What Do Diet-Induced Alterations in Colorectal Polyps and Aberrant Crypts Indicate for Risk?1,2

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Expanded Abstract

Introduction
One of the great advantages to our understanding of the genesis of colon cancer lies in the recognition that the disease progresses in stages, often characterized by discrete intermediate lesions that, with mutations and deletions in key regulatory genes, ultimately may progress to metastatic disease. Colon cancer evolves from a normal epithelium that functions to provide an extended surface area for the absorption of water and nutrients and excretes mucin in the process. Aiding in these processes are the individual anatomic units collectively known as colonic crypts, comprised of at least 4 different cell types, intimately tied to a supportive connective tissue and interlaced with further intimate contact with cells of the immune system. A great disadvantage of this intricately constructed system is that disruption of the intercellular network quickly results in the death of colonocytes; hence, it is almost impossible to culture and maintain normal epithelium. For this reason the study of colon cancer has utilized somewhat imperfect animal models that nevertheless have been highly informative in aiding our understanding of the underpinnings of colon cancer (1). In this article we review what has been learned from 1 intermediate precancerous lesion for colon cancer, first identified in animal models, the aberrant crypt focus (ACF).3 Additionally, we will examine what has been learned about a bona fide premalignant lesion for colon cancer in humans, the adenoma, to which some ACFs may progress.

Core findings: diet-induced changes in animal studies
ACF is a term that now encompasses a variety of precancerous lesions found in animal and human colon (2). As shown in Figure 1, ACFs, which can number as many as several hundred in the carcinogen-treated rat colon, can further be characterized by degree of dysplasia or manifestation of other biological changes. It is now conjectured that ACFs that display any degree of dysplasia are more likely to progress toward adenoma (3). Dysplastic ACFs are characterized by increased basophilia, nuclear atypia, loss of mucin, and atypical mitoses. Further along the pathway are ACFs that, arguably, have mutation either in the apc gene or the β-catenin gene leading to overaccumulation and, in some cases, nuclear accretion of β-catenin; hence the term, β-catenin accumulated ACFs (BCACFs) (4). ACFs in animal models have been targeted for efficacy tests of dietary agents, and many cancer preventive compounds have been tested in the ACF animal assays; a few compounds have been evaluated for their ability to suppress BCACFs (5,6). An excellent web-based database exists that has very current summaries of diet-induced prevention of ACFs in animal models (7).

β-Catenin expression has been shown to be regulated by both p53/Siah and the GSK3β APC-dependent pathways. Recently, a new regulatory pathway involving the retinoic X receptor (RXR) has been suggested (8). In the azoxymethane-treated ApcMin mouse we have found that RXRα expression is often lost in multiple-crypt foci, including some that are BCACFs. This is highly suggestive of the importance of dysregulation of the β-catenin pathway in advancing premalignant lesions and may be a large step toward identifying ACFs with the potential to generate adenomas, through mutation or suppression of at least 3 routes involving the stability and half-life of β-catenin.

Figure 1 A proposed pathway for aberrant crypt foci leading to cancer.

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3 Abbreviations used: ACF, aberrant crypt focus; BCACF, β-catenin accumulated ACFs; LCM, laser capture microscopy; RXR, retinoic X receptor.

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TABLE 1  Dietary factors and risk for colon adenoma

<table>
<thead>
<tr>
<th>Dietary Item</th>
<th>Note</th>
<th>Effect</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tea</td>
<td>&gt;2 c/d</td>
<td>RR = 0.77 (NS)</td>
<td>Il'yasova et al. (9)</td>
</tr>
<tr>
<td>Meat fish</td>
<td>No effect</td>
<td></td>
<td>Matthew et al. (10)</td>
</tr>
<tr>
<td>CHO</td>
<td>RR = 0.95 (NS)</td>
<td></td>
<td>Oh et al. (12)</td>
</tr>
<tr>
<td>Fruits vegetables</td>
<td>Small polyps left in</td>
<td>RR = 0.3, RR = 0.1</td>
<td>Almendingen et al. (13)</td>
</tr>
<tr>
<td>(n&gt;3) FA</td>
<td>Small &gt; large adenomas</td>
<td>RR = 0.74 (NS)</td>
<td>Oh et al. (11)</td>
</tr>
<tr>
<td>Mediterranean diet</td>
<td>Tertile 3</td>
<td>RR = 0.5</td>
<td>Cottet et al. (14)</td>
</tr>
</tbody>
</table>

Core findings: diet-induced changes in adenoma, human studies

Information about diet and risk for adenoma comes from 2 types of studies. In the first, associations have been evaluated for dietary patterns and risk for adenoma. These are summarized in Table 1. In the second type of study, prospective interventions with dietary elements or with wholesale changes in dietary intake have been evaluated for the prevention of recurrent adenomas (Table 2). The data supporting a preventive effect of vegetable and fruit consumption is in evidence in several studies, but consumption of other dietary elements such as fish and carbohydrates are more equivocal. When some of the prospective trial studies are reviewed, the clearest intervention effect seems to be by adding supplemental calcium to the diet. That supplemental calcium could potentially offset risk for colonic polyps and cancers has been fairly well documented in animal and epidemiologic studies.

Research needs

Until precancerous lesions such as ACFS, BCACFS, and adenomas of differing dysplastic content can be investigated at the molecular level; the majority of studies can only associate dietary elements with the prevention or progression of these lesions to advanced cancers. Research gaps that need to be addressed include interrogating ACFS and adenomas that “fail” preventive protocols at the molecular level; using laser capture microscopy (LCM) employed to rigorously compare the biology of ACFS and adenomas; employing limited microarray technology targeting effects of a diet on specific pathways; examining ACFS and adenomas for signatures of “resistance” to dietary interventions; and examining ACFS and adenomas for signatures of “progressor” lesions.

In summary, the recognition of discrete precancerous lesions in rodent models for colon cancer and in human colon cancer has enabled a plethora of studies on dietary elements that may impact both the risk for and prevention of this common cancer.

TABLE 2  Dietary intervention in randomized clinical trials for prevention of recurrent colonic adenomas

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Quantity</th>
<th>Effect</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>UCDA</td>
<td>8–10 mg/kg, 3 years</td>
<td>12% decrease</td>
<td>Alberts et al. (15)</td>
</tr>
<tr>
<td>Calcium</td>
<td>1200 mg, 3 years</td>
<td>25% decrease for large polyps</td>
<td>Wallace et al. (16)</td>
</tr>
<tr>
<td>Wheat bran</td>
<td>13.5 vs 2 g, 3 years</td>
<td>No effect</td>
<td>Jacobs et al. (17)</td>
</tr>
<tr>
<td>Low fat high fiber</td>
<td>3 years</td>
<td>No effect</td>
<td>Schatzkin et al. (18)</td>
</tr>
<tr>
<td>Beta carotene, vitamin C, vitamin E</td>
<td>25 mg, 1000 mg, 400 mg</td>
<td>13% increase</td>
<td>Baron et al. (19)</td>
</tr>
</tbody>
</table>

Literature Cited