K, Wu T, Grimaldi T, De Berry J 3rd, Schünemann H, Freudenheim JL, Hill H, Carruba G, Bradlow L. Urinary estrogen metabolites and prostate cancer: a case-control study in the United States. *Cancer Causes Control.* 2002 Dec;13(10):947-55.
3. Teas J, Cunningham JE, Fowke JH, Nitcheva D, Kanwat CP, Boulware RJ, Sepkovic DW, Hurley TG, Hebert JR. Urinary estrogen metabolites, prostate specific antigen, and body mass index among African-American men in South Carolina. *Cancer Detect Prev.* 2005;29(6):494-500.

References (continued):

4. Dalessandri, KM, Firestone GL, Fitch MD, Bradlow HL, Bjeldanes LF. Pilot study: effect of 3,3'-diindolylmethane supplements on urinary hormone metabolites in postmenopausal women with a history of early-stage breast cancer. *Nutr Cancer*. 2004;50(2):161-7.
 5. Zeligs, M.A., Sepkovic, D.W., Manrique, C., Macsalka, M., Williams, D.E., and Bradlow, H.L. Absorption-enhanced 3,3'-Diindolylmethane: Human Use in HPV-related, Benign and Pre-cancerous Conditions. *Proc. Am. Assoc. Cancer Res*. 2002 Apr; 43, 3198 (Abstract).
 6. Partin AW, Oesterling JE, Epstein JI, Horton R, Walsh PC. Influence of age and endocrine factors on the volume of benign prostatic hyperplasia. *J Urol*. 1991 Feb;145(2):405-9.
 7. Le HT, Schaldach CM, Firestone GL, Bjeldanes LF. Plant-derived 3,3'-Diindolylmethane is a strong androgen antagonist in human prostate cancer cells. *J Biol Chem*. 2003 Jun 6;278(23):21136-45.
 8. Ricke WA, McPherson SJ, Bianco JJ, Cunha GR, Wang Y, Risbridger GP. Prostatic hormonal carcinogenesis is mediated by in situ estrogen production and estrogen receptor alpha signaling. *FASEB J*. 2007 Nov 30.
 9. Bhuiyan MM, Li Y, Banerjee S, Ahmed F, Wang Z, Ali S, Sarkar FH. Down-regulation of androgen receptor by 3,3'-diindolylmethane contributes to inhibition of cell proliferation and induction of apoptosis in both hormone-sensitive LNCaP and insensitive C4-2B prostate cancer cells. *Cancer Res*. 2006 Oct 15;66(20):10064-72
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