Changes in Levels of Urinary Estrogen Metabolites After Oral Indole-3-Carbinol Treatment in Humans

Jon J. Michnovicz, Herman Adlercreutz, H. Leon Bradlow*

Background: The oxidative metabolism of estrogens in humans is mediated primarily by cytochrome P450, many iso-enzymes of which are inducible by dietary and pharmacologic agents. One major pathway, 2-hydroxylation, is induced by dietary indole-3-carbinol (I3C), which is present in cruciferous vegetables (e.g., cabbage and broccoli).

Purpose: Because the pool of available estrogen substrates for all pathways is limited, we hypothesized that increased 2-hydroxylation of estrogens would lead to decreased activity in competing metabolic pathways. Methods: Urine samples were collected from subjects before and after oral ingestion of I3C (6-7 mg/kg per day). In the first study, seven men received I3C for 1 week; in the second study, 10 women received I3C for 2 months. A profile of 13 estrogens was measured in each sample by gas chromatography–mass spectrometry. Results: In both men and women, I3C significantly increased the urinary excretion of C-2 estrogens. The urinary concentrations of nearly all other estrogen metabolites, including levels of estradiol, estrone, estriol, and 16α-hydroxyestrone, were lower after I3C treatment. Conclusions: These findings support the hypothesis that I3C-induced estrogen 2-hydroxylation results in decreased concentrations of several metabolites known to activate the estrogen receptor. This effect may lower estrogenic stimulation in women. Implications: I3C may have chemopreventive activity against breast cancer in humans, although the long-term effects of higher catechol estrogen levels in women require further investigation. [J Natl Cancer Inst 1997;89:718-23]

A battery of inducible and constitutive enzymes, collectively referred to as cytochrome P450, exists in humans and other animals to metabolize or detoxify endogenous and exogenous substances. Several hundred isoenzymes of cytochrome P450 have been identified, some of which are involved in the formation of various hydroxylated estrogen metabolites. The major metabolites in humans are either catechol estrogens (defined as a 2,3-dihydroxyestrogen [e.g., 2-hydroxyestrone] or a 3,4-dihydroxyestrogen [e.g., 4-hydroxyestradiol]) or 16α-hydroxyestrogens (e.g., 16α-hydroxyestriol and estradiol). Estradiol and estrone serve as immediate precursors in the formation of these metabolites and provide a limited substrate pool (I). We have hypothesized that selective enhancement of one cytochrome P450 enzyme pathway is likely to have the secondary effect of decreasing the production and excretion of other competing metabolites.

To examine this relationship more closely, we measured the levels of several urinary estrogens by using gas chromatography–mass spectrometry, a highly selective and sensitive technique capable of distinguishing between closely related steroid metabolites. Estrogen levels were measured before and after oral consumption of the dietary cytochrome P450 inducer indole-3-carbinol (I3C). I3C and its in vivo metabolites have been shown to be effective inducers of the P450IA family of enzymes (2-4). Ingestion of this agent leads to a substantial increase in estradiol 2-hydroxylation in humans measured by an in vivo radiometric method (5).

Subjects and Methods

Research Subjects

Two groups of research subjects were studied. The first group comprised seven men; the second group comprised 10 women. The men were initially enrolled as part of an I3C pilot study, whereas the women were enrolled in a larger study of the long-term effects of I3C. The clinical characteristics of the two groups are summarized in Table 1. All subjects were healthy, and the results of physical examination and routine blood-screening tests were normal. No subject received exogenous estrogen therapy during the study. These experiments were approved by the institutional review boards of the Rockefeller University Hospital and the Strang Cancer Prevention Center, and written informed consent was obtained from the subjects prior to participation. During these studies, dietary records were not obtained, and no attempt was made to measure or control the I3C content of foods consumed by the participants.

Experimental Design

In the first study, a group of men received I3C orally at a daily dose of 500 mg (6-7 mg/kg per day) for a period of 7 days. Two overnight urine samples were collected, before ingestion of I3C and after the last daily dose of I3C. Urine samples were mixed with 0.1% sodium ascorbate as an antioxidant and frozen at -20°C prior to shipment. All urine samples were shipped frozen to the analytic laboratory in Finland (Dr. Adlercreutz) and were analyzed in a blinded fashion.

In the second study, urine samples from 10 women were collected, stored, and shipped in a fashion similar to that used for the men. Each woman received I3C orally at a daily dose of 400 mg (6-7 mg/kg per day). Urine samples were collected from the women between day 3 and day 8 of the follicular phase of their menstrual cycle, before I3C ingestion and after 2 months of I3C ingestion.

The indole carbinol used in these studies was provided by Dr. William Hennen (Pharmatech/Enrich, Orem, UT). In both studies, I3C was found to be more than 98% pure by either thin-layer chromatography or gas chromatography–mass spectrometry.

Analysis of Urinary Estrogen Metabolites

The analytic method for the determination of the urinary estrogen profile was described previously (6); it was based on ion-exchange chromatographic purification procedures and capillary gas chromatography–mass spectrometry in the selected ion-monitoring mode. A considerable improvement in the accuracy and precision of the method included the addition of deuterated (d₆)-ethoestriol derivatives (7,8) of all ketonic estrogens as internal standards immediately before hydrolysis of the urine extract. In this way, stable-isotope dilution mass spectrometry could be used for all ketonic estrogens, as well as for estradiol. For the other fractions, radioactive unconjugated or conjugated internal standards were used and corrections were made for losses during the procedure. For these metabolites, deuterium-labeled (d₆)-estrone (methylsilyl) ether derivatives of authentic standards were added just before gas chromatography–mass spectrometry to correct for losses during this step. The final determination was carried out by use of a Hewlett-Packard 5895B quadrupole instrument equipped with a 0.2 mm × 12.4 m bonded phase BP-1 (equivalent to silicone SE-30) capillary vitreous silica column directly connected to the ion source. The coefficients of variation for all fractions and details regarding the reliability of the procedure

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were published (6,8). Coefficients of variation in midfollicular-phase urine samples ranged from 3.8% to 6.9% for the 10 major estrogens and were 15% for the minor metabolites, including 15α-hydroxyestrone, 17-epiestradiol, and 16β-hydroxyestrone.

Within-subject variability of urinary estrogen metabolites during the period studied for these subjects (men, 1 week; women, 2 months) is below 10%, as already published (4). Variability is further reduced in premenopausal women by obtaining samples at the same time of the menstrual cycle (9), which we did in this study (follicular phase).

Because urine collections in these subjects were not timed (e.g., 24 hours), analytic results from each sample are standardized against urinary creatinine concentrations. Thus, units are reported for all metabolites as nanomoles per millimoles of creatinine.

### Statistical Analysis

Results were analyzed statistically by use of SPSS for Windows (software version 6.1). Student’s t-test (two-tailed) was used to assess significance of changes in the mean percent increase (or decrease) for a given metabolite from paired samples after I3C treatment. This change was calculated as [(post-I3C − pre-I3C)/(pre-I3C)]/100 and was averaged for the seven men and the 10 women for the mean percent change.

### Results

Urinary estrogen data from seven men receiving I3C for 1 week are shown in Table 2. Following I3C, the urinary concentration of 2-hydroxyestrone increased by an average of 91% (mean percent change over pre-I3C values), whereas that of 2-hydroxyestradiol more than doubled. Only the changes in 2-hydroxyestrone reached statistical significance, however, partly a result of the higher standard deviation for 2-hydroxyestradiol measurements in this small group of men. There was a trend toward higher 4-hydroxyestrone excretion after I3C treatment, which was not significant. In contrast, nearly all other measured estrogens, including the 16-oxygenated metabolites, were decreased in concentration following I3C treatment. Many of these latter changes were statistically significant. There was a 45% decrease in the urinary 16α-hydroxyestrone levels, with a narrow 95% confidence interval (61% to 33% decrease).

Results from urinary estrogen profiles in 10 women receiving oral I3C for 2 months are presented in Table 3. As with the men, I3C increased the urinary excretion of catechol estrogens in the women. Significant changes were observed for 2-hydroxyestrone and 2-hydroxyestradiol, with smaller (nonsignificant) increases in 4-hydroxyestrone and 2-methoxyestrone. The increased excretion of catechol estrogens in women was accompanied by lower concentrations of most other urinary estrogens measured. These differ-

### Table 1. Summary of clinical characteristics of all subjects*

<table>
<thead>
<tr>
<th>Study group</th>
<th>Age, y</th>
<th>Height, m</th>
<th>Weight, kg</th>
<th>Body mass index, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>28.2 ± 3.8</td>
<td>1.79 ± 0.11</td>
<td>75.1 ± 4.2</td>
<td>23.3 ± 1.1</td>
</tr>
<tr>
<td>Women</td>
<td>32.3 ± 4.2</td>
<td>1.62 ± 0.24</td>
<td>59.3 ± 3.1</td>
<td>22.4 ± 0.8</td>
</tr>
</tbody>
</table>

*Values in columns = means ± standard deviation.

### Table 2. Summary of urinary estrogens in men before and after indole-3-carbinol (I3C) treatment

<table>
<thead>
<tr>
<th>Metabolite*</th>
<th>Before I3C, mean ± standard deviation</th>
<th>After I3C, mean ± standard deviation</th>
<th>Change over pre-I3C values† (95% confidence interval)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>2OHE₁</td>
<td>0.958 ± 0.370</td>
<td>1.698 ± 0.614</td>
<td>0.740 (−0.003 to 1.493)</td>
<td>.011</td>
</tr>
<tr>
<td>2OHE₂</td>
<td>0.650 ± 0.707</td>
<td>1.327 ± 1.331</td>
<td>0.677 (−0.341 to 1.695)</td>
<td>.30</td>
</tr>
<tr>
<td>4OHE₁</td>
<td>0.156 ± 0.079</td>
<td>0.211 ± 0.147</td>
<td>0.556 (−0.041 to 0.152)</td>
<td>.25</td>
</tr>
<tr>
<td>2METE₁</td>
<td>0.340 ± 0.141</td>
<td>0.301 ± 0.112</td>
<td>−0.040 (−0.202 to 0.122)</td>
<td>.44</td>
</tr>
<tr>
<td>17-EPI</td>
<td>0.260 ± 0.265</td>
<td>0.169 ± 0.114</td>
<td>−0.091 (−0.252 to 0.070)</td>
<td>.53</td>
</tr>
<tr>
<td>16-EPI</td>
<td>0.305 ± 0.237</td>
<td>0.244 ± 0.129</td>
<td>−0.061 (−0.269 to 0.147)</td>
<td>.89</td>
</tr>
<tr>
<td>E₂</td>
<td>0.545 ± 0.213</td>
<td>0.362 ± 0.087</td>
<td>−0.183 (−0.480 to 0.114)</td>
<td>.016</td>
</tr>
<tr>
<td>E₁</td>
<td>1.507 ± 0.518</td>
<td>1.083 ± 0.347</td>
<td>−0.424 (−1.120 to 0.273)</td>
<td>.008</td>
</tr>
<tr>
<td>E₃</td>
<td>1.201 ± 0.470</td>
<td>0.654 ± 0.222</td>
<td>−0.547 (−1.201 to 0.097)</td>
<td>.14</td>
</tr>
<tr>
<td>16αOHE₁</td>
<td>0.360 ± 0.172</td>
<td>0.183 ± 0.076</td>
<td>−0.177 (−0.464 to 0.110)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>15βOHE₁</td>
<td>0.026 ± 0.008</td>
<td>0.020 ± 0.008</td>
<td>−0.006 (−0.033 to 0.019)</td>
<td>.84</td>
</tr>
<tr>
<td>16βOHE₁</td>
<td>0.183 ± 0.128</td>
<td>0.096 ± 0.059</td>
<td>−0.087 (−0.350 to 0.177)</td>
<td>.55</td>
</tr>
<tr>
<td>16OXO</td>
<td>0.229 ± 0.135</td>
<td>0.100 ± 0.024</td>
<td>−0.129 (−0.360 to 0.092)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sum§</td>
<td>6.72 ± 2.89</td>
<td>6.45 ± 2.24</td>
<td>−0.270 (−1.360 to 0.820)</td>
<td>.34</td>
</tr>
</tbody>
</table>

*All metabolites expressed as nanomoles/millimoles creatinine. 2OHE₁ = 2-hydroxyestrone; 2OHE₂ = 2-hydroxyestradiol; 4OHE₁ = 4-hydroxyestrone; 2METE₁ = 2-methoxyestrone; 17-EPI = 17-epiestradiol; 16-EPI = 16-epiestradiol; E₂ = estradiol; E₁ = estrone; E₃ = estriol; 16αOHE₁ = 16α-hydroxyestrone; 15βOHE₁ = 15β-hydroxyestrone; 16βOHE₁ = 16β-hydroxyestrone; 16OXO = 16-oxoestradiol.

†Mean percent change/100.

‡P values for mean percent change (decrease) over pre-I3C values.

§Total measured urinary estrogens.
ences achieved statistical significance for the excretion of estrone, estradiol, estriol, and the other 16-oxygenated metabolites shown in Table 3.

In both men and women, average urinary concentrations of estradiol and estriol were lower after I3C treatment. However, despite the various changes in several metabolites, total measured urinary estrogens for both groups of subjects (indicated by “Sum” in Tables 2 and 3) did not appear to be substantially altered by I3C.

We were unable to find any significant correlations for individuals between the percent change in catechol estrogen excretion and decreased excretion of the various metabolites shown in Tables 2 and 3, which is most likely due to the small sample sizes.

Fig. 1 illustrates individual variability in changes of selected estrogen metabolites before and after I3C exposure for the women. Although average post-I3C values of 2-hydroxyestrone and 2hydroxyestradiol were significantly higher and post-I3C values of 16α-hydroxyestrone and estriol were significantly lower, an opposite trend was evident for some individuals, whereas for others little change in some of the metabolites occurred after I3C treatment. Similar variability was observed among the smaller group of male subjects (data not shown).

### Discussion

The present gas chromatography–mass spectrometry study of urinary estrogens confirms earlier radiometric data showing that the enzymes catalyzing estradiol 2-hydroxylation are strongly induced in men and women by the dietary substance I3C (5,10). This induction of cytochrome P450 metabolism of estrogens occurs at modest doses of I3C (400-500 mg, or approximately 6-7 mg/kg per day). Consumption of 25-100 mg of dietary I3C per day in various populations has been recommended (13,14). We hypothesized that such an effect may help lower estrogenic stimulation and thereby reduce breast cancer risk in women.

A previous study (13) showed that C-16α estrogens, such as estradiol and 16α-hydroxyestrone, retained estrogen agonist activity. In addition, 16α-hydroxyestrone formed covalent bonds with such proteins as the estrogen receptor (14) and generated DNA adducts in cell culture (15), properties possibly linked to mammary cell carcinogenesis. In contrast, C-2 metabolites have been shown to be relatively weak estrogens or antiestrogens (16,17), although in other cell culture studies Knuppen and colleagues (18) found that highly purified catechol estrogens can function as agonists of estrogen-depen-

### Table 3. Summary of urinary estrogens in women before and after indole-3-carbinol (I3C) treatment

<table>
<thead>
<tr>
<th>Metabolite*</th>
<th>Before I3C, mean ± standard deviation</th>
<th>After I3C, mean ± standard deviation</th>
<th>Change over pre-I3C values† (95% confidence interval)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>2OHE1</td>
<td>3.332 ± 1.971</td>
<td>6.620 ± 3.632</td>
<td>1.77 (0.04 to 3.50)</td>
<td>.046</td>
</tr>
<tr>
<td>2OHE2</td>
<td>0.822 ± 0.459</td>
<td>1.260 ± 0.491</td>
<td>0.48 (0.08 to 1.60)</td>
<td>.033</td>
</tr>
<tr>
<td>4OHE1</td>
<td>0.339 ± 0.226</td>
<td>0.430 ± 0.260</td>
<td>0.74 (−0.35 to 1.84)</td>
<td>.16</td>
</tr>
<tr>
<td>2METE1</td>
<td>0.569 ± 0.208</td>
<td>0.611 ± 0.283</td>
<td>0.09 (−0.24 to 0.43)</td>
<td>.54</td>
</tr>
<tr>
<td>17-EPI</td>
<td>0.264 ± 0.214</td>
<td>0.195 ± 0.160</td>
<td>−0.11 (−0.44 to 0.21)</td>
<td>.44</td>
</tr>
<tr>
<td>16-EPI</td>
<td>0.570 ± 0.243</td>
<td>0.397 ± 0.137</td>
<td>0.0 (−0.75 to 0.75)</td>
<td>.99</td>
</tr>
<tr>
<td>E2</td>
<td>0.757 ± 0.636</td>
<td>0.462 ± 0.211</td>
<td>−0.26 (−0.46 to −0.06)</td>
<td>.018</td>
</tr>
<tr>
<td>E1</td>
<td>2.092 ± 0.930</td>
<td>1.460 ± 0.524</td>
<td>−0.22 (−0.45 to 0.0)</td>
<td>.05</td>
</tr>
<tr>
<td>E3†</td>
<td>1.051 ± 0.440</td>
<td>0.768 ± 0.375</td>
<td>−0.24 (−0.46 to −0.01)</td>
<td>.044</td>
</tr>
<tr>
<td>16αOHE1</td>
<td>0.569 ± 0.262</td>
<td>0.421 ± 0.356</td>
<td>−0.29 (−0.47 to −0.10)</td>
<td>.007</td>
</tr>
<tr>
<td>15αOHE1</td>
<td>0.035 ± 0.031</td>
<td>0.047 ± 0.040</td>
<td>0.33 (−0.45 to 1.11)</td>
<td>.35</td>
</tr>
<tr>
<td>16βOHE1</td>
<td>0.378 ± 0.153</td>
<td>0.252 ± 0.107</td>
<td>−0.23 (−0.50 to 0.08)</td>
<td>.07</td>
</tr>
<tr>
<td>16O XO</td>
<td>0.367 ± 0.122</td>
<td>0.226 ± 0.095</td>
<td>−0.33 (−0.56 to −0.11)</td>
<td>.009</td>
</tr>
<tr>
<td>Sum§</td>
<td>11.16 ± 3.27</td>
<td>13.14 ± 5.21</td>
<td>0.23 (−0.52 to 0.79)</td>
<td>.40</td>
</tr>
</tbody>
</table>

*All metabolites expressed as nanomoles/millimoles creatinine. 2OHE1 = 2-hydroxyestrone; 2OHE2 = 2-hydroxyestradiol; 4OHE1 = 4-hydroxyestrone; 2METE1 = 2-methoxyestrone; 17-EPI = 17-epiestriol; 16-EPI = 16-epiestriol; E2 = estradiol; E1 = estrone; E3 = estriol; 16αOHE1 = 16α-hydroxyestrone; 15αOHE1 = 15α-hydroxyestrone; 16βOHE1 = 16β-hydroxyestrone; 16O XO = 16-oxoestriol.

†Mean percent change/100.

‡P values for mean percent increase (decrease) over pre-I3C values.

§Total measured urinary estrogens.
dent gene expression in MCF-7 human breast cancer cells. Numerous examples exist for compounds that act as estrogen agonists biochemically, yet block breast cell proliferation in vivo (19). Finally, catechol estrogens are efficiently methylated by the ubiquitous enzyme catechol O-methyltransferase, and though demethylation of 2-methoxyestrogens has been reported (20), this latter metabolic step would probably further reduce the overall estrogenicity of catechol estrogens (27).

Taken together, these and other experimental data (22) support the hypothesis that 2-hydroxyestrone and 16α-hydroxyestrone have inverse effects on risk. For example, conditions that have been shown to specifically elevate 2-hydroxylation, including leanness (23), aerobic exercise (24), and high intake of cruciferous vegetables (5), are generally breast protective; yet, other studies have shed doubt on whether increased estrogen 16α-hydroxylation in women is a risk factor for breast cancer. Among Oriental women at low risk, for example, Adlercreutz et al. (25) found that the ratio of urinary 16α-hydroxyestrone to 2-hydroxyestrone was higher than that in non-Oriental women. However, all urinary estrogens were lower among the Oriental subjects, possibly diminishing the carcinogenic potential of any individual metabolite. Other studies by these investigators (25,26) have shown greater overall estrogen production among western populations consuming a high-fat/low-vegetable diet. Urinary estrogens may be lower among Oriental women because of increased fecal estrogen excretion and lower overall estrogen production (27). Adlercreutz has therefore proposed that the greater danger for women in western populations may not be due to higher 16α-hydroxyestrogens per se but rather to higher overall levels of all active estrogens.

In our study, estrogen profiles were significantly altered by the dietary agent I3C. A shift toward increased catechol estrogen excretion occurred, leading to decreased activity in competing pathways. A metabolic shift similar to that found with I3C was also observed by Adlercreutz et al. (26) in vegetarian women on a macrobiotic diet. In that study, concentrations of urinary catechol estrogens were higher and those of 16α-hydroxyestrogens were lower, although levels of other estrogen metabolites were not affected to the degree seen with I3C. The fact that I3C lowered most other measured estrogens, including estradiol and estrone, supports the conclusion that overall estrogenic exposure was decreased. Some studies have found endogenous estrogen levels to be related to breast cancer risk, as was demonstrated by Toniolo and co-workers (28) in a large prospective study of postmenopausal women. In light of the inverse association between vegetable consumption and cancer risk (29), including risk of breast cancer (30), it is possible that the protective effect of a diet high in vegetables for the breast is due in part to intake of dietary indoles.

A potential weakness in our study design is the absence of placebo control subjects for gas chromatography–mass spectrometry measurements. However, we have reported placebo testing of I3C (31), and an extensive study (22) has documented its ability to induce C-2 estrogen metabolism in animals and humans. In our study, we evaluated the effects of I3C on the entire profile of estrogen metabolites under conditions of greatly enhanced C-2 estrogen formation. The overall validity of our results was confirmed by the demonstration of increased excretion of 2-hydroxyestrone and 2-hydroxyestradiol in both groups of subjects and the consistent decreases in other metabolites for both men and women. Nevertheless, despite the difficulties inherent in the methodology reported here, a placebo-controlled gas chromatography–mass spectrometry study of I3C in a larger population would be useful in confirming our hypothesis.
The chemopreventive potential of I3C has been well documented in animal models (32), yet few clinical trials have been performed with this agent. Using a battery of screening assays designed to predict cancer-preventing activity, researchers at the National Cancer Institute (33) compared 90 natural and synthetic compounds. I3C was among the few agents in that extensive study to display protective activity in each of the eight assays used.

Enhanced C-2 estrogen metabolism by dietary indoles in humans results from stimulation of cytochrome P450, including P450IA (34,35). I3C is converted in vivo into several other indole metabolites, one of which (indolo[3,2-b]carbazole or ICZ) displays relatively strong binding affinity for the aryl hydrocarbon (AH or dioxin) receptor (2). Activation of the AH receptor by I3C or its metabolites results in increased production of the CYP1 gene products, primarily P450IA2, capable of catalyzing estrogen 2-hydroxylation (36,37). Important new studies by Bjeldanes and colleagues (38) have demonstrated that ICZ has a complex effect on cytochrome P450 systems. In addition to its enzyme-inducing activity, ICZ is capable of selectively inhibiting P450IA1. This latter fact may reduce the ability of I3C to activate procarcinogens in vivo, helping to ensure its chemopreventive safety in humans.

Further confirmation of the breast cancer prevention potential of I3C comes from studies of CYP1A1 polymorphisms in women. Taioli et al. (39,40) reported that African-American women with the homozygous Msp I variant of CYP1A1 have a nearly 10-fold higher risk of breast cancer than African-American women with the wild-type CYP1A1 variant, and women in the former group appear to be inefficient inducers of 2-hydroxylation following ingestion of 400 mg of I3C. A similar Msp I polymorphism linked to breast cancer risk was not found among Caucasian women. It is interesting that, compared with Caucasian women, African-American women also appear to have higher endogenous levels of serum estrogens (41) as well as lower levels of 2-hydroxyestrone (42).

I3C displays other important properties that may be beneficial in cancer chemoprevention. It is a relatively effective antioxidant (43), and it can induce phase II drug-metabolizing enzymes, similar to the crucifer-derived sulforaphane (44). I3C acts as an antiestrogen in cell culture (34) and may decrease tumor growth by non-hormonal means as well.

In summary, I3C was found by gas chromatography–mass spectrometry analysis to enhance the production of catechol estrogens in humans, which confirms our earlier radiometric studies. Greater 2-hydroxylation was accompanied by decreased excretion of other active estrogen metabolites capable of tumor promotion and/or initiation, including estradiol, estrone, 16α-hydroxyestrone, and estriol. I3C also increased 2-hydroxylation in postmenopausal women (Michnovicz JJ: unpublished data), indicating that the effect of this phytochemical is not age dependent. Although the long-term consequences of chronically stimulated 2-hydroxylation are not fully understood, these findings indicate a potential role for I3C in the chemoprevention of estrogen-dependent tumors of the breast.

References

(23) Schneider J, Bradlow HL, Strain G, Levin J,


Notes

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