Crohn's Disease and the Risk of Cancer

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Abstract

Keywords

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- cancer
- inflammatory bowel disease

Crohn's disease is associated with various intestinal and extraintestinal malignancies. This article reviews the current literature regarding Crohn's disease and subsequent risk of cancer formation. Recognition of risk factors (both modifiable and unmodifiable) is essential for prevention and appropriate screening. Future investigations into the molecular mechanisms associated with Crohn-related malignancy will provide additional insight into carcinogenesis, potential for early intervention, and identification of at-risk patients.

Crohn's disease (CD) is a chronic, transmural, inflammatory gastrointestinal condition that can involve any portion of the gastrointestinal tract. Complications such as strictures, fistulas, abscesses, and malignancies are a consequence of transmural inflammation. Malignancies associated with CD, both gastrointestinal and extragastrointestinal, are the focus of this article. This is likely to become an increasingly important subject of investigation, as worldwide incidence of CD has been increasing over the last five decades, including in the pediatric population.^{1,2}

Overall Cancer Risk

Several multicenter studies have examined the overall cancer risk in the setting of CD. The Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) conducted a prospective, nested case-control study with the overall aim of characterizing the incidence of cancer in inflammatory bowel disease (IBD) patients. A secondary aim was to determine the role of immunomodulatory medications versus clinical characteristics as risk factors for cancer development. For this study, each IBD patient with cancer was matched with two IBD patients without cancer. The patients were also matched based on IBD type, gender, and age. Risk factors were assessed via a multivariate regression analysis. The study looked at 21,953 patients with CD, 99 of whom developed cancer. The authors noted an increase in cancer incidence in patients with CD compared with those with ulcerative colitis (UC) ($p = 0.042$). They found that penetrating CD was a risk factor for cancer overall. This multicenter

study also found that the combination of thiopurine and anti-tumor necrosis factor (anti-TNF) inhibitors was a risk factor for cancer (odds ratio [OR]: 2.33).³

The Inflammatory Bowel South-Eastern Norway (IBSEN) study was completed to determine the prevalence of cancers in an IBD cohort 20 years after diagnosis. The study's secondary outcome measure evaluated cancer-specific risk factors compared with a matched population. Data on all cancer cases, mortality, and cause of death were collected from the national cancer and death registry. There were 237 CD patients in this study. Each patient was matched with 25 individuals who were randomly selected from the general population. The patients were then matched with respect to age, gender, and country of residence. The authors noted no increased risk of cancer in CD patients overall. Interestingly, they did note an increase in the ratio of breast cancers diagnosed in patients with CD.⁴

In Denmark, another long-term study—a nationwide, retrospective, cohort study utilizing the Danish healthcare database—had 30 years of patient follow-up. The primary outcome was the risk of gastrointestinal and extraintestinal cancers in IBD patients. Patients were identified between 1978 and 2010, and then followed up until the first occurrence of cancer or death. Authors utilized standardized incidence ratios (SIR) to compare the incidence of cancer in the IBD patients compared with the general population. There were 13,756 CD patients identified in this study, with 772 patients developing cancer. The authors found that CD was only weakly associated with both gastrointestinal and extraintestinal cancer development; CD was associated with

a higher risk of cancer of the small bowel and hepatobiliary malignancies. There was also a stronger association between CD and hematologic malignancies, smoking-related cancers, and melanoma. In this population study, CD patients had a 30% higher long-term risk of invasive cancer compared with the general population. The authors noted a stable relative risk of extraintestinal cancers among all IBD patients, with a decreased risk of gastrointestinal malignancies over time. The authors speculated that the increase in extraintestinal malignancies may be related to the increased use of immunosuppressive medications. Finally, it was noted that the relative risk of cancer development in patients diagnosed with IBD prior to 20 years of age was twice that of patients diagnosed after the age of 40, and the cancers were mainly of gastrointestinal origin.⁵

A large-scale registry study from Finland examined the long-term risk of malignancy in their IBD patient population. In this study, there were 5,315 CD patients. The number of cancers observed was compared with those expected in the general population. This study demonstrated a higher incidence of cancer among male patients with IBD (UC and CD) compared with the background population, with a higher SIR for CD patients in comparison to UC patients. In CD patients, there was no overall increased risk for developing colorectal cancer. However, patients with CD had a significantly increased risk for cancer of the small intestine, anus, and the biliary tract. The risk of gastric cancer was slightly increased in female patients with CD. There was also an increased risk of non-Hodgkin's lymphomas (NHLs) in male CD patients, along with myeloma and kidney cancer. The risk of basal-cell carcinoma was elevated in all CD patients, with a slight increase in melanoma in male CD patients.⁶

A meta-analysis from 2009 examined the risk of extraintestinal malignancies in IBD patients. Eight population-based cohort studies were included in this analysis. CD patients had an increased risk of cancer of the upper gastrointestinal tract (mainly gastric), pulmonary (lung), urinary bladder, and skin (squamous cell) cancer. There was also a significantly increased risk of hepatobiliary cancer and lymphoma noted in this study.⁷

In the Netherlands, the IBD South Limburg (IBDSL) cohort was established to study cancer risk in IBD patients. The associations of cancer risk with disease phenotype and medication usage were examined as secondary outcomes. There were 1,157 CD patients in this cohort. This study demonstrated no increased risk of intestinal cancer compared with the background population. However, the risk for intestinal cancer was increased when patients had colonic CD involvement, with or without ileal involvement. The authors also observed this increase only in females, not in male patients with CD. No increased risk for intestinal cancer was noted based on age of IBD diagnosis, location of CD, CD diagnosis era, or CD duration. Increased risk of hematologic malignancies was noted in CD patients older than 40 years at the time of diagnosis. There was also a noted increased risk for skin cancer (melanoma and NMSC), which was associated with ileal CD. Squamous cell carcinoma (SCC) risk was associated with male gender and age more than 40 years

at the time of CD diagnosis. The risk of melanoma and basal cell carcinoma was similar to the background population. Overall cancer risk was noted to be increased in CD patients, and associated with male gender, age greater than 40 years at CD diagnosis, and ileal CD.⁸

The Florence Inflammatory Bowel Disease study examined the causes of death of IBD patients. There were 231 CD patients in this study. The authors noted an increased overall mortality in CD patients, and noted a higher rate of mortality from malignancies from any site. In particular, there was an increased risk of mortality from primary respiratory and brain malignancies. All-cause mortalities appeared to be stable over time for CD, but decreased for patients with UC.⁹

A single-center cohort study from Italy examined the clinical characteristics of IBD that are independent risk factors for cancer development. This study specifically examined cancer risk associated with thiopurine and anti-TNF use. There were 615 CD patients in this cohort study, 34 of whom were diagnosed with cancer (breast, gastrointestinal tract, and skin). Risk factors for cancer development included older age at the time of diagnosis and a fistulizing pattern of CD. Thiopurine and anti-TNF use were not associated with an increased cancer risk in CD.¹⁰

Skin Malignancies

Skin cancer is the most common form of malignancy in the United States and IBD has been strongly associated with skin cancer development. The underlying pathophysiology is hypothesized to be secondary to chronic inflammation, cellular damage, and underlying immune dysfunction leading to altered tumor surveillance. The use of immunosuppressive medications in the treatment of IBD has been shown to lead to a four- to seven-fold increased risk of skin cancer. About half of IBD patients are exposed to these immunosuppressive medications within 5 years of IBD diagnosis.¹¹

Although IBD may serve as a risk factor for nonmelanoma skin cancer (NMSC), in patients older than 50 years there appears to be no difference in IBD patients versus non-IBD patients. The highest and most consistent risk factor in NMSC is linked to thiopurine use.¹² This risk seems to be higher in patients with CD, and tends to increase with age.^{12,13} In the prospective French cohort study *Cancers Et Sur-risque Associé aux Maladies inflammatoires chroniques intestinales En France* (CESAME), the incidence of NMSC was also associated with thiopurine use, and increased with age. The highest rates of development were in current and former thiopurine users older than 65 years. It is unclear if the risk of NMSC persists after discontinuation of thiopurine use. The CESAME study noted increased risk with past use, inferring a persistent risk following thiopurine removal.¹⁴ Anti-TNF monotherapy has not been associated with an increased risk of NMSC, but concomitant use with thiopurine drugs increases the risk by almost fourfold.¹²

The role of IBD or IBD therapy on melanoma skin cancer is unclear. There is no significant association between thiopurine use and melanoma. The risk of melanoma with anti-TNF therapy is controversial. Long et al reported a twofold

increase in melanoma with anti-TNF therapy; however, other studies have not found this to be true.^{12,15,16}

Based on the increased risk of skin cancer development, IBD patients should protect themselves from the sun and undergo annual skin cancer screening exams, especially if they take a biologic or immunomodulating agent. Prevention efforts should also include limiting ultraviolet exposure and using sunscreen.

Oral Cancer

Oral cancer refers to cancers of the mucosal surfaces of the lips, floor of mouth, tongue, buccal mucosa, lower and upper gingival surfaces, hard palate, and retromolar trigone. Patients with IBD belong to the high-risk group of patients for developing precancerous and cancerous oral lesions, as is seen in other immunosuppressed patients.¹⁷ Immunosuppressive drugs (thiopurines, methotrexate, corticosteroids, and biologic therapies) contribute substantially to skin/lip and oral cancer development.

Thyroid Cancer

Inflammatory bowel disease has been associated with autoimmune thyroid diseases such as Hashimoto thyroiditis. A case-control study using the National Inpatient Sample demonstrated that CD is associated with a higher risk (OR: 2.3) for thyroid cancer.¹⁸

Cervical Cancer

A nested case-control study from Kaiser Permanente examined 427 CD patients and demonstrated a trend (45% greater) of elevated risk for cervical cancer for patients with IBD. CD patients who took 5-ASA, corticosteroids, and immune modulators had an elevated risk of cervical cancer, but the risk was not statistically significant.¹⁹ In a study from southern England, undertaken to determine the risk of cancer in cohort of patients with IBD, an increase in cervical cancer was observed in CD patients but not in UC patients.²⁰

Gastric Cancer

Since CD can affect any portion of the gastrointestinal tract, it is logical to think that chronic inflammation of the stomach could lead to an increased risk of gastric cancer. A meta-analysis of population cohort studies revealed that CD patients have an increased risk of stomach cancer.⁷ A retrospective review of Dutch IBD patients found that survival for gastric cancer patient is worse in those with IBD, and that early onset of IBD was associated with an increased risk of gastric cancer development.²¹

Small Bowel Malignancies

Small bowel adenocarcinoma (SBA) is a rare malignancy (2%), with 5-year survival rate of 30%.²² Unfortunately, symptoms

caused by a malignant obstruction due to small bowel malignancies are similar to benign strictures in CD. Ruffolo et al examined the clinical presentation of SBA in CD, and found that rectal bleeding and weight loss were unrelated to a diagnosis of cancer.²³ Two of the best indicators of malignancy are symptoms not relieved by medical management, and the abrupt onset of severe symptoms.

Patients with CD have a higher risk of developing SBA.²⁴ The exact risk is unknown; however, several meta-analyses have reported SIR of 27 to 33.²⁵⁻²⁷ A recent meta-analysis of 20 clinical trials estimated the incidence of SBA in CD patients as 0.3/1,000 patient-years, which was increased by a factor of 18.7 with respect to that found in age-matched controls.²⁸ After 25 years of ileal CD, the risk of SBA is 2.2%, accounting for 45% of gastrointestinal carcinomas.²⁵ A prospective study in France (CESAME) revealed the standard incident rate of SBA was 0.5/1,000 patient-years among patients with greater than 8 years of CD.¹⁴ There was no noted increased risk in patients with late-onset IBD.

SBA is usually found in an area of inflammation, which suggests that the sequence of carcinogenesis is inflammation-to-dysplasia-to-carcinoma. In terms of histology, patients with CD have a higher rate of mucinous SBA compared with de novo cases.²⁵ SBA tends to involve the distal small bowel, and occurs more often in younger-onset IBD. Age of cancer diagnosis is earlier than in sporadic cases.²⁹ Risk factors include distal jejunal/ileal CD, strictures and chronic penetrating disease, long disease duration, young age at diagnosis, male sex, use of steroids and immunomodulators, small-bowel bypass loops, stricturoplasties, and environmental factors.³⁰

In terms of prognosis, a large-scale retrospective cohort study utilizing the Surveillance, Epidemiology, and End Results (SEER) database found that CD-associated SBA patients present at earlier stages than de novo SBA and receive more surgery, but have similar rates of chemotherapy, and similar overall survival and cancer-specific survival. Therefore, the authors concluded that CD does not worsen survival following treatment of SBA.³¹ A retrospective cohort study examining 484 patients who were undergoing resections for stricturing CD found 6 patients (1.2%) with incidental SBA (stages I-IV). After a median follow-up of 2 years, only one patient was still alive. The authors concluded that the frequency of incidental SBA in patients undergoing surgery for stenotic CD is low, but associated with poor prognosis.³²

Early diagnosis is key to successful treatment of SBA in CD. In most cases, SBA is not diagnosed preoperatively (<14% of cases).³³ Of patients with incidental SBA, 30 to 35% will have metastatic disease, while 55% have node-positive disease.^{34,35} Similar to de novo SBA, surgery is the mainstay of treatment of SBA in CD. However, as noted earlier, most SBAs are diagnosed intraoperatively, and half of these carcinomas are not even suspected at the time of operation. These malignancies are only diagnosed upon histological examination of the surgical specimen. Therefore, half of these patients will not have undergone an aggressive lymphadenectomy, the standard of care for treatment of SBA.

Due to low incidence of SBA, and the absence of primary prevention data, there are no current screening guidelines. Capsule endoscopy has an 83.3% sensitivity for tumor detection, with a negative predictive value of 97.6%.³⁶ Currently, for early detection of SBA, patients experiencing a prolonged duration of small bowel stricturing disease, symptomatic strictures after a prolonged period of remission, or small bowel strictures refractory to medical management are required to undergo further evaluation for SBA. Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID) suggests that prolonged use of salicylate therapy can decrease the risk of SBA in patients with longstanding ileal CD.³⁷ They also note that surgery has a very important role in SBA prevention, and thus advocate for prophylactic surgery. However, as noted earlier, SBA is rare, and to prevent SBA the number of patients needed to treat (undergo surgery) would be unnecessarily high.

Peritoneal Mesothelioma

This malignancy occurs rarely in patients with IBD, but has only been observed in the setting of CD, not in UC. There is one case report of three patients with peritoneal malignant mesothelioma. All patients carried the diagnosis of CD for over 3 years.³⁸

Cholangiocarcinoma

Cholangiocarcinoma (CC) is a rare bile duct cancer with an incidence of less than 1/100,000. Epidemiological studies have found that primary sclerosing cholangitis (PSC), liver fluke infection, and cholecystitis are risk factors in CC development.³⁹ PSC affects up to 3.6% of CD patients and 5% of UC patients.⁴⁰ IBD itself is a risk factor for CC, independent of PSC presence, with a fourfold increased incidence compared with non-IBD patients. In patients with IBD and PSC, the lifetime risk of CC is 10 to 15%. A multi-institutional cohort study of IBD patients in the United States was examined to determine the risk of extraintestinal and digestive malignancies. There were 5,506 patients with CD, and 5,522 patients with UC. Upon examination, 224 patients (2%) had PSC, and those patients had an increased risk of CC (OR: 55.31).⁴¹ A cohort study of 199 IBD patients with PSC from Sweden also found an increased risk of CC.⁴²

The Danish population-based study revealed that extrahepatic CC is increased in patients with CD.⁴³ For this study, the authors utilized the National Registry of Patients and the Danish Cancer Registry. In the study, 10,430 patients had CD. In patients with IBD, a predominance of male patients developed CC, versus no gender predominance in non-IBD patients. In those patients with IBD, twice as many patients with UC were diagnosed with CC over patients with CD. CD patients were 6 years younger at diagnosis than UC patients. However, in patients who do not have PSC, there was no evidence linking CC with IBD. A meta-analysis of several population studies was performed, demonstrating that patients with CD as well as those with UC are at increased risk of CC, though the risk in CD patients was found to be lower.⁴⁴

Prognosis is poor for patients with CC, with a life expectancy of less than 1 year after diagnosis, whether or not the patient has IBD. There are no current screening guidelines for CC in IBD, with or without PSC.

Pancreatic Cancer

A multi-institutional cohort study of IBD patients in the United States was examined to determine the risk of extraintestinal and digestive malignancies. There were 5,506 patients with CD, and 5,522 patients with UC. Overall, 224 (2%) patients had PSC. Those patients with PSC were noted to have an increased risk of pancreatic cancer (OR: 11.22).⁴¹

Colorectal Cancer

The association between IBD and colorectal cancer (CRC) has been recognized for almost a century. Chronic inflammation is known to promote carcinogenesis in combination with genetic factors. Instead of the adenoma-to-carcinoma sequence that is associated with non-IBD colorectal cancer, in IBD the sequence of inflammation–dysplasia–carcinoma is thought to occur. Colorectal tumors that develop in patients with IBD have genetic features that are distinct from sporadic colorectal tumors. There is an early loss of p53 function, unlike sporadic colorectal cancers. Almost all sporadic CRC tumors have altered WNT pathways, most commonly in adenomatous polyposis coli (APC). By contrast, there is less APC inactivation, but a higher relative number of inactivating mutations in the SOX9 transcription factor, an intestinal stem cell marker that antagonizes WNT/beta catenin signaling in patients with IBD. There are also recurrent mutations in components of the Rho and Rac GTPase network and cytokine signaling that support the role for non-canonical WNT signaling in IBD-associated neoplasia. The prevalence of KRAS mutations in IBD CRC is much lower, while this is not true for SMAD4 and PI3KCA. Clinicopathological and molecular profiles (*BRAF/KRAS/NRAS*) of CD-associated colorectal cancer are similar to those observed in sporadic colorectal cancer.⁴⁵ Alterations of the colonic flora has also been speculated as an etiology for carcinogenesis in IBD. These findings could potentially be used in the future to develop disease-specific markers for diagnosis and treatment of patients with IBD and CRC.

Data on the relative risk of colorectal cancer in IBD patients are highly variable. In a meta-analysis, the overall incidence was 5/1,000 person-years in the United States, 4/1,000 in the United Kingdom, and 2/1,000 in Scandinavia.⁴⁶ Due to improvements in medical management of patients with IBD, it has been suggested that an increased risk for colorectal cancer may be no longer present. One study demonstrated that the risk for colorectal cancer in patients with Crohn's colitis is similar to UC, with an estimated 8% incidence after 20 years of disease.⁴⁷ Recent studies have shown a progressive decrease in risk of CRC in IBD patients over the last two decades. Surveillance programs and new therapies (top-down) might be the reason for this decrease.⁴⁸ In 2007, Von Roon et al reported a relative risk

of colon cancer of 2.59 in CD patients.²⁶ Laukoetter et al in a meta-analysis reported an incidence rate of 0.5/1,000 patients per year. Patients with IBD develop CRC at a younger age and have a slight increase in mortality at 5 years compared with the general population.²⁸ Canavan et al reported a cumulative incidence of colorectal cancer of 2.9% at 10 years, 4.6% at 20 years, and 8.3% at 30 years.⁴⁹ Finally, a study by Von Roon et al reported that in 885 patients with ileocolic disease the relative risk was 4.63, and 704 had colonic CD with a relative risk of 13.36, and those with extensive Crohn's colitis have a relative risk of 18.2.²⁶

Risk factors for CRC development include longer disease duration, extent of disease, young age at diagnosis, PSC, severity of inflammation, and family history of colorectal cancer. Patients with CD diagnosed at a young age have a significantly increased relative risk of CRC. Choi and Zelig reported an average age of 55 for onset of CRC in patients with CD, versus 65 in patients without CD.⁵⁰ PSC is a risk factor for colorectal cancer development in IBD patients, more so in UC patients compared with CD patients. Lindström et al demonstrated that patients with PSC and CD were more likely to develop CRC or dysplasia compared with control CD patients without PSC.⁵¹ In a recent meta-analysis of cohort studies, the risk of CRC in CD patients had an OR of 1.9, while the risk of small bowel cancer was 27.1.²⁷ A study of 3,454 patients in Japan demonstrated that the incidence of intestinal cancer associated with CD has increased yearly. Cancer most often developed on the left side of the colon, in particular in the rectum and anal canal. Four percent were diagnosed intraoperatively, while the remaining 20% were diagnosed pathologically after surgery.⁵²

The Danish cohort study found that those with CD CRC had lower frequency of Dukes A and B stage tumors, and higher frequency of Dukes C and D. The 5-year adjusted mortality rate ratios for patients with CD was 1.26, compared with patients without IBD.⁵³ The Irish population study found that IBD patients are diagnosed at a younger age (7 years younger), but that they survived 3 years longer. When propensity matching was done, there were no significant differences in survival.⁵⁴

When examining the chemotherapy tolerance and oncologic outcomes of patients with CRC with IBD, those with IBD have more treatment alterations (mostly delays) than those without IBD. Patients with stage IV CRC with IBD have shorter survival than patients without IBD.⁵⁵

A study from Finland followed up patients for 20 years to evaluate the efficacy of endoscopic surveillance in colorectal cancer prevention. Of the 1,915 IBD patients in this study, 550 patients had CD. The colorectal cancer risk for all IBD patients was 3.09, while the risk for patients with CD affecting the colon was 3.62. The authors concluded that the risk of colorectal cancer in this cohort was significantly increased compared with the general population. In their population, they did not find that surveillance prevented the development of colorectal cancer, and therefore concluded that endoscopic surveillance was of limited benefit. How-

ever, they go on to recommend intensive endoscopic surveillance in patients in the setting of risk factors such as family history, extensive colitis with active endoscopic or histologic inflammation, PSC, and pseudopolyposis.⁵⁶ Since Crohn's colitis is one of the risk factors for colorectal cancer, there have been studies to assess colonoscopic surveillance for detecting cancer in patients with Crohn's colitis. One study evaluated 904 screening/surveillance examinations on patients with Crohn's colitis. The study detected cancer or dysplasia in 5.6% of patients. Noted risk factors for development of dysplasia include younger age at diagnosis, longstanding disease, and greater interval between exams.⁵⁷ The most recent guidelines from the Crohn's and Colitis Foundation of America recommend a screening colonoscopy 8 to 10 years after the onset of CD involving at least one-third of the colon. If the screening colonoscopy is negative for dysplasia, surveillance examination is recommended every 1 to 2 years thereafter.⁵⁸

Patients with CD face an 80% lifetime risk of requiring a surgical resection.³² Strictures are a common indication for surgical intervention. Unfortunately, symptoms related to a malignant stricture are very similar to those of a benign stricture. The majority of colorectal cancers in CD are not diagnosed preoperatively.⁵⁹ In terms of extent of resection, surgical treatment of a malignant stricture is approached differently from a benign stricture. Therefore, an incidental postoperative diagnosis of a malignancy poses an oncologic issue resulting in inadequate staging. A study by Kristo et al examined the frequency and clinical course of incidental colorectal cancer in patients undergoing surgery for structuring CD. This was a single-institution retrospective review of 484 patients. At histological evaluation, 1.4% had colon cancer, 66.7% had rectal cancer, and 85.7% were found incidentally. At 2-year follow-up, 83.3% of the patients had died, resulting in the authors' conclusion that poorer prognosis is associated with incidental diagnosis of malignancy.³²

Anal Cancer

Patients with chronic perianal CD are at a substantial risk of developing squamous cell carcinoma (SCC) or adenocarcinoma arising from the epithelium of fistula ulcerations or strictures. However, population-based studies on the incidence of anal cancer in IBD patients are lacking. In a systematic review that included 11 studies, the incidence of SCC of the anus was comparable to the general population; it should be noted that this review excluded cancers arising from fistulas. In this review, females and HIV-positive patients were at higher risk. The authors also noted that patients with IBD were more likely to develop anal cancer at a younger age compared with the general population. Many of the cases of anal SCC that developed in patients with CD occurred in the context of the patient having CD longer than 10 years, with concomitant chronic anal disease. Early disease onset, disease duration exceeding 10 years, chronic colitis with high inflammatory activity, and persistence of chronic fistulas and stenosis all seem to be associated with

malignant transformation.⁶⁰ The prevalence of HPV, the most common risk factor for anal cancer development, has not been established in IBD patients. There is no specific data regarding anal adenocarcinoma in IBD patients. The largest systematic review of the malignant transformation of perianal fistulas in CD identified adenocarcinoma as more frequent than SCC. The authors noted a female predominance, with female patients developing cancer at younger ages. This review notes a time interval greater than 15 years between CD diagnosis and cancer diagnosis of the anus. Most of the fistulas examined were complex in nature, arising from the rectum rather than the anus.⁶¹ The prognosis for IBD patients with anal cancer is poor, with 5-year survival rates of 37%, in contrast to 60% in the general population.⁶² The hypothesis behind this poor prognosis is a delay or difficulty in making the diagnosis. Examination under anesthesia with biopsy is required when patients note a change in their anal symptom, especially if they are experiencing new, increasing, unexplained pain.⁶³

Respiratory Tract Malignancies

Respiratory malignancies are rare in IBD. However, the Florence Inflammatory Bowel Disease study, which included 231 CD patients, evaluated over 5,128 person-years. The authors noted an increased risk from dying from cancer of respiratory tract, with an increased risk of diseases of the respiratory system.⁹ The IBSEN study, which contained 237 CD patients, exhibited increased standard incidence rate of 2.91 for trachea/lung cancer in CD patients compared with controls ($p = 0.039$).⁴ Finally, a meta-analysis of several population-based cohort studies found an increased risk for lung cancer in CD patients (SIR: 1.82).⁷

Lymphoma

Lymphoma is a cancer of lymphocytes. It is divided into Hodgkin's lymphoma (HL) and NHL, based on the type of lymphocyte affected. CD patients have a higher incidence of lymphoma compared with the general population. This was noted in a Swedish study and seen in the Canada population-based study.^{64,65} In a population study of 9,462 immunosuppressive medication-naïve CD patients, the risk of lymphoma was twice as high as the general population, suggesting that the excess risk is indeed related to CD itself.²⁶ In the Finnish study, NHL was slightly increased in CD patients, but the risk was more pronounced in those patients over the age of 75 who carried the diagnosis of CD for more than 3 years.⁶

The incidence of lymphoma is increased in IBD patients, especially in patients on immunosuppressive medications. Lymphoma, particularly NHL, is associated with thiopurine use, and is more prevalent in older patients. The CESAME study determined that when compared with those without previous thiopurine exposure, IBD patients 50 to 65 years old who are actively taking thiopurines had a sixfold higher incidence of lymphoproliferative disorders such as lymphoma. The absolute risk was noted to be highest in those

patients over the age of 65. Finally, those patients with concomitant anti-TNF and thiopurine use had the highest SIR of lymphoproliferative disease.¹⁴ A recent meta-analysis found that compared with the general population, there is a nearly sixfold increase of NHL and HL in patients with at least 1 year of exposure to thiopurines, and that this risk does go away with cessation of thiopurine use. In a meta-analysis of several cohort studies and nationwide studies, IBD patients treated with thiopurines had a three- to fivefold increased risk of developing lymphoproliferative disorders, especially hepato-splenic T cell lymphoma, Epstein-Barr virus related posttransplant lymphoproliferative disease, and post-mononucleosis lymphoproliferations.⁶⁶⁻⁶⁸ Jess et al found that CD patients were at higher risk for lymphoma, particularly NHL, and this effect was independent of thiopurine exposure.⁶⁹ Finally, a meta-analysis evaluating anti-TNF therapy alone as a risk factor for lymphoma development did not report an increased risk when anti-TNFs were utilized in isolation.⁷⁰

Urinary Tract Cancer

In a prospective multicenter, nested case-control study from Italy that included 21,953 CD patients, the authors found an increased incidence of urinary tract cancers in patients with IBD (regardless if UC or CD). A meta-analysis of urinary tract cancers in all adult patients found an increased risk of urinary cancer in CD patients (SIR of 2.03).⁷ In the Danish registry, an examination of risk factors for urinary tract cancer in CD patients revealed that nonusers of AZA were at increased risk for urinary tract cancers. The CESAME study found a sixfold increase in UT cancers with thiopurines in males older than 65 years.⁷¹

Breast Cancer

Breast cancer is one of the most common cancers found in female patients. Several studies have identified increased breast cancer risk in patients with IBD.⁴

Role of Medications to Treat CD in Malignancy

Immunosuppression plays an important role in carcinogenesis in general. There is a fine balance between decreasing inflammation to prevent carcinogenesis and the loss of cancer surveillance due to immunosuppression. Patients with IBD being treated with thiopurines are at increased risk for cancer. Thiopurines incorporate 6-thioguanine instead of guanine during DNA replication in target cells. The error stimulates the mismatch repair system, but repair is incomplete and thus leads to cell death instead of recovery. The CESAME and Danish studies examined the risk associated with thiopurine exposure for cancer in general, as assessed by multivariate analysis with adjustments for age, sex, and IBD subtype. The risk associated with cancer development in the CESAME cohort was 68% and it was 41% in the Danish study.^{5,14}

A recent systematic review of pooled data from 22 randomized controlled trials found no significant difference between anti-TNF medications or placebo groups in terms of the frequency of malignancies diagnosed within the first year of treatment.⁷⁰ A pooled analysis of data from clinical trials of adalimumab use in IBD was also published in 2014, and revealed no evidence of excess risk of cancer in general, but the risk was significantly increased in patients receiving adalimumab and other immunomodulators.⁷² A nationwide study from Denmark found no evidence that TNF- α antagonists increased the overall risk of cancer in IBD patients over a median follow-up of 3.7 years.⁷³ A pooled analysis of 1,594 CD patients demonstrated that the incidence of malignancy with TNF- α inhibitors was not greater than the general population, but coadministration of immunomodulatory therapy was associated with a greater than expected incidence of malignancies.⁷²

Conclusions

Crohn's disease is associated with several intestinal and extra-intestinal cancers. Further, in the setting of CD, several disease characteristics and therapies are linked to an increased risk of carcinoma development. These identifiable factors can be utilized to determine the risk of cancer formation.

Conflict of Interest

None declared.

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