Can Indole-3-Carbinol–Induced Changes in Cervical Intraepithelial Neoplasia Be Extrapolated to Other Food Components?1–3

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Expanded Abstract

Indole-3-carbinol (I3C)4 and its congener diindolylmethane (DIM) are derived from cruciferous vegetables such as broccoli and cabbage. In addition to being available in food, both I3C and DIM are available as supplements. Glucosinolates from cruciferous vegetables break down into I3C, and I3C is further converted into a range of polyaromatic derivatives, primarily DIM, which may be more effective. These and many other promising food components have anticancer properties that should do much to halt or prevent certain cancers. In animal studies, I3C/DIM not only prevents breast, endometrial, and cervical cancers (1–3) but helps prevent or ameliorate certain diseases such as recurrent respiratory papillomatosis (4) and systemic lupus erythematosus (5).

A case exists for the benefits I3C/DIM for the treatment of cervical intraepithelial neoplasia (CIN) and thus potential inhibition of cervical cancer. Development of cervical cancer can be monitored because of the ease of monitoring cervical abnormalities with the Papanicolaou test (pap smear). Additional biomarkers can be included using colposcopy and tests for the presence and type of human papillomaviruses (HPVs). Abnormalities in the cervix range from a mild dyskaryosis to progression of these early abnormalities can progress to cancer. Infection with one of several types of HPVs is generally accepted to be a necessary step in the etiology of cervical dysplasia (6). The K14-HPV16 transgenic mouse expresses HPV oncogenes and develops cervical cancer when given estrogen chronically. The progression of the severity of cervical abnormalities to cancer in this mouse resembles that of humans (7). I3C prevents the development of cervical cancer in this transgenic mouse (3). Additionally, I3C can reduce cervical dysplasia caused by estradiol in the normal mouse (3). A small randomized controlled clinical trial in women with biopsy-confirmed high-grade cervical intraepithelial neoplasia (CIN2 and CIN3) indicated efficacy for I3C for regression of CIN (8). In addition, an investigation into the effects of DIM in a cervical randomized intervention study for cervical cytological abnormalities involving 3000 women is under way at the University of Wales College of Medicine in the United Kingdom.

Core findings and discussion

Based on some apparent mechanisms by which I3C causes regression of CIN and prevents cervical cancer, other food components may act similarly and enhance the effect of I3C as a (potential) treatment and prevention strategy. I3C alters expression of >100 genes (9) inducing many phase I and II enzymes. It also modulates estrogen metabolism (10), induces G1 cell cycle arrest (11), induces apoptosis (12), alters estrogen signaling (13), decreases activity of NF-κB (14), and induces the endoplasmic reticulum response (15). Important risk factors for CIN (and by extension cervical cancer) include elevated estrogen levels (7), HPV infection (6), and increased cyclooxygenase-2 (COX-2) activity in the target tissues (16). Along with I3C/DIM, the (n-3) fatty acids and genistein from soy should target these same factors and decrease, or possibly reverse, CIN because of their known activities in modulating the cell environment (Fig. 1). The combination of these food components could be additive and possibly synergistic.

As noted earlier, estrogen and HPV are cofactors for CIN and cervical cancer. This is supported by population data and clinical observations; HPVs infect the genital track of men and women equally, but little pathology occurs in men (17). The HPV mouse model provided clear evidence of estrogen-related pathological changes serving as a cofactor for cervical cancer (7). In contrast to activities of estrogen, which support the transition to CIN and cervical cancer, I3C reduces severe dysplasia (3), decreases proliferation (3), and increases apoptosis (12) in the cervical epithelium. Moreover, I3C results in the formation of less

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4 Abbreviations used: CIN, cervical intraepithelial neoplasia; COX-2, cyclooxygenase-2; DIM, diindolylmethane; HPV, human papillomavirus; I3C, indole-3-carbinol; pap, Papanicolaou.

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I3C/DIM) all decrease NF-κB downstream of COX-2. The (n-3) fatty acids and genistein, like increased gene expression of inflammatory cytokines and are involved in NF-κB activation (20). Moreover, the (n-3) fatty acids, should enhance the effectiveness of I3C/DIM. Moreover, combinations are likely to be more advantageous and be effective at lower concentrations. Trials with I3C/DIM indicate that differences in responses occur (4,8), the basis of which must be investigated to be able to predict which individuals would benefit from a particular food component or combination.

Many food components alter gene expression and modify the microenvironment of a cell, making it less susceptible to transformation. More knowledge of nutragenomics and identification of targets that decrease the risk of cancers are necessary to use nutrients to their best advantage to treat precancerous conditions and prevent cancer. Importantly for the implementation of translational studies, the appropriate animal models and good biomarkers are needed to be able to validate and effectively use food components.

Conclusions
Studies with I3C or DIM indicate a benefit for their use in the treatment of CIN and prevention of cervical cancer. These food components from cruciferous vegetables are available as supplements. Other food components, namely genistein from soy and the (n-3) fatty acids, should enhance the effectiveness of I3C/DIM because they can also target risk factors for the development of CIN. CIN provides a prototype target model for studies into the effectiveness of food components as a prevention and treatment strategy because there is an animal model that mimics the human condition. In addition, good biomarkers (pap smear and HPV detection) are available in humans.
Literature Cited


