Original Article

Thiopurine Therapy Reduces the Incidence of Colorectal Neoplasia in Patients with Ulcerative Colitis. Data from the ENEIDA Registry

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Abstract

Background and Aims: Patients with ulcerative colitis (UC) are at increased risk of developing colorectal cancer (CRC), but recent studies suggest a lower risk than previously reported. The aim was to evaluate the incidence of dysplasia, CRC and related risk factors in UC patients from a Spanish nationwide database.

Methods: All UC patients were identified and retrospectively reviewed. Clinical–epidemiological data and the finding of dysplasia and/or CRC were collected.

Results: A total of 831 UC patients were included. Twenty-six cases of CRC in 26 patients and 29 cases of high-grade dysplasia (HGD) in 24 patients were found, accounting for 55 diagnoses of advanced neoplasia (AN = CRC and/or HGD) in 45 patients (33% of them within the first 8 years after UC diagnosis). The cumulative risk of AN was 2, 5.3 and 14.7% at 10, 20 and 30 years, respectively. Concomitant primary sclerosing cholangitis (odds ratio [OR] 10.90; 95% confidence interval [CI] 3.75–31.76, \( p < 0.001 \)), extensive UC (OR 2.10, 95% CI 1.01–4.38, \( p = 0.048 \)), UC diagnosis at an older age (OR 2.23, 95% CI 1.03–4.83, \( p = 0.043 \)) and appendectomy prior to UC diagnosis (OR 2.66, 95% CI 1.06–6.71, \( p = 0.038 \)) were independent risk factors for AN. Use of thiopurines (OR 0.21, 95% CI 0.06–0.74, \( p = 0.015 \)) and being in a surveillance colonoscopy programme (OR 0.33; 95% CI 0.16–0.67; \( p = 0.002 \)) were independent protective factors for AN.
Conclusions: The risk of AN among UC patients is lower than previously reported but steadily increases from the time of UC diagnosis. The widespread use of thiopurines may have influenced this reduced incidence of UC-related neoplasias.

Keywords: Ulcerative colitis; advanced neoplasia; thiopurines

1. Introduction

Crohn and Rosenberg\(^1\) described the first association of inflammatory bowel disease (IBD) with colorectal cancer (CRC) in 1925. Since then, many studies aiming to describe the real magnitude of this relationship and to identify its associated risk factors have been published. Several meta-analyses concluded that patients with long-standing colonic IBD have an increased risk of developing CRC compared with the general population.\(^2-4\) Although patients with IBD make up only 1–2% of all CRC cases,\(^6\) they constitute a population at risk since CRC still accounts for 10–15% of deaths among them.\(^6,7\) Eaden et al.,\(^3\) in a meta-analysis of 116 studies, most of them from tertiary referral centres and including more than 50,000 ulcerative colitis (UC) patients, found the global risk of CRC to be 3.7%, and a cumulative risk of developing CRC of 1.6, 8.3 and 18.4% at 10, 20 and 30 years from UC diagnosis, respectively. Other studies, also from tertiary referral centres, showed similar figures.\(^8-10\) Nevertheless, since such studies are likely to include patients with more severe and extensive disease, it has been suggested that the CRC risk might be underestimated. In fact, recent population-based studies reported a decrease in IBD-related CRC and, in many of them, no increased risk compared with the general background population.\(^11-15\) Moreover, a decreasing risk of CRC development in UC patients over the last six decades has been described in a recent systematic review, with an incidence rate of 1.24/1000 patient-years (95% CI 1.01–1.47) in population-based studies.\(^16\)

Many epidemiological factors, such as extensive disease, longer UC duration, co-existing primary sclerosing cholangitis (PSC) or a familial history of CRC, have been repeatedly identified as risk factors for UC-related CRC.\(^2,11,12,17-20\) More recently, indirect signs of uncontrolled or persistent macroscopic or microscopic inflammatory activity have been associated with a higher risk of CRC.\(^21-23\) Many studies of the effects of both aminosalicylates\(^24-26\) and thiopurines\(^27-30\) on the development of dysplasia and CRC in patients with UC reported conflicting results.

Finally, most available studies addressing the incidence of dysplasia and CRC come from Northern and Central Europe. Southern European data are scarce and could differ from other geographical areas, taking into account the fact that the incidence of both sporadic and IBD-related CRC seems to be higher in Northern than in Southern European countries.\(^31,32\)

From this perspective, we aimed to evaluate the incidences of dysplasia and CRC and to identify their risk factors in patients with UC included in a Spanish multicentre nationwide IBD database.

2. Methods

The ENEIDA registry (Estudio nacional en Enfermedad Inflamatoria Intestinal sobre determinantes genéticos y ambientales) is a nationwide, hospital-based, prospectively maintained, Spanish database of incident and prevalent IBD patients that started in January 2006, promoted by the Spanish Working Group in IBD (GETECCU). Many epidemiological and clinical data, as well as data regarding the use of several IBD therapies, are routinely collected in the registry.

Events occurring before the patient’s inclusion in the registry were acquired retrospectively from local databases or case records. After their inclusion in the database, all data are updated prospectively. The ENEIDA database is kept under continuous external monitoring for completeness and consistency of the data entered, but only the local investigator can modify data.

Regarding dysplasia and CRC, inclusion in a surveillance colonoscopy programme (SCP), the date of inclusion in the programme and the date and findings of each colonoscopy are recorded in the registry. Moreover, colonoscopies with a neoplastic finding (CRC or any type of dysplasia) performed in patients not included in an SCP are also usually registered in the database.

At the time data were extracted from the registry, the colonoscopies included in the database were performed with white light following the standard procedure (i.e. random biopsies and targeted biopsies of any visible lesion). The SCP followed the current European recommendations for dysplasia surveillance in IBD patients\(^18\) at any given time; nevertheless, SCP could vary depending on both the physician’s discretion and the patients’ decisions.

The ENEIDA registry was approved by the local ethics committee of each participating centre. Informed consent to participate in the registry was obtained from all patients. The study was approved by the ENEIDA Steering Committee of GETECCU.

2.1. Patient selection and data collection

For the purposes of our study, we included those UC patients in whom at least one colonoscopy had been performed since UC diagnosis. Patients without any colonoscopy recorded or lost to follow-up before any colonoscopy was performed were excluded. Patients diagnosed with CRC prior to UC diagnosis were also excluded. Each colonoscopy registered in the database was included, regardless of the time elapsed since UC diagnosis and the extent of UC, in order to obtain an accurate description of dysplasia and CRC incidences. All cases of CRC and dysplasia diagnosed by means of random biopsies (in the case of surveillance colonoscopies) and/or targeted biopsies (in the case of macroscopic lesions) were collected from their histological diagnosis reports. Based on the standardized classification of dysplasia in IBD published in 1983,\(^19\) dysplasia findings were defined in this study as negative for dysplasia; indefinite for dysplasia; low-grade dysplasia (LGD); and high-grade dysplasia (HGD). Since a worse prognosis has been reported in cases of CRC or HGD compared with LGD, and colectomy is generally advised in both situations,\(^18\) we grouped HGD and CRC under the term ‘advanced neoplasia’ (AN) for statistical analysis purposes.

Demographic data (date of birth, gender), epidemiological data (smoking history, personal history of malignancies, appendectomy prior to UC diagnosis, familial history of IBD or CRC), clinical data (date of UC diagnosis, disease extent, extraintestinal manifestations) and IBD-related drug therapies (use of systemic corticosteroids, oral aminosalicylates, thiopurines and biological therapies) and date and type of surgery (if performed) were collected from every patient. As recommended according to the Montréal classification\(^40,41\) UC extent was defined as the maximal macroscopic involvement of disease at

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1. Crohn and Rosenberg \(^1\)
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41. Eaden et al. \(^3\)
colonoscopy. Regarding drug use, neither duration nor total dose of oral aminosalicylates was available in the ENEIDA database at the time the study was undertaken. Therefore, only exposure to these drugs was included in the statistical analyses. In contrast, the dates of introduction and discontinuation of thiopurines and biological agents were available in the registry. Because the onset of thiopurine action is expected to be from 12 weeks after treatment initiation, we defined as thiopurine exposure cases in which thiopurines were used for a minimum of 4 months. We did not consider the time of thiopurine exposure when these were started after the colonoscopic study. Similarly, a single dose of anti-tumour necrosis factor (TNF) drugs was considered to be exposure to such drugs.

Participating centres were consulted if any data were not complete in the registry for the final analysis.

End of follow-up was defined as the date of diagnosis of AN or the date of the last colonoscopy performed when no event occurred.

2.2. Statistical analysis

Results are expressed as frequencies or mean and SD, as required. For the univariate analysis, categorical variables were analysed using Pearson’s $\chi^2$ or Fisher’s exact test, and continuous variables were compared using Student’s $t$ test. For the multivariate analysis, those variables with a $p$-value < 0.05 in the univariate analysis were included in a stepwise multiple logistic regression analysis. The adjusted odds ratio (OR) of AN and its 95% confidence interval (CI) were calculated for each independent predictor included in the final model. Time of follow-up was defined as the time from UC diagnosis to the end of follow-up. Cumulative risk of AN was evaluated by the Kaplan–Meier method. Confidence Interval Analysis (CIA) software 1.0 was used to calculate incidence. The remaining statistical analyses were performed using the SPSS 18.0 package for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

At the time of data extraction (January 2010), 5086 UC patients (46% extensive UC, 39.4% left-sided UC, and 14.6% proctitis) were included in the registry. Three patients were excluded because the diagnosis of CRC preceded that of UC and 4 patients diagnosed with CRC and UC were excluded because of insufficient available information; 10 additional patients were diagnosed with UC at colectomy without previous colonoscopy and were also excluded. In the remaining excluded patients there was no colonoscopy recorded in the database or CRC diagnosis performed. Eight hundred and thirty-one patients fulfilled the inclusion criteria and were available for analysis.

Among the 831 patients finally included, the median duration of UC at the end of follow-up was 14.5 years (range, 0–64), which represents a total follow-up of 12,050 patient-years. Fifty-six percent of patients presented extensive UC, whereas only 10% presented ulcerative proctitis. Forty-seven percent of patients were current or former smokers, up to 3% had co-existing PSC, and 12 and 16% had a familial history of IBD and CRC, respectively.

With respect to IBD-related drug therapy, up to 70% had received systemic corticosteroids (32 and 11% of them met the criteria for steroid-dependency and steroid-refractoriness, respectively). Most patients had received oral aminosalicylates at some time since UC diagnosis (90%), and 28% had been exposed for a minimum of 4 months to thiopurines at any time during the disease. Finally, <10% of patients were exposed to infliximab and 6.5% did not receive any medical therapy.

3.1. Incidence of dysplasia, CRC and AN

A total of 1860 colonoscopies were registered (median 1 per patient, interquartile range 1–3). Mean UC duration (years) at the first colonoscopy included in the registry of patients under an SCP (688, 82.8%) was greater than that of patients not in an SCP (14.2 ± 7.0 and 6.2 ± 7.8 years, respectively; $p < 0.001$). Moreover, although not statistically significant, patients included in an SPC were older at the first colonoscopy than those not following an SCP (50.9 ± 13.9 and 48.0 ± 17.1 years, respectively; $p = 0.063$).

One thousand five hundred and eighty colonoscopies (85%) from 654 patients showed no neoplastic findings, and 225 colonoscopies (12%) from 141 patients were indefinite for dysplasia or low-grade dysplasia. Twenty-six patients were diagnosed with 26 cases of CRC (mean age at CRC diagnosis 59.4 ± 13.5 years), representing an incidence of 3.1% (95% CI 2.1–4.6).

Twelve CRC cases (46%) were located in the recto-sigmoid, 5 (19%) in the descending colon and 7 (27%) in the ascending colon. The location of CRC was not available in 2 cases (8%). Clinical characteristics and tumour staging of patients with CRC are shown in Table 1. Almost half of the CRC cases (14 out of 26, 54%) were diagnosed in the setting of an SCP. The duration of UC was longer, albeit not significantly so, in patients with CRC diagnosis under an SCP at the time the first colonoscopy was registered (13.3 ± 10.8 versus 11.8 ± 10.2, $p = 0.739$). Moreover, there were no differences regarding age at first colonoscopy registered in the database between patients with CRC undergoing SCP and patients not in an SCP (61.6 ± 14.4 versus 55.8 ± 12.4, $p = 0.285$). Among CRC patients who were diagnosed while in an SCP, 45% had stage 0 or I tumours (according to the American Joint Committee on Cancer Classification (AJCC)) compared with 42% in the non-surveillance group ($p = 0.5$). Eleven out of 14 CRC cases (78.6%) diagnosed in patients in the setting of an SCP were performed at the first colonoscopy. In the remaining 3 patients, a previous diagnosis of dysplasia (LDG in one case and HGD in the other case) was found in 2 of them, while no neoplastic findings were diagnosed in the third case. Interestingly, 11 out of 26 CRC cases (42%) were diagnosed within the first 8 years after UC diagnosis (7 extensive UC, 2 left-sided UC and 2 proctitis). The cumulative probability of developing CRC was 1.4, 3.2 and 5.2% at 10, 20 and 30 years after UC diagnosis, respectively.

Twenty-nine HGD cases in 24 patients were found. Taken together with the above-mentioned 26 CRC cases, they account for a total of 55 AN cases in 45 patients, with an incidence of 5.4% (95% CI 4.0–7.2). Baseline characteristics of patients with and without AN are summarized in Table 2. In 64% of patients, AN was found while on an SCP. Again, in 15 out of these 45 patients (33%) the first AN diagnosis was performed within the first 8 years after UC diagnosis (Figure 1). There were no differences regarding UC duration and age at the time of the first colonoscopy registered in the database between patients on an SCP and patients not on an SCP (14.4 ± 9.3 versus 11.0 ± 10.7 and 60.1 ± 14.2 versus 58.6 ± 13.3 years, respectively). The cumulative probability of developing AN was 2.1, 5.3 and 14.7% at 10, 20 and 30 years after UC diagnosis, respectively (Figure 2).

3.2. Risk factors for AN

In the univariate analysis, male gender, older age at UC diagnosis, co-existing PSC, appendectomy before UC diagnosis and extensive UC were associated with an increased risk of AN, whereas being on a surveillance programme and exposure to thiopurines were associated with a lower risk of developing AN. In the multivariate analysis, co-existing PSC, extensive disease, UC diagnosis at an older age and appendectomy before UC diagnosis were independent risk factors for AN. On the other hand, exposure to thiopurines and being on a
surveillance programme were independent protective factors for the development of AN (Table 2).

4. Discussion

Data regarding CRC and dysplasia development in patients with UC in Southern Europe are scarce. Kekilli et al. reported a CRC prevalence of 1.1% in a series of 275 Turkish UC patients, and a population-based study from Italy that included 689 UC patients reported a standardized incidence ratio of 1.79 (0.85–3.28). In Spain, in a 10-year follow-up prospective, observational study including 39 UC patients (mean 15 ± 8 years of disease duration), no cases of CRC were found. Thus, to our knowledge the present study is the largest nationwide Southern European series assessing the incidence of CRC and/or HGD and their risk factors to date.

We found an incidence of CRC lower than that reported in the early meta-analysis by Eaden et al. and closer to but slightly higher than that obtained in more recent studies. One possible explanation for these differences could be the characteristics of our own database, since the majority of patients included in the ENEIDA registry come from tertiary and referral centres for IBD. In Spain, those patients with a less complex disease (mainly patients with ulcerative proctitis and/or those with a milder form of the disease) are usually managed in the primary care system or in small community hospitals, and they are less often included in the ENEIDA registry. In fact, the proportions of proctitis (10%) and extensive disease (56%) in our series are not in agreement with most population-based epidemiological studies. A selection bias is apparent and this surely leads to the inclusion of patients with a more aggressive disease, considered in terms of relapse rates, severity of flares or persistent extensive inflammatory activity. Furthermore, many studies defined the follow-up period as the interval from UC diagnosis to CRC diagnosis, death or end of follow-up. In contrast, we used the last colonoscopic examination as the end of follow-up in those patients in whom no AN occurred. This might lead to a shorter time of follow-up and the greater cumulative risk of both CRC and dysplasia observed in our study. Finally, our inclusion criteria may overestimate the risk of CRC. Since we aimed to assess the development of dysplasia (in addition to CRC), we decided to include only those patients who underwent colonoscopies after UC diagnosis (and were recorded in the database). In fact, if we take into account the whole UC population in the ENEIDA database (N = 5086, with a total of 28 CRC cases reported), the cumulative risk of CRC falls to 0.55% (95% CI 0.35–0.75) with a cumulative probability of developing CRC of 0.3, 1.3 and 2.3% at 10, 20 and 30 years after UC diagnosis, respectively. Moreover, these data are even lower than those reported in a meta-analysis that included only population-based studies describing the risk of developing CRC in UC patients and also lower than those reported in a recent systematic review.

As previously reported for both CRC and AN occurrence, extensive UC, co-existing PSC and UC duration were found to be independent risk factors for AN development. We also observed a steady increase in risk beyond 35 years of UC, a finding previously described by Rutter et al. in a prospective study of surveillance colonoscopies in patients with long-standing extensive UC. Interestingly, we observed that a relevant proportion of AN was diagnosed within the first 8 years of UC evolution. This finding is in agreement with the results of Lutgens et al., who reported a
greater percentage of CRC cases when considering the time from symptom onset instead of the time from UC diagnosis, suggesting that the time of uncontrolled colonic inflammation (before diagnosis and treatment) might play a role in carcinogenesis. In any case, if this finding is confirmed in other large studies, surveillance screening programmes should start earlier than currently recommended.

The impact of age at UC diagnosis on dysplasia and CRC development is still controversial, with some studies reporting it as a risk factor, while others do not. We found older age at UC diagnosis to be a risk factor for developing AN. The timely introduction of salvage therapies in severe flares, as well as for thiopurines in chronic active UC, might have decreased the effect of inflammation on carcinogenesis, leading to age becoming a major determinant of carcinogenesis risk, as in the background general population.

Evidence of appendectomy as a risk factor for the development of dysplasia in IBD is scarce. A retrospective study from Australia found HGD and CRC to be more frequent in UC patients with prior appendectomy, although without statistical significance. When combining their data with those from another

Table 2. Risk factors for advanced neoplasia (AN = colorectal cancer and/or high-grade dysplasia).

<table>
<thead>
<tr>
<th></th>
<th>AN (n = 45)</th>
<th>No AN (n = 786)</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>31 (69)</td>
<td>419 (53)</td>
<td>0.046</td>
<td>1.77</td>
<td>0.85–3.66</td>
<td>0.121</td>
</tr>
<tr>
<td>Extensive UC</td>
<td>33 (73)</td>
<td>432 (55)</td>
<td>0.02</td>
<td>2.10</td>
<td>1.01–4.38</td>
<td>0.048</td>
</tr>
<tr>
<td>Age at UC diagnosis (years)*</td>
<td>47 ± 16</td>
<td>37 ± 14</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>15.7 ± 11.0</td>
<td>15.6 ± 8.0</td>
<td>0.99</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&gt;8 years of UC duration</td>
<td>33 (73.3)</td>
<td>678 (86.2)</td>
<td>0.027</td>
<td>0.83</td>
<td>0.35–1.96</td>
<td>0.563</td>
</tr>
<tr>
<td>Smoking history</td>
<td>26 (58)</td>
<td>364 (46)</td>
<td>0.16</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Familial history of CRC</td>
<td>3 (6)</td>
<td>58 (16)</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Familial history of IBD</td>
<td>5 (11)</td>
<td>88 (12)</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Co-existing PSC</td>
<td>8 (18.0)</td>
<td>18 (2.3)</td>
<td>&lt;0.001</td>
<td>10.90</td>
<td>3.75–31.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>7 (17.0)</td>
<td>53 (7.2)</td>
<td>0.029</td>
<td>2.66</td>
<td>1.06–6.71</td>
<td>0.038</td>
</tr>
<tr>
<td>Number of colonoscopies</td>
<td>2.6 ± 2.2</td>
<td>2.2 ± 1.8</td>
<td>0.169</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Included in SCP</td>
<td>28 (62)</td>
<td>660 (84)</td>
<td>0.001</td>
<td>0.33</td>
<td>0.16–0.67</td>
<td>0.002</td>
</tr>
<tr>
<td>Exposure to corticosteroids</td>
<td>27 (61.4)</td>
<td>556 (73.0)</td>
<td>0.117</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Steroid-dependency</td>
<td>4 (18)</td>
<td>186 (26)</td>
<td>0.10</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Exposure to aminosaliclylates</td>
<td>37 (82.2)</td>
<td>711 (90.4)</td>
<td>0.118</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Exposure to thiopurines</td>
<td>6 (13.3)</td>
<td>229 (29.2)</td>
<td>0.026</td>
<td>0.21</td>
<td>0.06–0.74</td>
<td>0.015</td>
</tr>
<tr>
<td>Duration of thioumine use (years)</td>
<td>5.6 ± 2.6</td>
<td>5.4 ± 3.7</td>
<td>0.93</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Aminosaliclylates and thiopurines</td>
<td>2 (4.4)</td>
<td>204 (26.0)</td>
<td>0.001</td>
<td>0.52</td>
<td>0.04–7.03</td>
<td>0.564</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>1 (2)</td>
<td>55 (7)</td>
<td>0.356</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>No medical treatment</td>
<td>4 (8.9)</td>
<td>50 (6.4)</td>
<td>0.527</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are absolute numbers and percentages in parentheses, or mean and standard deviation.
AN, advanced neoplasia; Anti-TNF, Anti-tumour necrosis factor-α; CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; OR, odds ratio; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

*Not included in multivariate analysis; evaluated by categorical variable median age.
#36 years.

Figure 1. Time interval between ulcerative colitis diagnosis and diagnosis of advanced neoplasia (colorectal cancer [CRC] or high-grade dysplasia [HGD]).
study, the authors found prior appendectomy to predispose to CRC development. Similarly, we found appendectomy to be an independent risk factor for the development of AN. The explanation for this finding is uncertain. Appendectomy may protect against the onset of UC and even against severe colitis, while promoting a milder but more extensive disease.\textsuperscript{41,47} However, when analysing the effect of potential confounding factors, such as disease extent, medical treatment, co-existing PSC and gender, no correlation between them and previous appendectomy was found (data not shown).

Beyond epidemiological risk factors, the impact of UC-related drug therapy on dysplasia development remains a matter of debate. Although a protective effect of oral aminosalicylates was initially reported,\textsuperscript{27} recent studies suggested no beneficial effects on dysplasia development.\textsuperscript{51,52} We did not observe any correlation between oral aminosalicylate use and AN. However, it has to be taken into account that the vast majority of patients were exposed to these drugs in our study (90%). Moreover, our database did not include relevant information such as treatment duration and dosage, preventing us from reaching any robust conclusion. Conversely, we found a protective effect of thiopurines on dysplasia development, in agreement with other recently published studies.\textsuperscript{52,53} It has been suggested that this could be related to an anti-inflammatory effect.\textsuperscript{56} In our study, patients on thiopurines had neither more extensive disease nor longer UC duration (data not shown). Moreover, no correlation between corticosteroid requirement and AN was found, though we did observe greater corticosteroid use and higher prevalence of steroid-dependency and resistance in patients with thiopurine exposure (99 versus 63%, 65.8 versus 13.4%, and 24.6 versus 4.6%, respectively, \( p < 0.001 \)). This might suggest that patients with a more aggressive disease (extensive UC, frequent relapses, steroid-refractoriness) may benefit from more potent therapies. In this sense, no similar effect was observed with anti-TNF drugs, although only a small proportion of patients were exposed to these drugs in our series.

We observed a significantly lower proportion of AN among patients on an SCP. However, and as previously reported,\textsuperscript{49} no differences in AN tumour staging were found according to whether or not the patient was on a surveillance programme. In patients undergoing periodic colonoscopies, therapy may be escalated if mucosal inflammation is found (regardless of symptoms), and this may lead to mucosal healing in a higher proportion of patients compared with those not undergoing repeated endoscopic examinations. Beyond the protective effect of SCP in our cohort, we also found that the first colonoscopy among patients in an SCP was surprisingly late in the disease course. The implementation of SCP in Spain has become widespread in the last decade, and this may account for such long-lasting disease among those patients in our cohort.

The present study was hindered by several drawbacks that must be taken into account. Firstly, the use of the ENEIDA registry has many limitations in addition to the above-mentioned bias of referral centres. The inclusion of patients in the registry depends on the investigator in each centre and it is difficult to ascertain what proportion of IBD patients at each centre are included. However, in an inner survey performed recently, more than 75% of the participating centres had included in the registry more than 90% of their IBD patients. Similarly, we cannot be absolutely sure that all AN cases had been registered in the registry, given that some of the data were collected retrospectively. However, it is reasonable to think that colectomy or cancer diagnosis constitute data less prone to be missed from the registry. Secondly, we were only able to collect information on exposure to oral aminosaliclytes, but not the dosage and duration of therapy with these compounds. Therefore, our results do not allow the exclusion of a protective effect of 5-aminosalicylates (5-ASA), an issue still under debate. Endoscopic findings were also lacking in the present study, although some lesions have been associated with an increased risk of developing CRC, such as the presence of pseudopolyps.\textsuperscript{21} Moreover, an important proportion of patients (51.5%) underwent only one endoscopic examination, apparently reducing the chance of diagnosing dysplasia. This was mainly due to the design of our study, which included only those patients who underwent at least one colonoscopy after UC diagnosis. In our opinion, this inclusion criterion increases the chance of finding patients with dysplasia compared with those studies including all UC patients or only those with long-standing disease regardless of whether they had endoscopic examinations. This particular approach allowed the confirmation of a relevant finding, which is the development of CRC in patients with less than 8 years of disease duration.

Finally, we could not guarantee a second expert gastrointestinal pathologist review of histological slides when dysplasia was diagnosed, which is recommended.\textsuperscript{38} Similarly, the occurrence of CRC outside the segments involved by UC was only based on the maximal reported extent of the disease, but not on the histopathological reports of the colectomy specimens.

In conclusion, in this large Spanish nationwide registry, the incidence of CRC was similar or slightly higher than recently reported in population-based studies, though lower than reported in the first meta-analysis published more than 10 years ago. A relevant proportion of AN cases were diagnosed within the first 8 years from UC diagnosis. The use of thiopurines was associated with a lower risk of AN development, whereas, in addition to previously known risk factors, older age at UC diagnosis and appendectomy prior to UC diagnosis were identified as risk factors for the development of AN.

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Author Contributions
Jordi Gordillo collected data, designed the study, performed statistical analysis and drafted the article. Eduard Cabré and Eugeni Domènech designed the study, interpreted the results and drafted the article, and is the guarantor of the article. All the remaining authors collected data in their centres, and reviewed and approved the article.

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