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BRIEF ARTICLE

Risk of cancer, with special reference to extra-intestinal malignancies, in patients with inflammatory bowel disease

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Abstract

AIM: To determine the incidence and characteristics of intestinal and extra-intestinal cancers among patients with inflammatory bowel disease in a Spanish hospital and to compare them with those of the local population.

METHODS: This was a prospective, observational, 7-year follow-up, cohort study. Cumulative incidence, incidence rates based on person-years of follow-up and relative risk were calculated for patients with inflammatory bowel disease and compared with the background population. The incidence of cancer was determined using a hospital-based data registry from Hospital Universitario de Fuenlabrada. Demographic data and details about time from diagnosis of inflammatory bowel disease to occurrence of cancer, disease extent, inflammatory bowel disease treatment, cancer therapy and cancer evolution were also collected in the inflammatory bowel disease cohort.

RESULTS: Eighteen of 590 patients with inflammatory bowel disease developed cancer [cumulative incidence = 3% (95%CI: 1.58-4.52) *vs* 2% (95%CI: 1.99-2.11) in the background population; RR = 1.5; 95%CI: 0.97-2.29]. The cancer incidence among inflammatory bowel disease patients was 0.53% (95%CI: 0.32-0.84) per patient-year of follow-up. Patients with inflammatory bowel disease had a significantly increased relative risk of urothelial carcinoma (RR = 5.23, 95%CI: 1.95-13.87), appendiceal mucinous cystadenoma (RR = 36.6, 95%CI: 7.92-138.4), neuroendocrine carcinoma (RR = 13.1, 95%CI: 1.82-29.7) and rectal carcinoid (RR = 8.94, 95%CI: 1.18-59.7). Colorectal cancer cases were not found.

CONCLUSION: The overall risk of cancer did not significantly increase in our inflammatory bowel disease patients. However, there was an increased risk of urinary bladder cancer and, with less statistical power, an increased risk of appendiceal mucinous cystadenoma and of neuroendocrine tumors. Colorectal cancer risk was low in our series.

Key words: Extra-intestinal cancer; Inflammatory bowel disease; Cancer risk; Background population; Urothelial carcinoma; Appendiceal mucinous cystadenoma; Neuroendocrine carcinoma; Rectal carcinoid

Core tip: Several studies have reported increased rates of colorectal cancer in patients with inflammatory bowel diseases but limited data are available regarding incidence of extraintestinal malignancies in these patients. The present study demonstrates a higher risk of urinary bladder cancer, mucinous cystadenoma of the appendix and of neuroendocrine tumors, and a low colorectal cancer risk, in patients with inflammatory bowel dis-

ease in our environment. We raised the question of whether current cancer screening strategies need to be reviewed and adapted to the characteristics of each patient.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic condition that involves several portions of the gastrointestinal tract and includes periods of activity of variable severity. This pathology can be associated with involvement of other organs in 35% of patients with IBD, with rheumatologic, ophthalmologic and dermatologic disorders being the most common extra-intestinal manifestations[1,2].

To date, a number of studies have reported increased rates of colorectal cancer (CRC) in patients with IBD[3-8]. The reported risk varies widely between studies due to the different methodologies used. The current trend published in the most recent studies suggests a lower rate of CRC than previously described[9]. The location and duration of IBD[6-12], as well as previous family history of CRC[13,14] and primary sclerosing cholangitis[15,16], have been described as determinant factors associated with CRC. Additionally, the severity of chronic inflammation of the colon is another important risk factor for this kind of cancer in patients with both ulcerative colitis (UC) and Crohn's disease (CD)[17,18]. IBD-specific and non-IBD specific medications have also been associated with an increased or decreased risk of CRC[19,20].

On the other hand, limited and disparate data are available for incidences of extra-intestinal malignancy in these patients[21-24]. In addition, several of these studies are not population based, or have retrospective designs. Other studies only contain information on cumulative cancer risk or represent select populations.

We present a prospective, cohort study designed to determine the incidence and characteristics of intestinal and extra-intestinal cancers among patients with IBD in our environment and to compare these incidences with those of the local population.

MATERIALS AND METHODS

Patients and design

This was a prospective, observational, 7-year follow-up, cohort study. We identified all cases of cancer observed between January 2005 to the end of December 2011 in a cohort of patients diagnosed with IBD in our hospital (n = 590). Diagnosis of IBD was confirmed by routine clinical, radiological, endoscopic and histological criteria[25]. The incidence and characteristics of intestinal and extra-intestinal cancers were obtained in the IBD group and were compared to those of the background population (n = 222219). The incidence of cancer in our population was determined using a hospital-based data registry from Hospital Universitario de Fuenlabrada. This registry contains all cases of cancer diagnosed and/or treated in a 7-year follow-up period in the patients of our area. In each case, cancer was confirmed by a pathologist who classified the lesions according to the International Classification of Diseases for Oncology (ICD-O-3 histology codes).

Demographic data and details of time from diagnosis of IBD to occurrence of cancer, disease extent according to the Montreal Classification[26], IBD treatment, cancer therapy and cancer evolution were also collected in the IBD cohort. The study was approved by the Research Ethics Committee at Hospital Universitario de Fuenlabrada.

Statistical analysis

The descriptive analysis of quantitative variables calculated the mean and standard deviation or median and interquartile range (IQR) depending on whether or not the data were normally distributed. Qualitative variables were expressed as percentages with 95%CI. Cumulative incidences for each cancer were calculated for patients with IBD and compared with the background local population. The incidence rates based on person-years of follow-up and relative risk (RR) with 95%CI were also analysed. Analysis was performed assuming that the IBD cohort had the same risk of developing malignancies as the general population.

RESULTS

Eighteen of 590 patients with IBD were diagnosed with cancer between 2005 and 2011 in our hospital. The clinical and demographic characteristics of all patients with IBD are shown in Table 1. The cumulative incidence of cancer was 3% (95%CI: 1.58-4.52) *vs* 2% (95%CI: 1.99-2.11) in the local population; RR = 1.5; 95%CI: 0.97-2.29. The mean age in IBD patients with a diagnosis of cancer was 49.9 ± 11.9 years; 61.1% were males. In the cohort of patients with IBD, 9 had CD (50%) and 9 UC (50%). The clinical characteristics of these patients are shown in Table 2. By type of IBD, the cumulative incidence was 2.8% (95%CI: 0.86-4.84) for CD *vs* 3.5% (95%CI: 1.06-5.92) for UC patients. At the time of cancer diagnosis, 33% of patients were being treated with thiopurines [median duration of treatment was 6 mo (IQR 2.4-27)], and one patient (6%) was on anti-tumour necrosis factor-alpha therapy (39 mo of treatment with adalimumab). The median time from IBD diagnosis to cancer development was 54 mo (IQR 21-111). The cancer incidence among IBD patients was 0.53% (95%CI: 0.32-0.84) per patient-year of follow-up.

Ten different kinds of cancers were identified. The

Table 1 Clinical features of the total studied inflammatory bowel disease patients *n* (%)

Clinical features	Value
Age (yr, mean ± SD)	43.4 ± 13.8
Gender	
Female	305 (51.70)
Male	285 (48.3)
Type of IBD	
CD	313 (53.05)
UC	256 (43.39)
IBDU	21 (3.56)
Disease extension (UC)[1]	
Proctitis	61 (23.83)
Left-sided colitis	124 (48.44)
Pancolitis	71 (27.82)
Age at diagnosis (CD)[1]	
A1 < 17	24 (7.67)
A2 17-40	208 (66.45)
A3 > 40	81 (25.88)
Disease location (CD)[1]	
L1 ileal	112 (35.78)
L2 colic	76 (24.28)
L3 ileocolic	111 (35.46)
L4 upper gastrointestinal tract	6 (1.92)
L1 + L4	5 (1.60)
L3 + L4	3 (0.96)
Behaviour (CD)[1]	
B1 non-stricturing non-penetrating	179 (57.19)
B2 stricturing	30 (9.58)
B3 penetrating	41 (13.10)
B1 + perianal disease	51 (16.29)
B2 + perianal disease	1 (0.32)
B3 + perianal disease	11 (3.52)
Immunosuppressive or biological treatment	
Thiopurines	259 (43.90)
Anti-TNF-α drugs	84 (14.23)

[1]In accordance with the Montreal classification. IBD: Inflammatory bowel disease; IBDU: Inflammatory bowel disease type unclassified; CD: Crohn's disease; UC: Ulcerative colitis.

Table 2 Clinical features of the cohort of patients with inflammatory bowel disease and cancer diagnosis *n* (%)

Features	Value
Disease extension (UC)[1]	
Proctitis	1 (11.1)
Left-sided colitis	4 (44.45)
Pancolitis	4 (44.45)
Age at diagnosis (CD)[1]	
A2 17-40	8 (88.89)
A3 > 40	1 (11.11)
Disease location (CD)[1]	
L1 ileal	4 (44.45)
L2 colic	2 (22.22)
L3 ileocolic	2 (22.22)
L3 + L4 upper gastrointestinal tract	1 (11.11)
Behaviour (CD)[1]	
B1 non-stricturing non-penetrating	7 (77.78)
B2 stricturing	1 (11.11)
B1 + perianal disease	1 (11.11)
Treatment at time of cancer diagnosis	
Aminosalicylates	10 (55.56)
Thiopurines	6 (33.34)
Anti-TNF-α drugs	1 (5.55)
Nonspecific inflammatory bowel disease treatment	1 (5.55)
Immunosuppressive or biological treatment previous cancer diagnosis	
Thiopurines	1 (5.55)
Anti-TNF-α drugs	1 (5.55)

[1]In accordance with the Montreal classification. CD: Crohn's disease; UC: Ulcerative colitis; TNF-α: Tumor necrosis factor α.

Table 3 Specific cancers diagnosed in the cohort of patients with inflammatory bowel disease between 2005 and 2011

Location	*n*	Histological type
Urinary bladder	4	Urothelial carcinoma
Breast	3	Carcinoma
Skin	1	Melanoma
	2	Basal cell carcinoma
Appendix	2	Mucinous cystadenoma
Stomach	1	Adenocarcinoma
Pancreas	1	Adenocarcinoma
Lung	1	Adenocarcinoma
Liver	1	Hepatocellular carcinoma
Small intestine	1	Neuroendocrine carcinoma
Rectum	1	Carcinoid

specific types of cancer observed in the cohort of IBD patients are shown in Table 3. Compared with the local population, patients with IBD had a significantly increased RR of urothelial carcinoma, mucinous cystadenoma of the appendix, neuroendocrine carcinoma and rectal carcinoid (Table 4). The RR of breast, skin, stomach, pancreas, lung and liver cancers were not significantly different with respect to the background local population (Table 4). CRC diagnoses were not found, and only two patients had biopsies with low grade dysplasia despite dysplasia screening by colonoscopy being performed following standard recommendations[27].

All patients with a diagnosis of urinary bladder cancer were men: 2 UC and 2 CD, 1 smoker and 3 former smokers. All patients with breast cancer had a previous family history (none of the remaining patients had family history for other types of tumours).

Regarding the evolution of cancer, 16 of the 18 patients diagnosed with cancer (88.9%) needed oncological surgery and 27.7% (n = 7) were treated with chemotherapy or radiation therapy. Treatment was maintained in 50% of patients on thiopurines at the time of their cancer diagnosis. In the remaining patients, immunosuppressive therapy was withdrawn and in only one of them was thiopurine therapy reintroduced three years later in agreement with the oncologist's recommendations. An association between thiopurine treatment and malignancy risk was not found. Adalimumab treatment was also withdrawn after the cancer diagnosis. Patients were followed up for an average of 3.5 ± 2.3 years from tumour diagnosis. During this period, two patients died (11.1%) due to cancer (patients with lung and liver cancer diagnoses) and 3 (16.7%) had tumour recurrence.

DISCUSSION

The present cohort study of patients with IBD revealed

Table 4 Cumulative incidences in both the inflammatory bowel disease cohort and the non-inflammatory bowel disease cohort and relative risk for different types of cancer

Cancer site	Cumulative incidence in IBD cohort	Cumulative incidence in local population	RR	95%CI
Urinary bladder	0.68	0.13	5.23	1.95-13.87[a]
Breast	0.51	0.26	1.95	0.63-5.87
Melanoma	0.17	0.06	2.56	0.34-17.63
Basal cell carcinoma	0.33	1.26	0.26	0.06-1.00
Appendix	0.33	0.009	36.6	7.92-138.4[a]
Stomach	0.17	0.06	2.83	0.41-20.9
Pancreas	0.17	0.028	6.07	0.84-40.4
Lung	0.17	0.067	2.54	0.34-17.6
Liver	0.17	0.037	4.59	0.64-32.5
Small intestine	0.17	0.013	13.1	1.82-29.7[a]
Rectum	0.17	0.019	8.94	1.18-59.7[a]

[a]$P < 0.05$. IBD: Inflammatory bowel disease.

that the overall risk of cancer did not significantly increase in our IBD patients compared to the background population. However, the study found patients with IBD to have an increased risk of developing urothelial carcinoma and, with less statistical power, an increased risk of mucinous cystadenoma and neuroendocrine tumours.

The results obtained in our population regarding overall risk of cancer and risk of urinary bladder cancer are in accordance with those reported previously by Pedersen *et al*[23]. The association between CD and urinary bladder cancer described in other populations by other authors[23,28] could be related to the high prevalence of smokers. Pedersen *et al*[23] explain in their meta-analysis that tobacco smoking could have a causal role in the development of a number of cancers including urinary bladder cancer. They did not find this association in UC patients. In our study, out of the two patients diagnosed with urothelial carcinoma with UC and two patients with CD, only one patient was a smoker at time of cancer diagnosis, while the remaining three patients were former tobacco users. Although different factors may be involved in the development of bladder cancer, the results obtained in several studies, including our work, indicate that tobacco could be a key factor and it would be recommended to encourage CD patients to quit smoking. A recent publication finds that the risk of bladder cancer in former smokers remains elevated more than 32 years after quitting, even among those with moderate smoking histories[29]. Nonsteroidal anti-inflammatory drugs seem to have a chemo-preventive role in urothelial carcinoma of the bladder in subjects who have quit for long periods[30]. Dietary factors may also affect the risk of these carcinomas[31-33]. Ros *et al*[32] suggest that high consumption of certain types of vegetables and fruits may reduce the risk of aggressive or non-aggressive urothelial cell carcinoma of the bladder.

On the other hand, the increased risk of appendiceal mucinous cystadenoma and neuroendocrine tumours observed in the present study were not described before in the meta-analysis carried out by Pedersen *et al*[23].

Mucocele of the appendix is a rare group of lesions that includes four histological types: retention cyst, mucosal hyperplasia, cystadenoma and cystadenocarcinoma. In our study, IBD patients were at an increased risk of mucinous cystadenoma of the appendix. Although a causal relationship between IBD and this type of mucocele cancer is still being elucidated, some authors have suggested that obstruction of the appendiceal orifice might play a role in the development of appendiceal mucocele. This obstruction could be due to inflammation by IBD or associated with colorectal neoplasm[34-36].

Several publications suggest that appendectomy appears to reduce the extent and recurrence of UC and is associated with a less severe course of this pathology[37,38]. These findings could support the hypothesis that an appendicectomy related to mucinous cystadenoma diagnosis may have a secondary beneficial effect on the severity and the course of UC. In contrast, data regarding CD patients are controversial[39,40]. In our series, the two patients with mucocele of the appendix had CD and ileocolic involvement.

The present study also identified one case of neuroendocrine carcinoma of the small intestine and one carcinoid of the rectum. Carcinoids and, in particular, neuroendocrine neoplasms other than carcinoids are uncommon tumours and are infrequently described in UC and CD. Some authors suggest that a permanent inflammation at the level of the colon could increase the number of neuroendocrine cells and help the development of this kind of neoplasm[41]. Greenstein *et al*[42] included eleven patients with IBD-associated carcinoid tumours (11 in the appendix, 2 in the ileum). They found that all carcinoids were diagnosed incidentally after surgery for IBD. These findings are consistent with our results, in which the patient was diagnosed with carcinoid of the rectum during a colectomy. Sigel *et al*[43] evaluated 14 cases of neuroendocrine neoplasms. All of the tumours arose in areas with IBD involvement. Tumour sites were the rectum (6 cases), appendix (4 cases), small bowel (2 cases) and sigmoid colon (2 cases). Conversely, in our case, the patient with neuroendocrine carcinoma of the small intestine had UC (extensive colitis) without ileum involvement.

Concerning the IBD-specific medications, it has been reported that patients with IBD who receive thiopurines are at increased risk of non-melanoma skin cancer or lymphoproliferative disorders[44,45]. However, data about other malignancies are less clear. Moreover, studies in patients taking azathioprine for a long time are scarce. In the present study, a possible effect of thiopurines on the risk of extra-colonic cancer was evaluated but a clear association between variables was not found; this probably could be due to the small size of our series and the short period of treatment.

A higher RR of CRC has been described in patients with IBD[5,7,46]. However, in the present study, CRC was not found despite dysplasia screening by colonoscopy. These data are consistent with current publications

that show a lower incidence of CRC than previously reported[9,47-49]. Some authors have found that only IBD patients with a longer disease duration, extensive disease and an IBD diagnosis at a young age have a significantly higher risk of CRC. IBD patients without these characteristics would have a similar risk for colorectal cancer as the general population[9,47,48,50]. IBD-specific and non-IBD specific medications have also been associated with an increased or decreased risk of CRC[19,20,51]. The anti-inflammatory action of IBD drugs such as 5-ASA seems to have a protective effect on the occurrence of CRC[52,53]. Jess *et al*[48] suggest that changes in IBD-specific treatment may reduce the risk of CRC among UC patients. Currently, it has also been suggested that agents that control chronic inflammation, such as thiopurines and tumour necrosis factor-alpha antagonists, could have a protective role against the development of CRC[48,50,54,55].

Study design could also have an influence on the CRC risk obtained. Patients with IBD from population-based cohorts have a lower risk for CRC than reference centre cohorts[47]. Regarding this fact, we present a cohort study that included all patients with IBD followed in our hospital. We believe that this cohort of patients is a good representative for the entire IBD population in our area. Our hospital is a reference centre with a specific unit for patients with IBD. There are no other hospitals or reference centres in our area. In our opinion, only an insignificant number of patients with IBD are treated by general practitioners at primary care centres. In addition, the incidence of IBD is not lower than that expected for our population: 590 cases in a population of 222219 people. The present manuscript has the value of its prospective design and its well-defined population using a data registry that contains all cases of cancer diagnosed and/or treated in a 7-year follow-up period. In this regard, the results obtained in this survey probably will serve as a base for future studies aimed at elucidating the real risk of extra-intestinal malignancies and the utility of current cancer screening strategies used in these patients.

However, the observations obtained in the present study should be considered with caution due to the potential limitations of this study, which included a small number of cases over a limited period of time.

In conclusion, our prospective study revealed that patients with IBD in our area have a similar overall risk of cancer as the local population. However, they are at a higher risk of developing specific types of extra-intestinal cancers such as bladder, appendiceal cystadenoma or neuroendocrine tumours. Smoking and specific IBD characteristics could be risk factors associated with the development of cancer, so it is recommended that patients be encouraged to quit smoking. On the other hand, the present study did not show a higher risk of CRC, in line with recent publications that suggest a lower incidence of CRC than previously reported. Further evaluations are required to know if the current CRC screening strategies need to be reviewed and adapted to patients according to the characteristics of their IBD.

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COMMENTS

Background

To date, many studies have analyzed the rates of colorectal cancer in patients with inflammatory bowel disease. The reported risk varies widely between studies due to the different methodologies used. However, limited and disparate data are available for incidences of extra-intestinal malignancy in these patients.

Research frontiers

Inflammatory bowel disease is a chronic condition that involves several portions of the gastrointestinal tract but also can be associated with involvement of other organs. Accordingly with the special characteristics of this pathology, the risk of development of different kind of cancers in these patients could be different from the general population.

Innovations and breakthroughs

The present study demonstrates a higher risk of urinary bladder cancer, appendiceal mucinous cystadenoma and of neuroendocrine tumors and a low colorectal cancer risk in patients with inflammatory bowel disease in a Spanish hospital setting. These results could suggest the revision and adaptation of current cancer screening strategies according to characteristics of each patient.

Applications

The results obtained in this survey could serve as the basis of future studies aimed at elucidating the real risk of extra-intestinal malignancies and the utility of current cancer screening strategies used in these patients.

Terminology

Appendiceal mucinous cystadenoma is a rare tumour of the appendix characterized by a cystic dilatation of the appendiceal lumen with stasis of mucus inside it.

Peer review

The authors present a prospective, cohort study designed to determine the incidence and characteristics of intestinal and extra-intestinal cancers among patients with inflammatory bowel disease and to compare these incidences with those of the local population.

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