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Cancers Complicating Inflammatory Bowel Disease

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Crohn's disease and ulcerative colitis are lifelong inflammatory bowel diseases of unknown origin that generally begin in young adulthood. It is estimated that at least 0.4% of Europeans and North Americans live with inflammatory bowel disease.[1] Life expectancy is reduced in patients with Crohn's disease and in patients with ulcerative colitis that is diagnosed when colitis is extensive or that is diagnosed in childhood.[2–4] There are excess deaths from infection, cardiovascular diseases, and cancers in patients with inflammatory bowel disease.[3] Some differences in the risk of cancer between patients with inflammatory bowel disease and the general population may be the result of differences in the distribution of lifestyle factors. For example, smokers are overrepresented among patients with Crohn's disease, and this overrepresentation results in an excess rate of smoking-related cancers in the total population with Crohn's disease.[2] Conversely, nonsmokers are overrepresented among patients with ulcerative colitis, so there is a decreased rate of such cancers in the total population with ulcerative colitis.[4] The focus of this review is on the epidemiologic characteristics, carcinogenesis, and prevention of excess cancers that can be attributed to chronic intestinal inflammation or to the carcinogenic effects of the immunosuppressive drugs used to treat inflammatory bowel disease.

Cancers Complicating Intestinal Inflammation

COLORECTAL CANCER

Epidemiology

Colorectal cancer is the third most common cancer worldwide.[5] Sporadic colorectal cancers and colitis-associated cancer may develop in patients with inflammatory bowel disease. The main risk factors for sporadic colorectal cancer are increasing age after 50 years, male sex, and a history of colorectal cancer in first-degree relatives (Table 1). Although lifestyle factors are associated with as much as a 20% alteration in the risk of sporadic colorectal cancer, these have not been assessed in patients with inflammatory bowel disease.

Risk factors for colorectal cancer that are specific to patients with inflammatory bowel disease have been identified in studies of population-based registries,[6] nationwide cohorts,[7,8] and referral-center cohorts.[9,10] Patients with inflammatory bowel disease without colonic inflammation and patients with ulcerative colitis limited to the rectum are not at excess risk for colorectal cancer.[6] In contrast, patients with primary sclerosing cholangitis associated with inflammatory bowel disease are at high risk for colorectal cancer, beginning at the time of the diagnosis.[7] In other patients with inflammatory bowel disease, the excess risk of colorectal cancer, as compared with the risk among persons of the same age and sex without inflammatory bowel disease, is driven by the extent, duration, and severity of colonic inflammation. Up to 15% of colorectal cancers that occur in patients with inflammatory bowel disease are

TABLE 1

factors for colorectal cancer. Whether a young age at diagnosis of inflammatory bowel disease is a risk factor independent of disease duration is controversial (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

In contrast to the relatively high risk of colorectal cancer (approximately 0.5 to 1% per year) suggested in a 2001 meta-analysis,[14] a progressive decrease in the excess risk of colorectal cancer in patients with inflammatory bowel disease has been noted over time, with no excess risk found in a Danish population-based study.[7] This trend, confirmed in another meta-analysis,[12] was attributed to better control of inflammation, better implementation of colonoscopic surveillance, increased implementation of colectomy in some countries, and the possible chemopreventive effect of 5-aminosalicylates (5-ASAs).

Still, as compared with the risk in the general population, the risk of colorectal cancer in patients with inflammatory bowel disease is 1.5 to 2 times greater in North America[15] and some European countries.[8] Stratification of the population with inflammatory bowel disease according to the duration of disease and the extent of colitis gives insight into incidence rates and the standardized incidence ratio of colorectal cancer among patients with inflammatory bowel disease (Table 2): teenagers with pancolitis have a lifetime risk of colorectal cancer that exceeds 15%.

> Cigarette smoking†
> High consumption of red meat†
> Consumption of alcohol†
> Risk factors specific to patients with inflammatory bowel disease
>   Coexisting primary sclerosing cholangitis
>   Increasing cumulative extent of colonic inflammatory lesions‡
>   Increasing duration of inflammatory bowel disease§
>   Active chronic endoscopically assessed inflammation
>   Active chronic histologically assessed inflammation
>   Anatomical abnormalities
>   Foreshortened colon
>   Strictures
>   Pseudopolyps
>   Personal history of flat dysplasia

> * This factor has been confirmed as a risk factor in epidemiologic studies that were restricted to patients with inflammatory bowel disease.
> † This factor has not been specifically assessed in studies restricted to patients with inflammatory bowel disease.
> ‡ In ulcerative colitis, there is no excess risk of proctitis, an intermediate excess risk for left-sided colitis, and a maximal excess risk for pancolitis. In Crohn's disease, the excess risk appears when more than 30 to 50% of the colonic surface is ever involved.
> § The excess risk becomes significant from the time of diagnosis for patients with primary sclerosing cholangitis and becomes significant 7 to 10 years after diagnosis for other patients.

Risk Factors for Colorectal Cancer in Patients with Inflammatory Bowel Disease.

Pathogenesis

Much is known about the molecular genetic events that drive the onset and progression of sporadic colorectal cancer,[16] although the environmental factor or factors that trigger the carcinogenesis remain to be elucidated. The molecular pathogenesis of colitis-associated cancer shares many features with sporadic colorectal cancer, but there are differences with respect to the timing and frequency of some alterations in the dysplasia–carcinoma sequence (Figure 1).[17] Chronic inflammation is assumed to underlie the cause of colitis-associated cancer, with oxidative stress–induced DNA damage resulting in the activation of procarcinogenic genes and silencing of tumor-suppressor pathways. Insights from the study of animal models suggest that both the initiation and the progression of colonic neoplasia can be exacerbated or expedited by an inflammatory insult.[18] Moreover, mucosal-mapping studies indicate that the chronically inflamed colonic mucosa of patients with inflammatory bowel disease undergoes a "field change" of cancer-associated molecular alterations before there is any histologic evidence of dysplasia.[19,20] This suggests that the chronically inflamed colonic mucosa is primed to develop multifocal precancerous and cancerous changes. For example, TP53 mutations occur before the onset of dysplasia as a field change in human colitic mucosa.[21] Microsatellite instability, CpG island methylation, and microRNA alterations have been described in the early phases of both sporadic and colitis-associated neoplasia.[22]

An altered microbiota probably contributes to colitis-associated cancer by promoting chronic inflammation, producing carcinogenic factors, or both. In studies of genetically engineered mouse models of colitis-associated cancer that are susceptible to inflammation or cancer, cancer did not develop when the mice were either germ-free or treated with antibiotics.[23–25] Although certain bacteria (e.g., enterotoxigenic *Bacteroides fragilis*, fusobacterium, and *Enterococcus faecalis*) have been shown to play a procarcinogenic role, it is predicted that the complex interplay

TABLE 2

Crude Incidence Rate and Standardized Incidence Ratio of Colorectal Cancer in Patients with Inflammatory Bowel Disease.
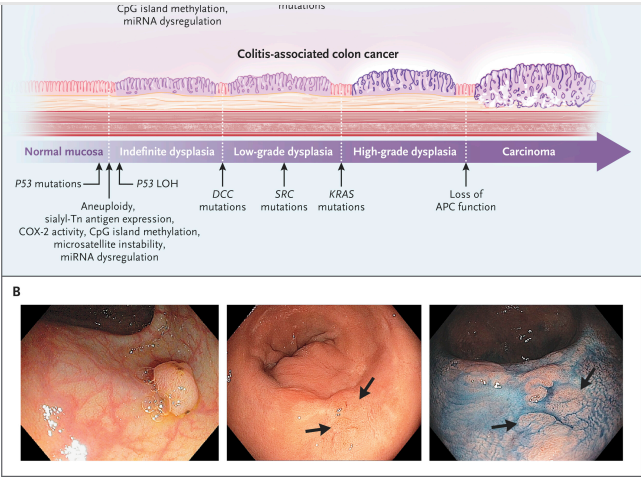
FIGURE 1

Bowel Disease

Successful surveillance for colorectal neoplasia depends on adequate cooperation from the patient, adequate bowel cleansing, sufficient mucosal sampling, and the ability of the endoscopist to recognize and, if possible, to resect dysplastic lesions. The presence of strictures, actively inflamed mucosa, and inflammatory pseudopolyps makes surveillance colonoscopy more difficult. As in sporadic colorectal cancer, in which the precursor dysplastic lesion is usually a visible polyp, in colitis, most dysplasia is also visible in the colon.[26] However, colitis-associated dysplastic lesions are often flatter and have less distinct borders, and they can even be invisible when standard endoscopic techniques are used. This

Pathogenesis of Colorectal Carcinoma.

has prompted the recommendation to perform extensive biopsies throughout the colorectum, taking care to target any raised or suspicious lesions. Newer endoscopic techniques, especially high-definition white-light colonoscopy and chromoendoscopy with mucosal dye-spraying, enhance the detection of dysplasia, as compared with standard-light colonoscopy (Figure 1). This is why most international authorities now favor chromoendoscopy with targeted biopsies over random biopsies,[27,28] although the latter approach, alone or in combination with targeted biopsies, has not yet been fully abandoned.[28]

There are only minor differences in the recommendations from medical societies for colonoscopic surveillance (Figure 2).[27–30] After a dysplastic lesion is found, whether of a low-grade or high-grade histologic type, if it can be completely resected endoscopically and no dysplasia is noted elsewhere in the colon, the patient should remain under close colonoscopic surveillance. A meta-analysis has confirmed that after endoscopic removal of polypoid dysplasia, the risk of subsequent colorectal cancer is relatively low (5 per 1000 patient-years), but the risk of dysplasia remains high (65 per 1000 patient-years).[31] Colectomy is indicated in cases of carcinoma and in cases of high-grade dysplasia that is not endoscopically resectable. Colectomy should also be considered for patients who have low-grade dysplasia that cannot be resected endoscopically; patients with anatomical difficulties, such as stricture or dense pseudopolyps, that limit the accuracy of surveillance; and patients who cannot or will not undergo regular surveillance exams. The decision to undergo a colectomy is highly individualized, and the physician must take into consideration the patient's coexisting conditions, life expectancy, and preferences.

Chemopreventive agents inhibit, delay, or reverse carcinogenesis. In theory, if reducing inflammation leads to a reduced incidence of colitis-associated cancer, all antiinflammatory drugs used in inflammatory bowel disease, including 5-ASA, thiopurines, and tumor necrosis factor α (TNF-α) antagonists, are potential chemopreventive agents. In addition, a specific anticarcinogenic effect of 5-ASA has been advocated on the basis of molecular data.[32]

FIGURE 2

Suggested Algorithm for Colorectal Cancer Surveillance in Inflammatory Bowel Disease.
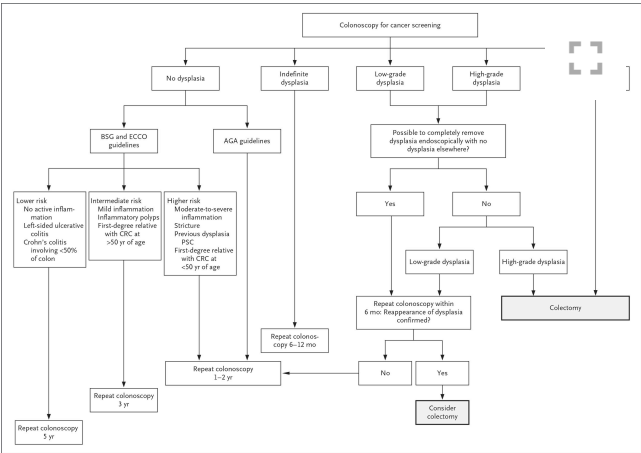
To date, however, none of the medicines used to treat inflammation in inflammatory bowel disease have been firmly established as being chemopreventive (Table S1 in the Supplementary Appendix). 5-ASA agents were the first drugs to be assessed for this purpose. Case–control and cohort studies, as well as an initial meta-analysis,[33] had suggested that there is a significant reduction in the risk of colorectal cancer in patients with inflammatory bowel disease who are exposed to 5-ASA. However, this was not confirmed in a more recent meta-analysis of nonreferral studies.[34] Nationwide cohort studies[8,35,36] and meta-analyses[37,38] of chemoprevention with thiopurines have also had conflicting results. The first data for TNF-α antagonists are also conflicting (Table S1 in the Supplementary Appendix). With regard to drugs that are not used for the treatment of inflammatory bowel disease, a potential preventive role of low-dose aspirin in persons with previous adenoma or dysplasia has not been assessed in patients with inflammatory bowel disease.

Given the lack of evidence, gastroenterologists are not comfortable prescribing inflammatory bowel disease drugs for the sole purpose of chemoprevention, even though this has been suggested for 5-ASA in some ulcerative colitis

colonic inflammation.

SMALL-BOWEL ADENOCARCINOMA

In the general population, small-bowel adenocarcinoma is rare. In patients with Crohn's disease, the risk of small-bowel adenocarcinoma is 20 to 30 times that in patients without Crohn's disease.[40] Small-bowel adenocarcinoma typically arises in the ileal lesions of patients with Crohn's disease more than 8 years after diagnosis. It is often associated with previous or synchronous ileal dysplasia,[41] which suggests that it may complicate chronic ileal inflammation in Crohn's disease through a dysplasia–adenocarcinoma sequence. In the Cancers et Surrisque Associé aux Maladies Inflammatoires Intestinales en France (CESAME) cohort, the subgroup of patients who had small-bowel Crohn's disease for more than 8 years had a small-bowel adenocarcinoma incidence rate of 0.5 per 1000 patient-years,[42] which is similar to the risk of sporadic colorectal cancer. Findings on computed tomography and magnetic resonance imaging can be suggestive of the diagnosis of small-bowel adenocarcinoma,[43] but most cases are diagnosed incidentally during laparotomy performed for intestinal obstruction or perforation.[42,43]

Surgical excision of ileal lesions prevents the risk of subsequent malignant transformation, but no other preventive approach is currently available. One case–control study suggests that 5-ASA has a potential chemopreventive effect for small-bowel adenocarcinoma,[44] but no data exist for immunosuppressants. Consideration of an endoscopic surveillance program for patients at higher risk for small-bowel adenocarcinoma is problematic, because extensive and stricturing lesions make ileoscopy for the full visualization of the segments of the small bowel affected by Crohn's disease difficult or impossible.

INTESTINAL LYMPHOMAS

The risk of primary intestinal lymphomas is significantly higher in patients with inflammatory bowel disease, but the absolute risk (0.1 per 1000 patient-years) is low.[45] Excess intestinal lymphomas in inflammatory bowel disease are mainly B-cell non-Hodgkin's lymphomas, typically arising in the chronically inflamed intestinal lesions of middle-aged men with Crohn's disease after 8 years of disease.[45] Epstein–Barr virus (EBV) is often identified in lymphoma cells,[45] which suggests that local inflammation-promoted EBV replication plays a role in lymphomagenesis in these cases.[46]

ANAL CANCERS

Anal squamous-cell carcinoma occurs with a low annual incidence of approximately 0.01 to 0.02 per 1000 person-years in the general population and in patients with inflammatory bowel disease.[47] Persons at higher risk include men who have sex with men, as well as women with high-grade cervical dysplasia. Although immunosuppression after organ transplantation promotes human papillomavirus (HPV)–related anal carcinoma, the risk in patients with inflammatory bowel disease who are receiving immunosuppressants is unknown. Anal cancers may also arise in the fistulae of patients with long-standing (>10 years) fistulizing perianal Crohn's disease, with an incidence rate of approximately 0.2 per 1000 patient-years.[48] These cancers include adenocarcinomas and squamous-cell carcinomas that have no consistent relationship with HPV infection. Diagnosis is often delayed because of a nonspecific clinical presentation and because access to lesions is difficult in the presence of stenosis. A change in anal symptoms and unexplained pain should alert the clinician. The overall prognosis for patients with fistula-associated cancers is poor.

CHOLANGIOCARCINOMA

The risk of cholangiocarcinoma in patients with inflammatory bowel disease is approximately 2 to 4 times as high as in the general population, although the absolute risk is low, with an incidence of approximately 0.08 per 1000 person-years.[49] Most but perhaps not all[50] of the increased cholangiocarcinoma risk in patients with inflammatory bowel disease is seen in patients with associated primary sclerosing cholangitis; these patients have a risk that is approximately 160 times as high as that in the general population, as well as a 5 to 10% lifelong risk.[51] Most experts recommend noninvasive annual imaging of the biliary tract (magnetic resonance cholangiopancreatography or ultrasonography) and serum CA 19-9 measurement. If the results are abnormal, clinical judgment is used to decide on diagnostic confirmation and consideration for liver transplantation. Despite this approach, the prognosis of cholangiocarcinoma remains poor.

with Crohn's disease, as well as in patients with moderately to severely active ulcerative colitis. Immunosuppressants may be carcinogenic by directly altering cell DNA,[52] impairing immune control of chronic infection by mutagenic viruses,[53] or reducing immunosurveillance of tumor cells.[54] Here, we review the cancers for which a higher risk has been established or suggested in patients with inflammatory bowel disease who have long-term exposure to immunosuppressants.

HEMATOLOGIC CANCERS

Lymphomas

Non-Hodgkin's lymphomas are frequent cancers; the risk of these cancers is greater in men and increases with age. There is no overt excess risk of non-Hodgkin's lymphoma due to inflammatory bowel disease itself.[55,56] Thiopurines were shown in the 1970s to increase the incidence of non-Hodgkin's lymphoma after kidney transplantation. This phenomenon was established in the early 2000s in patients with inflammatory bowel disease.[56,57] Most of the thiopurine-promoted lymphomas are posttransplant-like EBV-associated B-cell lymphomas.[56] These lymphomas may occur in patients seropositive for EBV (i.e., almost all adults >30 years of age); in these patients, non-Hodgkin's lymphoma is attributed to the cytotoxic effects of thiopurines on EBV-specific immune cells that prevent the proliferation of EBV-infected B lymphocytes.[58]

Young men (<35 years of age) who are seronegative for EBV may also have fatal early post-mononucleosis lymphomas develop; these lymphomas mimic those encountered in X-linked lymphoproliferative disease.[56] Finally, non–EBV-related hepatosplenic T-cell lymphomas may occur in patients exposed to thiopurines alone or in combination with TNF-α antagonists. These very rare lymphomas are most typically seen in young men after 2 years of therapy with thiopurines and TNF-α antagonists.[59]

The epidemiologic aspects of the three subtypes of thiopurine-induced lymphoproliferation are detailed in Table 3. The resulting standardized incidence ratio for patients with inflammatory bowel disease to have any lymphoproliferation develop is 5 to 6 in current thiopurine users and is not significantly increased in patients who used thiopurines in the past or never used them.[56,61] The highest absolute risk is observed in patients older than 65 years of age (5 per 1000 patient-years),[56] and the highest standardized incidence ratio is seen in men younger than 30 years of age.[61] In current users, the excess risk becomes apparent from the second year of treatment and appears to be roughly constant thereafter.[61] The excess risk disappears after thiopurine withdrawal.[61]

The risk of lymphoproliferation associated with methotrexate use is unknown in inflammatory bowel disease. In rheumatoid arthritis, reversible polyclonal EBV-associated lymphoproliferation has been reported, but no excess risk of lymphoma has been demonstrated in nationwide cohorts.[68]

Whether TNF-α antagonists promote lymphomas by themselves in patients with inflammatory bowel disease is difficult to assess because of the substantial proportion of patients who have previously been treated with immunomodulators.[69] However, after adjustment for cotreatments, no excess risk of lymphoma was found in a recent adequately powered study involving a cohort of patients with inflammatory bowel disease who had been exposed to TNF-α antagonists.[60]

Other Hematologic Cancers

In the long term, thiopurines may promote acute myeloid leukemia and severe myelodysplastic syndromes because of proliferation of blood cells with defective DNA-mismatch repair that escape the cytotoxic effect of drugs.[70] This proliferation results in an increased risk of acute myeloid leukemia and myelodysplastic syndromes in past users of thiopurines.[62]

TABLE 3

Risks of Cancer in Patients with Inflammatory Bowel Disease Exposed to Thiopurines and TNF-α Antagonists.

radiation on epithelial skin cells[71] and a direct mutagenic effect on the gene encoding PTCH.[52] In patients with inflammatory bowel disease, no excess risk of nonmelanoma skin cancer attributable to TNF-α antagonists was found in a large cohort drawn from a health plan claims database, after adjustment for thiopurine therapy.[65]

Patients with inflammatory bowel disease may have a slight unexplained intrinsic higher risk of developing melanoma.[72] Treatment with thiopurines is not associated with an alteration of this background risk.[65,66] In contrast, the risk of melanoma in patients with inflammatory bowel disease who were exposed to TNF-α antagonists has been reported to be 1.5 to 2 times higher than that in patients who were not exposed,[60,65] which represents an incidence rate of 0.5 per 1000 patient-years.[60] Given the excess risks of skin cancers associated with both inflammatory bowel disease and the drugs used to treat it, specialists increasingly propose that all patients with inflammatory bowel disease practice sun protection and skin surveillance from the time of diagnosis. Methods of skin surveillance should be discussed with the patient's dermatologist.

HPV-RELATED CERVICAL CANCER

It is still unclear whether the risk of HPV-related cervical cancer is intrinsically increased in women with inflammatory bowel disease[73] or independently worsened by exposure to an immunosuppressant. However, vaccination against HPV and regular Papanicolaou tests are recommended in all women with inflammatory bowel disease.

URINARY-TRACT CANCERS

Transplant recipients receiving immunosuppressive regimens that include thiopurines are at increased risk for kidney and bladder cancer.[74] As compared with patients with inflammatory bowel disease who had never taken thiopurines, patients who were currently using azathioprine were reported in a Danish registry study to have a higher incidence of urinary-tract cancers, whereas former users of azathioprine did not.[36] No excess risk of urinary-tract cancer has been reported in patients with inflammatory bowel disease who have been exposed to TNF-α antagonists.[60]

OVERALL RISK AND PREVENTION OF CANCERS RELATED TO DRUGS FOR INFLAMMATORY BOWEL DISEASE

After adjustment for confounders, current use of thiopurines for inflammatory bowel disease has been shown to be associated with an overall relative risk of cancer of 1.3 to 1.7 in adequately powered cohort studies.[36,67] This excess risk is reversible after thiopurine withdrawal.[36] There is no overall excess risk of cancer in patients treated with TNF-α antagonists for inflammatory bowel disease,[60] but a long-term excess risk due to accumulated doses cannot be yet ruled out because of the relatively recent use of biologics. The first guidelines for managing the risk of cancers related to inflammatory bowel disease drugs are being elaborated. Some key measures currently being discussed are listed in Table S3 in the Supplementary Appendix. Preventive tools include sun protection and skin surveillance for the prevention and detection of skin cancers.

Conclusions

Among the chronic inflammatory diseases that often require the prolonged use of immunosuppressants, inflammatory bowel disease is an intriguing model, because immunosuppressants may reduce the incidence of inflammation-related cancers through their antiinflammatory effects or promote immunosuppression-related cancers. In addition to cohorts in which the excess risk of cancers associated with the use of TNF-α antagonists and newer biologics can be assessed, we need cohorts in which general and inflammatory bowel disease–related risk factors for cancers, including inflammatory bowel disease activity, are prospectively recorded, to clarify whether healing of inflammatory lesions decreases the incidence of cancers related to inflammatory bowel disease and to grade the independent potential chemopreventive effects of drugs used to treat the condition.

The risks of cancers related to inflammatory bowel disease must be considered when assessing the risk–benefit ratios associated with long-term therapeutic strategies in inflammatory bowel disease. Given the large influence of age, sex, and inflammatory bowel disease phenotype on the extent of the risks of inflammatory bowel disease–related cancers, risk–benefit models should now be stratified for age,[75] sex, and inflammatory bowel disease phenotype to provide tailored quantification of risks for making individual therapeutic decisions.

SUPPLEMENTARY MATERIAL

Supplementary Appendix (nejmra1403718_appendix.pdf)

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Disclosure Forms (nejmra1403718_disclosures.pdf)

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