Risk Factors for Neoplasia in Chronic Colitis
An increasing amount of evidence has provided a link between chronically dysregulated inflammatory response and the incidence of cancer. In inflammatory bowel disease, chronically inflamed mucosa has been associated with an increased risk of neoplasia, and the risks for this association have been well-described as increasing duration of disease, greater extent of mucosal involvement, the presence of primary sclerosing cholangitis, and most recently, increased severity of histologic inflammation. Although molecular biomarkers such as inflammation associated DNA damage, including oxidative damage, telomere shortening, and chromosomal instability provide a partial link between inflammation and colorectal neoplasia, the mechanism and progression from inflammatory to neoplastic changes in carcinogenesis remain incompletely understood. Nonetheless, there are several studies demonstrating that the severity of inflammation is directly associated with the risk of developing neoplasia. These studies suggest that the converse could also be possible; reducing inflammation (with effective treatment) may lower the risk of carcinogenesis. Studies of chemopreventive effects of anti-inflammatory therapies are of interest in this regard, but many are limited by their inability to control for degree of inflammation and therefore their inability to adjust for a major confounding variable. The future approach to cancer prevention will incorporate the compounded risks in an individual patient with appropriate utilization of primary prevention (inflammation control) and secondary prevention (colonoscopic surveillance) in order to prevent dysplasia, cancer and colectomy.

Current Recommendations for Surveillance of Colorectal Cancer in Ulcerative Colitis
The current approach to cancer prevention in chronic colitis is based on an understanding of the known risk factors and the secondary preventive approach involving screening and surveillance colonoscopy in at risk patients. Current U.S. guidelines as well the British Society of Gastroenterology and other societies and professional organizations share a similar approach. Patients with chronic colitis for 8-10 years should undergo colonoscopy with the intention of identifying dysplasia. Dysplastic changes are associated with a predictive value for both concurrent (synchronous) and subsequent (metachronous) colorectal cancer. Historical precepts in the identification of dysplasia and recommendations for management once it is identified were based on the fact that dysplasia was often not visible and, therefore, must be identified only by microscopic examination of systematic biopsies from the colonic mucosa. The challenges to this approach to cancer prevention include the amount of time required, the lack of adherence to clinical recommendations, and the absence of evidence demonstrating overall benefit. In fact, recent studies demonstrate very low yield of random biopsies, and emerging strategies of surveillance don’t require this non-specific approach.

Newer technologies have provided information that has modified our approach. High definition colonoscopes provide enhanced visualization of the colonic mucosa and, therefore, are able to identify most lesions. In addition, there is a renewed appreciation for different grades and morphologies of dysplasia. There is little debate regarding high grade dysplastic lesions. Pathologists are able to identify these with a good degree of reliability and such lesions have an unacceptably high risk of synchronous or metachronous cancer and therefore warrant colectomy.

Low grade dysplastic lesions may have a more conservative approach, depending on the compounded risk factors in the individual patient and the morphology of such lesions. Current evidence supports a conservative approach to endoscopically discreet raised lesions. Such so called “polypoid dysplasia,” if removed completely, appears to have a favorable prognosis and may be followed, but with a more intensive surveillance protocol (3-6 month follow-up colonoscopy and, depending on subsequent findings, annually afterwards). This may be due to the fact that the molecular or genetic events that contribute to such lesions are similar to the polypoid lesions in the non-colitis patients, but that line of evidence is incomplete. In contrast, lesions that are identified in flat mucosa, either by random biopsies or by enhanced visualization techniques, appear to have a greater likelihood of progression to higher grade lesions, and warrant a more aggressive approach in follow-up, including discussion of colectomy, referral to a surgeon for consultation, and if colectomy is not pursued, an intensive surveillance plan. Multi-focal dysplasia, recurrent dysplasia in sequential examinations, and flat morphology are higher risk patients, and should be referred for colectomy.

Chromoscopy
There has been great interest in augmentation of our visualization of dysplasia using chromoendoscopy (also called “chromoscopy”), primarily dye-spraying with indigo carmine or methylene blue. There are two general principles of this strategy. First, dye-spray enhancement enables better visual-
ization of raised lesions. Secondly, dye-spray with or without magnification provides views of the cellular patterns. An understanding of pit patterns and their association with dysplasia is necessary in order to utilize this approach. The range of studies using chromoendoscopy has consistently demonstrated a greater number of dysplastic lesions utilizing this approach compared to white light examinations. However, none of these studies have demonstrated a change in outcome of the patients, begging the question of whether the dysplasia seen by chromoscopy is in fact an “earlier” lesion and providing a greater degree of comfort and ability to follow such patients without immediate colectomy.

The enhanced visualization with chromoendoscopy combined with the appreciation of the degree of inflammation as a risk factor for dysplasia was incorporated into the 2010 British Society of Gastroenterology guidelines. They discriminate between low, intermediate and high risk groups based on the patient’s compounded risks, including inflammation seen during the examination, and recommend the use of chromoscopy. Although not prospectively evidenced-based (none of our cancer prevention guidelines in IBD are), this practical approach appears reasonable. The key to these guidelines, however, is the ability to perform a careful and clean examination with chromoscopy. In the absence of that, due to an inadequate prep, active inflammation limiting histologic interpretation, or when a patient is non-compliant, longer intervals of follow-up should be considered carefully.

Future Strategies and Novel Approaches to Surveillance
An ideal surveillance approach would be highly sensitive and specific for early stage neoplasia, adequately sample the entire colorectal mucosa, be easy to implement in practice, and be affordable/cost effective. There are several novel techniques that are being developed and may offer stand-alone alternatives for future surveillance or, more likely, be used in conjunction with selective colonoscopic exams. Such techniques include fecal markers of DNA and methylation, or other techniques that provide fluorescent labeling of dysplastic lesions.

Skin Cancer and Screening
Extensive research has explored the risk of melanoma and non-melanoma skin cancer within the IBD patient population. The increased risk for non-melanoma skin cancer (NMSC) (e.g., squamous cell carcinoma and basal cell carcinoma) has been well recognized among IBD patients, particularly among those on thiopurine therapy. One possible mechanism that explains this finding suggests that thiopurine increases the vulnerability to UVA radiation. Several studies have also shown that biologic medication confer an increased risk for melanoma. In contrast, a meta-analysis by Singh and colleagues demonstrated that melanoma risk exists independent of exposure to biologic therapy. Both patients with CD and UC appear at increased risk for melanoma. All IBD patients should be counseled about their risk for skin cancer and specific concerns associated with their medications.

This discussion should focus on primary protection (such as sun avoidance and sun protection via sunscreen and clothing) and secondary protection (such as screening). In particular patients on immunosuppressive agents should undergo yearly screening by a dermatologist as suggested by NIH screening guidelines.

Lymphoproliferative Disorders
The comorbid occurrence of lymphoproliferative disorders and IBD has been described in the literature, particularly among patients on thiopurines. That is not surprising, as data from non-IBD literature has previously demonstrated a relationship between altered immune status (e.g., HIV/AIDS and post-transplantation patients on immunosuppressives) and lymphoma risk. The French CESAME study is the largest population-based cohort examination of thiopurine use and lymphoproliferative disorders in IBD patients. This study showed that patients who received thiopurines were five times more likely (Hazard Ratio 5.28 (2.01-13.9, p=0.0007) to develop a lymphoproliferative disorder. The majority of these cases were non-Hodgkin lymphomas (NHL), a trend that reflects results found in other studies as well. A meta-analysis of lymphoma rates by Siegel et al. demonstrated risk for NHL while on an immunomodulator at 3.6 per 10,000 patient-years. When an immunomodulator and an anti-TNF agent are combined, the risk increases to 6.1 per 10,000 patient-years. Although there also has been a risk association seen with EBV and lymphoma in these patients, the ubiquitousness of EBV infections has made screening for EBV in IBD patients prior to therapy or as a stratification approach related to lymphoma impractical. Therefore, at the current time, this is not recommended.

The increased risk of hepatosplenic T-cell lymphoma (HSTCL) among patients on dual therapy is real but the incidence remains rare. Overall 41 HSTCL cases among IBD patients were reported to the FDA Adverse Event Reporting System (FDA AERS) between 2003-2010. Among these, 23 (56%) had prior exposure to combination therapy consisting of anti-TNF and thiopurine agents. 17 patients with HSTCL received thiopurines alone and 1 patient received an anti-TNF agent alone. A literature review from 2010 of all Crohn’s disease patients with HSTCL showed that 22 of the 28 HSTCL cases reported had received combination therapy of infliximab and a thiopurine. Another analysis demonstrated elevated risk for young male patients younger than 35 years of age.
These statistics noted that there are no specific screening recommendations regarding lymphoproliferative disorders. Physicians should develop an empirically supported strategy to communicate risks associated with therapy to patients. This may include a visual representation of risk per 10,000 patients.29 Patients should receive enough adequate information to fully understand both benefits and risks of therapy.

**Cervical Dysplasia and Cervical Cancer**

Studies addressing cervical dysplasia and cervical cancer have reported conflicting data. Despite two studies that did not show an increased risk for dysplasia or carcinoma30,31 there have been several other studies that have suggested an increased risk in either cervical abnormalities or cervical cancer. The study done by the St. Mark’s hospital was the first that suggested an increased trend in invasive cervical carcinoma.32 There have been at least two tertiary center studies conducted that demonstrated an increased risk of cervical dysplasia (but not cancer) in IBD patients.33,34 Singh et al conducted a population based case-control study that suggested an increased odds ratio for cervical abnormalities among IBD patients.35 More recently a population-based Danish study showed an increased risk for cervical carcinoma (1.51; 95% CI: 1.08 2.13) in CD patients, but not in UC patients.36

There are no specific cervical cancer screening guidelines for women with IBD. Primary prevention should focus on patient education about risks associated with cervical cancer such as high parity, prolonged oral contraceptive use, number of sexual partners, smoking tobacco, and chlamydia infection. In addition, the role of HPV infections and HPV transmission should be discussed as they pertain to cervical cancer. Secondary prevention in cervical cancer should focus on the regular screening recommendations for women. This said, recent data from a health maintenance study conducted among women with IBD (the PIANO cohort study) reported that only 74% of patients were adherent to cervical screening recommendations.37 Furthermore, despite no available guidelines for IBD patients specifically, enhanced annual screening has been suggested for IBD patients on immunosuppressive drugs and those who smoke cigarettes.38,39

In addition, more recent recommendations for prevention in the IBD population (and other immune-compromised patients) include HPV vaccination (in both women and men).

**Anal Cancer**

The St. Mark’s Hospital study observed a higher than expected frequency of anal cancer among IBD patients. Anal cancer is a rare type of squamous cell carcinoma that is HPV-dependent. Though anal cancer is still rare among IBD patients, there is an increased risk in certain circumstances. Screening for anal-intraepithelial neoplasia (AIN) is recommended in high risk individuals. These include patients on immunosuppressive drugs and other factors such as HIV+, men who have sex with men, and women with high grade cervical dysplasia.40 Anal cancer should be ruled out in IBD patients with exuberant perianal tissue, persistent ulceration or anorectal pain or bleeding. There is often a delayed diagnosis in anal cancer due to misdiagnoses of benign strictures.40 Therefore, even if a stricture appears benign, physicians should keep anal cancer in their differential diagnosis. The approach to anal cancer screening may involve anal Pap smears or biopsies (in the anesthetized patient).

The role of HPV vaccination against this malignancy is not clear, but this recommendation seems prudent.

**Summary Non-CRC Cancer Risks in IBD and IBD Medication**

In conclusion, multiple studies have shown increased risks for certain non-CRC cancers in IBD patients. Prominent cancers related to IBD treatment include: lymphomas associated with thiopurine, the (rare) association between hepatosplenic T-cell lymphoma in young male patients treated with thiopurines and anti-TNF agents, non-melanoma skin cancer in patients treated with thiopurines and anti-TNF agents, and melanoma in patients on anti-TNF agents only. In addition, IBD patients may have higher rates of abnormal cervical Pap smears and cervical cancer, although these studies have demonstrated conflicting data. Although the discussed studies show an association of increased risk for certain cancers, (lymphoma and skin cancer, in particular,) one should remember that the absolute risks are still very low. We should provide patients with a comprehensive overview of the benefits and risks of IBD treatment and facilitate a conversation that can lead to optimal shared decision making and personalized treatment with our patients in clinic.

Clinicians may utilize checklists to assure that all recommended screening is completed. Checklists are useful for organizational purposes and to ensure standard of care. At a minimum, a checklist for cancer screening should address colorectal surveillance, cervical cancer assessment and skin cancer screening (Table 1).
Table 1: Recommendations for Screening and Prevention of Cancers Related to IBD

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Colorectal cancer</td>
<td>If UC or CD is present in at least 1/3 of the colon, perform annual or bi-annual surveillance colonoscopies with targeted mucosal sampling; chromoscopy preferred if available, to assess for dysplasia after 8 years.</td>
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<tr>
<td>Cervical cancer</td>
<td>Annual PAP smears if immunocompromised. HPV vaccination both in women and men (3 doses, ages 9-26).</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Annual visual exam of skin by dermatologist if immunocompromised. Avoidance of excessive sun exposure, judicious use of sunscreen.</td>
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REFERENCES


