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

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Expanded Abstract

Indole-3-carbinol (I3C)\textsuperscript{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 cancer; a percentage 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 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 advanced disease. Thus, cervical cancers (1–3) but helps prevent or ameliorate certain diseases such as recurrent respiratory papillomatosis (4) and systemic lupus erythematosus (5).

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 \textgreater 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-\textkappa B (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 advanced disease.
Figure 1  Target sites for food components in the development of CIN and cervical cancer.

Estrogenic metabolites systemically (unpublished data). Like I3C, other food components could ameliorate the effects of estrogen. Both I3C and genistein from soy compete for the estrogen receptor. Both nutrients are weakly estrogenic in the absence of estradiol but reduce estrogen‐dependent gene expression in the presence of estradiol, an effect that is synergistic when they are used together (13). I3C induces 2‐hydroxylation of estrone, leading to metabolites that are not estrogenic and are antiproliferative (18). Both genistein and the (n‐3) fatty acids inhibit aromatase activity, resulting in reduced estrogen synthesis from androgens (19,20), and genistein may inhibit the conversion of estrone to estradiol (21). Thus, the 3 food components should work together to ameliorate adverse effects of estrogen. This remains to be demonstrated directly.

The cofactors, HPVs and estrogen, increase proinflammatory processes in CIN as evidenced by presence of inflammatory cytokines (22) and the presence of cyclooxygenase 2 (COX‐2) (upstream to many inflammatory cytokines) in cervical dysplasia and cervical cancers (16). Moreover, the COX‐2 inhibitor celecoxib decreases the incidence of cervical cancer in the HPV mouse model (unpublished data). Because estradiol is known to increase COX‐2 (23), the 3 food components being considered should decrease COX‐2 by decreasing estrogen. More directly, I3C/DIM also decreases NF‐κB in a number of cell lines (14,24) including cervical cells (unpublished data). I3C decreases both the level of NF‐κB and its transport to the nucleus, where it is active. The NF‐κB family of transcription factors are involved in increased gene expression of inflammatory cytokines and are downstream of COX‐2. The (n‐3) fatty acids and genistein, (like I3C/DIM) all decrease NF‐κB (25,26). Additionally, the (n‐3) fatty acids suppress biosynthesis of (n‐6)‐fatty acid‐derived eicosanoids, which elevate levels of cyclooxygenases and are involved in NF‐κB activation (20). Moreover, the (n‐3)‐fatty acid‐derived eicosanoids are directly antiinflammatory in their own right. Both separately and together, these food components should diminish inflammatory processes known to contribute to the development of many cancers.

Increased proliferation and decreased apoptosis are hallmarks for the development of cancer. I3C/DIM causes growth arrest and increases apoptosis of cervical cells including CIN in vivo (3,12). The (n‐3) fatty acid decosahexaenoic acid has been shown to decrease proliferation of transformed cervical cells (27). The isoflavone genistein decreases breast and cervical cell proliferation but can increase proliferation in the absence of estradiol in breast cells (28) and cervical cells (unpublished data), possibly because of its pseudoestrogenic activity. I3C and genistein can synergistically cause apoptosis at low concentrations where neither phytochemical alone has an effect (13). I3C and genistein synergistically induce the growth arrest and levels of endoplasmic reticulum stress response proteins GADD 34, GADD 45, and GADD 153 (13). Further studies indicate that DIM induces apoptosis of already stressed (endoplasmic reticulum stressed) cells, typical of cancer cells in vivo (15), a possible explanation of a specific effect of I3C/DIM on apoptosis of cancer cells but not normal cells. This is another example in which the 3 food components should work together to reduce CIN to prevent cervical cancer.

A direct effect on the inhibition of HPV transcription, an important risk factor for CIN, is indicated for I3C/DIM. Several transcription factors induced by I3C/DIM have a direct effect on expression of a reporter gene driven by HPV regulatory sequences (9). In the cervical cell cancer cell line CaSki, which has HPV type 16 under control of its own promoter, I3C decreases expression of the papilloma viral oncoproteins E6 and E7 (9). Among the transcription factors induced by DIM that inhibit expression of HPVs, one of these is the bZIP protein GADD 153, which is also induced by genistein (13) and a number of other food components (29).

Research needs

Food components can be effectively monitored for effects on CIN because a suitable animal model resembling the human development of cervical cancer exists and effective biomarkers are available for translational studies in humans.

I3C and DIM appear to be promising food components for the treatment of CIN and prevention of cervical cancer. Based on known mechanisms, other food components should be able to replace or 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 is 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


