



# Journal of Coloproctology

www.jcol.org.br



## Review Article

# Crohn's disease: risk factor for colorectal cancer



Sandra Cristina Dias dos Santos<sup>a,\*</sup>, Laura Elisabete Ribeiro Barbosa<sup>a,b</sup>

<sup>a</sup> Universidade do Porto, Faculdade de Medicina, Porto, Portugal

<sup>b</sup> Hospital de São João, Serviço de Cirurgia Geral, Porto, Portugal

### ARTICLE INFO

#### Article history:

Received 19 June 2016

Accepted 29 June 2016

Available online 9 September 2016

#### Keywords:

Crohn disease

Colorectal neoplasms

Inflammation

Risk factors

### ABSTRACT

**Background:** Crohn's disease is an inflammatory disease that can reach any part of the gastrointestinal tract. This disease has been associated with an increased neoplastic risk, including colorectal carcinoma.

**Objective:** The objective of this work is to describe the mechanisms present in two diseases, and that are responsible for the increased risk in Crohn's disease.

**Methods:** A bibliographic research was conducted in PubMed database. In addition to the articles obtained with an inserted query in Pubmed, other references relevant to the topic in question were included.

**Results:** Colorectal cancer risk varies according to the presence of certain factors, and an example of this is Crohn's disease. Chronic inflammation seems to be an important contribution to carcinogenesis, since it creates a microenvironment suitable for the onset and progression of the disease. There are molecular changes that are common to two conditions, thus justifying the fact of Crohn's disease being a risk factor for colorectal carcinoma. The disease control with an appropriate therapy and with surveillance are two ways to control this risk.

**Conclusions:** A proinflammatory state is the cornerstone in the association between Crohn's disease and colorectal carcinoma. The implementation of surveillance strategies allowed a decrease in morbidity and mortality associated with this cancer.

Published by Elsevier Editora Ltda. on behalf of Sociedade Brasileira de Coloproctologia.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Doença de Crohn: fator de risco para o carcinoma colorretal

### RESUMO

**Introdução:** A doença de Crohn é uma doença inflamatória que pode atingir todo o trato gastrointestinal. Esta patologia tem sido associada a um risco neoplásico aumentado, nomeadamente de carcinoma colorretal.

**Objetivo:** O objetivo deste trabalho é descrever os mecanismos responsáveis pelo aumento do risco de carcinoma colorretal na doença de Crohn.

#### Palavras-chave:

Doença de crohn

Carcinoma colorretal

Inflamação

Fatores de risco

\* Corresponding author.

E-mail: [scristina.santos@hotmail.com](mailto:scristina.santos@hotmail.com) (S.C. Santos).

<http://dx.doi.org/10.1016/j.jcol.2016.06.005>

2237-9363/Published by Elsevier Editora Ltda. on behalf of Sociedade Brasileira de Coloproctologia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Métodos:** A pesquisa bibliográfica foi realizada na base de dados Pubmed. Para além dos artigos obtidos com a query inserida na Pubmed, foram também incluídas outras referências com relevância para o tema em questão.

**Resultados:** O risco de carcinoma colorretal aumenta na presença de determinados fatores, entres eles a doença de Crohn. A inflamação crónica presente parece ser um importante contributo para a carcinogénese, porque permite a criação de um microambiente adequado ao aparecimento e progressão da doença. Existem alterações moleculares comuns às duas patologias justificando-se o fato desta doença inflamatória ser fator de risco para o carcinoma colorretal. O controlo da doença com terapêutica adequada e estratégias de vigilâncias são duas formas de controlar o risco.

**Conclusões:** O estado pró-inflamatório é uma peça chave na associação entre doença de Crohn e carcinoma colorretal. A implementação de estratégias de vigilância permitiu a diminuição da morbi-mortalidade associada a esta neoplasia.

Publicado por Elsevier Editora Ltda. em nome de Sociedade Brasileira de Coloproctologia. Este é um artigo Open Access sob uma licença CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Inflammatory bowel diseases, of which Crohn's disease (CD), familial adenomatous polyposis, and the non-polypoid hereditary form are examples, are three diseases that confer a high risk of colorectal carcinoma (CRC).<sup>1</sup>

CD is a chronic, progressive disease characterized by a pro-inflammatory state. The quality of life of these patients is affected substantially, although benefits have occurred with the appearance of various therapies.<sup>2,3</sup>

The multifactorial etiology of this disease is not fully known, but some pathophysiological mechanisms underlying it have been described.<sup>4</sup>

CD is characterized by chronic diarrhea (the symptom most often present), weight loss, blood loss and abdominal pain. All the gastrointestinal tract can be affected, and distal ileum and colon are the parts most often affected.<sup>3-6</sup>

For the progression of this disease, genetic and environmental factors and dysbiosis are contributing factors.<sup>2,3,7</sup>

About 2 million Americans and Europeans suffer from CD, and its diagnosis is established mainly in the 2nd or 3rd decade of life.<sup>7</sup>

CD may have intestinal and extra-intestinal manifestations, and the disease shows two predominant patterns. According to the Montreal classification, patients are categorized according to their age at diagnosis, and disease location and behavior. With regard to age at diagnosis, the categories are  $\leq 16$  years, between 17 and 40 years, and  $\geq 40$  years. The disease can be found in the ileum, colon, ileum-colon, or upper gastrointestinal tract, showing a non-stenotic/non-penetrating behavior, a stenotic behavior, or a penetrating behavior.<sup>8</sup>

CRC arises due to a dysplasia of intestinal mucosa and is more common in these patients versus the general population. Thus, this inflammatory disease is a risk factor for CRC occurrence.<sup>5,9,10</sup>

CRC can cause death in these patients, and the diagnosis is rarely established before 7 years of disease progression.<sup>7,11</sup> There is no consensus as to the quantification of risk since this is influenced by several factors.<sup>12</sup>

The prognosis of CD varies from patient to patient, but there are some factors which lead to a worse outcome, including the perianal disease and the presence of upper gastrointestinal tract lesions, as well as an extensively affected colon.

## Material and methods

On July 6, 2015, a literature search in PubMed database was performed with the following query ((“crohn's disease” [MeSH Terms] OR (“crohn” [All Fields] AND “disease” [All Fields]) OR “crohn's disease” [All Fields]) AND (“neoplasms” [MeSH Terms] OR “neoplasms” [All fields] OR “cancer” [All Fields])). The inclusion criteria were: studies published in the last 10 years and articles written in Portuguese, English or Spanish. The titles and abstracts were read, and 75 articles were selected.

On December 22, 2015, a new search was conducted with the aim of updating the bibliography; the same query and the same inclusion criteria used in the previous survey were employed, and 48 articles were obtained.

Additional studies relevant to the issue in question were also included, through a cross-search with the articles already included, and a book relevant to the subject matter.

A total of 50 references were obtained.

## Results

### Epidemiology

Inflammatory bowel disease, which includes CD, is more prevalent in developed countries; this leads one to think of Westernization as a risk factor for this condition. Dietary habits and lifestyle contribute in some way to its appearance. One of the diagnostic peaks occurs in patients aged between 15 and 30 years, and 30% of patients are diagnosed under the age of 20 years.<sup>13,14</sup> The second peak occurs between 60 and 80 years, with a lower incidence versus the first peak.<sup>15</sup>

In CD, the inflammation occurs transmurally. The most commonly affected locations are the terminal ileum and colon. At the time of diagnosis, 40% of patients exhibit an

ileocolic location, 30% suffer from an isolated ileal disease, and 30% are affected only in the colon. Approximately 5–10% of patients exhibit associated lesions of the upper gastrointestinal tract, and 20–30% show perianal disease.<sup>2</sup>

The control of the disease with medical therapy, particularly with biological agents, constitutes an advantage for these patients; but despite the advances in science and in pharmacotherapy, the risk of complications involving bowel resection remains in the range of 80%.<sup>12,16</sup> Perianal lesions, i.e., ulcers, fissures or fistulas, are complications present in 20% of patients at diagnosis.<sup>5</sup> Despite the medical therapeutic efficacy, the percentage of refractory patients spins around 25–30%. All these aspects contribute to an inadequate control of the disease.<sup>7</sup>

CRC can arise in the context of CD, with a location in areas of chronic inflammation. Regarding the quantification of risk, the results of the studies are mixed. Some studies point to a risk 2–3 times higher, while other studies cite a risk six times higher. Each year, approximately 900,000 new cases of CRC and 500,000 deaths occur worldwide. This cancer accounts for about 10–15% of deaths in patients with inflammatory bowel disease and the amount attributable to CD has not yet been determined.<sup>10,11,14,17</sup> Other studies report that 1 in 12 deaths of patients with Crohn's disease is caused by CRC.<sup>1</sup>

The first case of CRC related to CD was described in 1948, and since then the cause of this association is not yet fully understood. In fact, the risk exists, but its magnitude has not yet been determined accurately.<sup>13</sup>

The incidence of CRC related to CD is variable, reaching higher values in tertiary hospitals, where the inflammatory disease attains more severe stages.<sup>12</sup>

Studies related to this association found that there is a cumulative risk of CRC development. In evaluating a population of Eastern Europe 20 years after the diagnosis, the cumulative risk was estimated at 1.1% (95% CI: 0.6–1.7%). Another study found that the risk would be 2.9% after 10 years, 5.6% after 20 years, and 8.3% after 30 years.<sup>13,18</sup>

The risk of cancer varies with the location of the disease. When the disease affects only the colon, the relative risk is 5.6, while in the case of ileocolic involvement, the relative risk is 3.2; and studies in patients with extensive involvement of the colon resulted in a calculated relative risk of 23.8.<sup>18</sup>

The presence of metachronous lesions is variable, ranging from a minimum value of 23% and a maximum of 70%.<sup>19</sup>

Basseri et al. conducted a study in which patients with Crohn's disease were monitored for 17 years; these authors found a CRC development in 5.6% of the study population.<sup>18</sup>

Other studies have concluded that there was a decrease in the incidence of CRC, but this finding can be explained by the onset of medical therapies increasingly effective, appropriate surgical treatment, and the existence of surveillance programs that allow an early detection of dysplasia.<sup>1</sup>

## Surveillance

An association between an increased risk of CRC in a Crohn's patient exists, although the mechanisms responsible have not yet been fully elucidated.<sup>6</sup> Thus, surveillance programs are of

great importance and are aimed at reducing morbidity and mortality.<sup>20,21</sup>

Given that one of the diagnostic peaks occurs between 15 and 30 years, the development of CRC associated with CD is earlier than in the sporadic form, similar to what occurs in patients with Lynch syndrome.<sup>10</sup>

Studies in patients with ulcerative colitis and CD revealed a very similar cumulative frequency after 20 years (8% vs. 7%, respectively). According to the American Gastroenterology Association (AGA), currently it is accepted that the risk of developing CRC is equivalent in both pathologies, and it was recommended that surveillance should begin eight years after the diagnosis.<sup>22</sup> The recommendations of the British Society of Gastroenterology (BSG) are toward an onset of monitoring about 10 years after diagnosis.<sup>6,10,21</sup>

However, in a study conducted in a tertiary hospital, two cases of CRC with a one-year interval after the diagnosis of CD were related; the remaining cases were reported at intervals from 11 to 14 years.<sup>12</sup> The prognosis of both types of CRC may be more favorable with an appropriate surveillance, considering that the neoplastic progression to more advanced stages will be avoided.<sup>10,18,23</sup>

In the case of establishing a diagnosis of primary sclerosing cholangitis (PSC), the surveillance should be started immediately, being held annually in accordance with the recommendations of the AGA.<sup>22,24</sup>

The evolution from an inflamed to a dysplastic mucosa may occur without macroscopically visible lesions, unlike what happens in patients with sporadic CRC, that in about 70–80% of cases follow the adenoma–carcinoma sequence.<sup>10,17,25,26</sup>

The lesions may be polypoid or flat, multifocal or unifocal.<sup>27</sup> Some studies have raised doubts about the efficacy of the surveillance with colonoscopy, as flat lesions are not visible and may not be targeted sites of randomized biopsies. The presence of dysplasia is a risk marker for carcinoma.<sup>17,25,27</sup> When the lesions are macroscopically visible, should be targeted for biopsy.<sup>28</sup>

In the case of flat lesions, biopsies will be randomized, not targeted; with this, one will count on a sample of only 0.03% of the mucosal surface of the colon. Therefore, if a dysplastic area exists, and this area is not targeted for a biopsy, cancer will progress and the diagnosis will be delayed.<sup>29</sup>

There is no consensus among different organizations and societies about surveillance strategies, which means that there are different recommendations. The application of surveillance strategies for all people with CD is not a consensual procedure. Studies were published arguing that surveillance should be carried out only for certain subgroups. The definition of these subgroups is based on factors that confer a greater risk of CRC, i.e., the extent and duration of the disease, and also an extrapolation from studies in patients with ulcerative colitis. Thus, these studies maintain that surveillance should be applied only to patients with a widely affected colon.<sup>30</sup> Other authors defined more specific conditions for surveillance recommendation, namely more than 1/3 of the affected colon and development of CD  $\geq$  8 years.<sup>21</sup> These are the criteria adopted by AGA to define which patients should undergo surveillance.<sup>22</sup>

According to AGA, biopsies at every 10 cm (min: 33) shall be obtained.<sup>21,24,29</sup> Undefined results are an indication for a repeat examination after 3–6 months. The presence of high-grade dysplasia is an indication for colectomy. Therefore, the histological results define which procedure to perform: Surveillance colonoscopy, or surgical treatment.<sup>18,28,31</sup>

AGA recommends conducting surveillance at intervals of 1–3 years, and never exceeding 8 years after diagnosis.<sup>3,24,32</sup> In the case of a positive family history for CRC in 1st-degree relatives, active inflammation and anatomical changes, for example, stenosis, monitoring intervals should be shorter.<sup>22</sup> BSG recommends that the colonoscopy should be carried out at intervals of 3 or 5 years, taking into account the underlying risk factors after 10 years.<sup>3,32,33</sup>

As already mentioned, metachronous lesions may occur in a significant percentage of patients. Thus, dysplasia can be detected in more than one biopsy, and in more than one location.<sup>31</sup>

The surveillance must be carried out in periods of remission unless in the case of a long-standing inflammation.<sup>22</sup>

The evolution of technology has allowed the use of chromoendoscopy instead of randomized biopsies; by this method, the biopsies are directed, allowing greater efficiency in detecting dysplasia.<sup>6</sup>

The chromoendoscopy allows the enhancement of dysplastic areas through light filters, or through agents such as methylene blue and indigo carmine.<sup>29,34</sup>

This type of endoscopy is recommended by various entities for the monitoring of patients at increased risk of CRC, for example, patients with CD.<sup>34,35</sup> This diagnostic method allows an increase of 7% (95% CI: 3.2–11.3) in the detection of dysplasia versus white light endoscopy; but it remains to be seen what is its degree of technical influence on patient survival. Despite this uncertainty, the SCENIC consensus statement (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) recommends chromoendoscopy as a technique of choice for monitoring dysplastic areas in patients with CD.<sup>3</sup> BSG also recommends chromoendoscopy as a monitoring method for all patients; but if this technique is not available, 2–4 biopsies every 10 cm should be obtained.<sup>22,29</sup> On the other hand, AGA recommends chromoendoscopy only in special cases.<sup>29</sup>

Techniques such as flow cytometry, immunohistochemistry, marker survey are essential to confirm the diagnosis of cancer.<sup>4</sup>

Neoplastic biomarkers can also be another way to detect or confirm the presence of cancer; however, they are not part of the surveillance strategies.<sup>12</sup>

The progress of anti-inflammatory therapy for CD and a proper monitoring of these patients have improved the diagnosis of CRC and increased survival.<sup>17</sup> Thus, surveillance strategies are an important way to improve the prognosis of these patients. Early diagnosis ensures a tumor detection in less advanced stages; thus, most frequently the treatment has a curative effect.<sup>36</sup>

The surveillance has proved to be a powerful weapon in the fight against CRC, since the presence of symptoms can be nonspecific, perhaps implying difficulty with a diagnosis based only on clinical findings.<sup>37</sup>

## Molecular changes

CRC development in patients with CD seems to be due to an interaction between genetic and acquired factors. The interaction between inflammation and regulatory genes of neoplastic pathways appears to play an important role in tumorigenesis. Some authors argue that the contribution from inflammation is more significant than the contribution of the genetic component.<sup>18,25,27</sup> Changes can occur in oncogenes, tumor suppressor genes (i.e., p53), and genes of DNA repair (MLH1, MSH2, MSH6).<sup>18</sup>

The genetic alterations are present even before the occurrence of histological alterations of the mucosa.<sup>27</sup>

The first genetic change related to CD was in NOD2/CARD15 (nucleotide-binding oligomerization domain containing 2/caspase recruitment domain-containing protein 15), which ultimately increases the production of pro-inflammatory cytokines. NOD2 protein is an intracellular sensor of bacterial peptidoglycans, which will act via nuclear factor kappa B (NF- $\kappa$ B).<sup>14,38</sup> Thus, this genetic change helps to perpetuate inflammation, being indirectly related to carcinogenesis.<sup>14</sup>

Pro-inflammatory factors play an important role in the development and evolution of CD, and there may also be changes in their genes. One of the altered genes can be the tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), which is located on chromosome 6. Polymorphisms occurring in the promoter region of this gene can alter cytokine production; thus, they can increase the susceptibility to conditions related to inflammation.<sup>39</sup> Thus, TNF- $\alpha$  contributes to inflammation in patients with CD, not only being involved in tumor proliferation, but also in the metastatic process. This factor is associated with an increased expression of cyclooxygenase-2 (COX-2), cell proliferation, and angiogenesis.<sup>7</sup>

The presence of a mutation in the tumor suppressor gene p53 in differs in sporadic cases and in cases associated with CD. In the first situation, the mutation is present in advanced stages; however, in this latter situation the mutation may be present in the non-dysplastic mucosa.<sup>10,27</sup>

Mutations in E-cadherin gene are one type of genetic change present in some cases. These mutations have been associated with the occurrence of cancer, i.e., gastric carcinoma; it is believed that this may be one of the mechanisms of carcinogenesis in CD.

Several studies have concluded that micro-RNAs (MIR) are involved in the pathophysiology of CD and CRC, and may be a key link in the relation of these two diseases. MIR may constitute early biomarkers of colon cancer and may also be important in the detection and prevention of breast cancer. Two types of MIR were described: those promoting tumor survival and growth (onco-micro-RNA) and those which suppress neoplastic progression (micro-RNA tumor suppressor). The second type of MIR, above mentioned, is that that is most often related to tumorigenesis, and the mechanism underlying this situation is the retardation of its activity. MIR deregulation that exacerbates existing inflammation in CD may increase the risk of CRC in patients who already exhibit a somatic mutation. From the above, one can conclude again that the relationship between these disorders includes the interaction of several factors. One of the mechanisms by which MIR exacerbate the inflammation is the interaction with COX-2. MIR-26b has only

one binding site located within the non-transcribed 3' zone of this enzyme, thus allowing its direct connection with the inflammatory process.<sup>37</sup>

MIR-191 has also been associated with CD and CRC, diseases in which it shows an aberrant expression. In the case of CRC, MIR-191 levels may be increased or decreased. In most cases the levels are high, and the cases described with low levels are associated with a worse prognosis. In the case of CD, MIR-191 may also be changed, and apparently regulating innate and acquired immunity.<sup>40</sup>

Autophagy seems to be another connecting link, acting as a tumor suppressor.<sup>7,14</sup> The gene for autophagy, ATG16L1, can be changed.<sup>38</sup> During tumorigenesis, autophagy is negatively regulated by several genes. Defects in autophagy have been associated with several pathologies, including CD and CRC.<sup>14</sup>

Oxidative stress and its underlying damage are changes that are present in CD and perhaps contributing to tumorigenesis. In the case of CD, an increase of reactive oxygen and nitrogen reactive species occurs, which in turn lead to alterations in DNA, RNA, proteins, and lipids.<sup>23,41</sup> These genetic alterations that affect the immune system have been described in these two diseases, with an involvement of innate and acquired immunity.<sup>23,27</sup> The result of these changes may be the loss of function of tumor suppressor genes, a gain of function of oncogenes, or loss of genetic stability.<sup>11</sup>

### Inflammation

CD is a condition in which, it is believed, non-pathogenic commensal bacteria trigger an unregulated immune response against the mucosa, whose function is to serve as a barrier.<sup>42</sup>

Chronic inflammation is related to tissue damage and to the recruitment of immune system cells that act to perpetuate inflammation. There is also a rapid renewal of the colonic mucosa, which increases the risk of DNA damage.<sup>11</sup>

Inflammation is a very important feature in CD, and several studies show that the increased neoplastic risk is due to their persistence, taking into account that the association between cancer and inflammation has been established.<sup>18,20</sup> Thus, the risk is substantially larger in situations where the control of the inflammatory response is inappropriate.<sup>43</sup> The presence of pro-inflammatory cytokines carries a permanent pro-inflammatory state which increases the neoplastic risk.<sup>18,25</sup>

Inflammation promotes the creation of a suitable microenvironment for neoplastic formation and progression. Several mechanisms contribute to the development of this microenvironment.

The expression of some genes related to inflammation is increased in mucosa of these patients, particularly COX-2.<sup>11</sup> The induction of this enzyme occurs thanks to the activation of toll-like receptor-4 (TLR-4) and to the increased production of proinflammatory cytokines by immune system cells.<sup>7,23</sup> This signaling pathway will lead to the production of prostaglandins in epithelial cells which, along with local cytokines, inhibit apoptosis, thereby favoring carcinogenesis.<sup>23</sup> The induction of COX-2 has another important consequence—the decrease of unesterified arachidonic acid. The importance of this fact lies in the pro-apoptotic function of this acid. In cases in which the acid is decreased, the

apoptosis process also will be decreased, which promotes cell proliferation.<sup>23</sup>

Aside TLR, there are other receptors that contribute to inflammation, the NOD-like receptors (NLRs). The first genetic change related to CD occurred precisely in one of these receptors, NOD-2. This receptor and NOD-1 contribute significantly to inflammation at the intestinal level. NOD-1 and NOD-2 recognize molecules, particularly bacterial peptidoglycans, which penetrate into cells by various processes, for example by phagocytosis. The binding of the peptidoglycans to NLRs activates pro-inflammatory and anti-microbial molecules. NLRs, in collaboration with TLRs, allow the detection of bacteria and activation of pro-inflammatory mechanisms.<sup>44</sup>

Rodent studies have concluded that the deficiency of transforming growth factor beta (TGF- $\beta$ ), exacerbates the activation of NF- $\kappa$ B and the secretion of proinflammatory cytokines, which protect cells from apoptosis.<sup>7,41</sup>

In patients with CD, in addition to changes in pro-inflammatory factors, alterations in cellular immunity also occur. The change of T cell phenotype is closely linked to the regulation of inflammation in CD as well as to related cancer; however, the results of previously published studies are contradictory.<sup>43,45</sup> Regulatory T cells are a major intervening factor in the inflammatory process. An inappropriate response to the microflora plays an important role in the pathogenesis of CD. In this inflammatory disease, there is a change in the balance between regulatory T cells in the blood and in the inflamed site in the bowel and, in addition, there is an excess of pro-inflammatory stimuli.<sup>18,27</sup> However, if on one hand it is believed that the regulatory T cells are important in controlling inflammation in CD and, therefore, have a protective role, on the other hand, it is known that, in the initial process of carcinogenesis, these cells suppress anti-tumor mechanisms, promoting neoplastic progression.

Studies in rodents showed that inflammation, in addition to its local role at bowel level, also acts at a distance, inducing thymic involution and therefore a change (i.e., a decrease) in the production of T cells. This suppression means that there will be less control of inflammation.<sup>43</sup>

Smoking can also be detrimental to the progress of the disease by altering the gene expression and by contributing to inflammation. Thus, in smokers the progression of the disease tends to be more severe.<sup>12,38,46</sup>

### Risk factors for colorectal carcinoma in patients with CD

The risk factors for CRC development are family history of CRC, the extent of the injury, disease duration, primary sclerosing cholangitis (PSC), histologic characteristics, disease phenotype and age at the time of diagnosis.<sup>12,23,30,47</sup>

The risk can be mitigated by an appropriate surveillance and surgical treatment when necessary.<sup>12</sup>

The gender of the patient is not considered a risk factor, and there is a disparity between the results. There are studies indicating that the difference is not significant. However, other authors found results that point to an increased incidence in men.<sup>6,13</sup>

A family history of CRC is an important factor that doubles the risk.<sup>24</sup> A study concluded that the risk of CRC in patients with CD and with a history of 1st-degree relatives with this

cancer is 3.7 times higher versus patients with no such family history.<sup>11,14</sup> However, it is important to note that having a family member with DC does not increase the risk of CRC.<sup>23</sup> It is evident that family history is an independent risk factor, but is an indication for smaller surveillance intervals.<sup>24</sup>

The risk of CRC is naturally higher in patients with extensive lesions in the colon.<sup>1,30,31</sup> It is also known that, in many cases, cancer occurs along fissures and fistulas.<sup>30,31</sup>

A diagnosis established at an early age and the presence of active inflammation also represent risk factors, as discussed above. Studies have concluded that if the diagnosis is made before the age of 30 years, the relative risk shows a considerable increase.<sup>11,23,48</sup>

The association between CD and PSC has been known since 1964. The coexistence of these diseases constitutes a summation with respect to CRC risk, with a contribution of inflammation in CD, and of the high concentrations of bile acids in the colon, secondary to cholangitis.<sup>10</sup> PSC is present in 1–3% of patients with CD, but there is no certainty about the actual risk of CRC in patients with both pathologies.<sup>1</sup>

Phenotypic presentation in the form of stenosis can also affect the risk of developing CRC. Studies indicate an increased risk when the disease is stenotic.<sup>13,30</sup>

With the medical therapy used in the treatment, the patient can be kept in remission for long periods of time; thus, surgery is avoided.<sup>6,16,49</sup> The role of thiopurines in the risk of CRC is controversial. The purpose of using these drugs is the reduction of inflammation; therefore, its use should decrease the risk of CRC. However, one of the effects of immunosuppressive drugs is a greater neoplastic risk. In fact, thiopurines increase the risk of some cancers, including skin cancers and lymphomas, but because of its anti-inflammatory effect, the use of this drug seems to contribute to a decreased risk of colorectal neoplasia. In parallel, non-steroidal anti-inflammatory drugs also appear to lower the risk.<sup>6,16</sup>

CRC associated with CD develops mostly in young people and it appears to be a more diffuse, extensive, multifocal and mucinous disease when compared with sporadic CRC. This cancer usually appears on the right side, and this is related to the known higher frequency of inflammation at this location.<sup>12,18</sup>

---

## Discussion

An increase in the risk of CRC in patients with CD is a fact, despite the still incomplete knowledge of the mechanisms involved.

The value of the relative risk varies in different studies since this variable depends on several factors. The heterogeneity in the methodology observed in several studies complicates the comparison of results.

A decrease in the risk of CRC has been described; it is likely that this is due to improved surveillance methods, with the possibility of increasing early diagnoses.

The monitoring of these patients is aimed not only to control the inflammation of the underlying disease, but also to avoid CRC. Obtaining directed biopsies by chromoendoscopy is the most effective method; this enables a higher percentage

of dysplasia detection, considering that most of the lesions are not visible by conventional colonoscopy.

In most studies, the interval from diagnosis of CD to the diagnosis of CRC was about 10 years. However, two cases of CRC, whose diagnosis was established one year after the onset of symptoms were related. The diagnosis of CRC may occur even before the diagnosis of CD.<sup>12,45</sup> In these situations, the CRC appears to be an independent event CD.

The increased risk may also be explained by the fact that the genetic changes that lead to the emergence of CD can also contribute to the onset of CRC.<sup>12</sup>

The presence of an affected colon entails increased risk because the underlying inflammation may contribute to carcinogenesis.

Regarding the intervening factors, some argue that the age of diagnosis cannot be considered as a true risk factor. These authors argue that the risk is related to the duration of the disease. Early diagnoses allow one to conclude that for the same age, such patients have a longer duration of the disease.<sup>23</sup>

In the case of a CRC diagnosis in a patient with CD, it is important to distinguish whether the carcinoma is sporadic, whether it is associated with the inflammatory disease, or whether it is a case of Lynch syndrome. This is particularly relevant as it will influence the treatment offered, consisting in total colectomy in cases where the diagnosis of CRC is associated with CD or Lynch syndrome. The distinction can be performed based on the patient's MIR profile. In patients with Lynch syndrome, there is an increased expression of MIRs 16-2 and 30-a, while in those suffering from CD there is an increased expression of MIRs 191, 23b and 16.<sup>32,37</sup>

MIRs play an important role in CD and CRC, but there is a need for further studies so that one can be able to establish the actual diagnostic and prognostic value of such substances.

---

## Conclusion

Inflammation is a key element in the association between CD and CRC, and its control decreases the risk of carcinogenesis. The pro-inflammatory state and molecular changes that occur partly explain the neoplastic risk underlying to this inflammatory disease.

Regarding CD, there are risk factors, in particular, the duration of disease (an already well-studied variable for ulcerative colitis, and now applied to CD) and the extent of colonic involvement.

Surveillance has become an increasingly important feature. In some cases, the conventional colonoscopy does not establish a diagnosis, and the appearance of chromoendoscopy increased the detection of a dysplastic mucosa. In those cases in which such a change is detected, the recommendation is to perform a complete colectomy.

Immunosuppression, along with the pro-inflammatory state, may explain this association although non-steroidal anti-inflammatory agents appear to delay the onset of cancer. The role of immunosuppression is controversial since studies have been published with different conclusions.

The use of appropriate surveillance protocols allows an early detection of the onset of cancer, and this translates into

decreased incidences and morbidity and mortality associated with this disease.

### Conflicts of interest

The authors declare no conflicts of interest.

### REFERENCES

- Andersen NN, Jess T. Has the risk of colorectal cancer in inflammatory bowel disease decreased? *World J Gastroenterol.* 2013;19:7561-8.
- Latella G, Papi C. Crucial steps in the natural history of inflammatory bowel disease. *World J Gastroenterol.* 2012;18:3790-9.
- Há F, Khalil H. Crohn's disease: a clinical update. *Therap Adv Gastroenterol.* 2015;8:352-9.
- Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis.* 2010;4:28-62.
- Beaugerie L. Natural history of intestinal lesions in inflammatory bowel disease. *Rev Prat.* 2014;64:1226-9.
- Kalla R, Venham NT, Satsangi J, Arnott ID. Crohn's disease. *BMJ.* 2014;349:g6670.
- Secher T, Gaillot O, Ryffel B, Chamaillard M. Remote control of intestinal tumorigenesis by innate immunity. *Cancer Res.* 2010;70:1749-52.
- Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut.* 2006;55:749-53.
- Harpaz N, Ward SC, Mescoli C, Itzkowitz SH, Polydorides AD. Precancerous lesions in inflammatory bowel disease. *Best Pract Res Clin Gastroenterol.* 2013;27:257-67.
- Dyson JK, Rutter MD. Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk. *World J Gastroenterol.* 2012;18:3839-48.
- Barral M, Dohan A, Allez M, Boudiaf M, Camus M, Laurent V, et al. Gastrointestinal cancers in inflammatory bowel disease: An update with emphasis on imaging findings. *Crit Rev Oncol Hematol.* 2016;97:30-46.
- Campos FG, Teixeira MG, Scanavini A, Almeida MG, Nahas SC, Ceconello I. Intestinal and extraintestinal neoplasia in patients with inflammatory bowel disease in a tertiary care hospital. *Arq Gastroenterol.* 2013;50:123-9.
- Lovasz BD, Golovics PA, Vegh Z, Lakatos PL. New trends in inflammatory bowel disease epidemiology and disease course in Eastern Europe. *Dig Liver Dis.* 2013;45:269-76.
- Brest P, Corcelle EA, Cesaro A, Chargui A, Belaïd A, Klionsky DJ, et al. Autophagy and Crohn's disease: at the crossroads of infection, inflammation, immunity, and cancer. *Curr Mol Med.* 2010;10:486-502.
- Kasper DL, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J. Harrison's principles of internal medicine, 19th ed. New York: McGraw Hill; 2015.
- Beaugerie L, Sokol H. Clinical, serological and genetic predictors of inflammatory bowel disease course. *World J Gastroenterol.* 2012;18:3806-13.
- Sanduleanu S, Rutter MD. Interval colorectal cancers in inflammatory bowel disease: the grim statistics and true stories. *Gastrointest Endosc Clin N Am.* 2014;24:357-448.
- Mescoli C, Albertoni L, D'incá R, Rugge M. Dysplasia in inflammatory bowel diseases. *Dig Liver Dis.* 2013;45:186-94.
- Coviello LC, Stein SL. Surgical management of nonpolypoid colorectal lesions and strictures in colonic inflammatory bowel disease. *Gastrointest Endosc Clin N Am.* 2014;24:447-54.
- Ahmadi A, Polyak S, Draganov PV. Colorectal cancer surveillance in inflammatory bowel disease: the search continues. *World J Gastroenterol.* 2009;15:61-6.
- Ullman T, Odze R, Farraye FA. Diagnosis and management of dysplasia in patients with ulcerative colitis and Crohn's disease of the colon. *Inflamm Bowel Dis.* 2009;15:630-8.
- Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology.* 2010;138:746-74.
- Viennot S, Deleporte A, Moussata D, Nancey S, Flourié B, Reimund JM. Colon cancer in inflammatory bowel disease: recent trends, questions and answers. *Gastroenterol Clin Biol.* 2009;33 Suppl 3:S190-201.
- Farraye FA, Odze RD, Eaden J, Itzkowitz SH, McCabe RP, Dassopoulos T, et al. AGA Institute Medical Position Panel on Diagnosis and Management of Colorectal Neoplasia in Inflammatory Bowel Disease. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology.* 2010;138:738-45.
- Neumann H, Vieth M, Langner C, Neurath MF, Mudter J. Cancer risk in IBD: how to diagnose and how to manage DALM and ALM. *World J Gastroenterol.* 2011;17:3184-91.
- Bonnington SN, Rutter MD. Surveillance of colonic polyps: are we getting it right. *World J Gastroenterol.* 2016;22:1925-34.
- Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. *Gastroenterology.* 2011;140:1807-16.
- van Rijn AF, Fockens P, Siersema PD, Oldenburg B. Adherence to surveillance guidelines for dysplasia and colorectal carcinoma in ulcerative and Crohn's colitis patients in the Netherlands. *World J Gastroenterol.* 2009;15:226-30.
- East JE. Colonoscopic Cancer Surveillance in Inflammatory Bowel Disease: What's New Beyond Random Biopsy. *Clin Endosc.* 2012;45:274-7.
- Lovasz BD, Lakatos L, Golovics PA, David G, Pandur T, Erdelyi Z, et al. Risk of colorectal cancer in Crohn's disease patients with colonic involvement and stenosing disease in a population-based cohort from Hungary. *J Gastrointest Liver Dis.* 2013;22:265-8.
- Bressenot A, Cahn V, Danese S, Peyrin-Biroulet L. Microscopic features of colorectal neoplasia in inflammatory bowel diseases. *World J Gastroenterol.* 2014;20:3164-72.
- Takeyama H, Mizushima T, Nakajima K, Uemura M, Haraguchi N, Nishimura J, et al. Metachronous, colitis-associated rectal cancer that developed after sporadic adenocarcinoma in an adenoma in a patient with longstanding Crohn's disease: a case report. *World J Surg Oncol.* 2013;11:295.
- Elsadani NN, East JE, Walters JR. New 2010 British Society of Gastroenterology colitis surveillance guidelines: costs and surveillance intervals. *Gut.* 2011;60:282-3.
- Leong RW, Butcher RO, Picco MF. Implementation of image-enhanced endoscopy into solo and group practices for dysplasia detection in Crohn's disease and ulcerative colitis. *Gastrointest Endosc Clin N Am.* 2014;24:419-25.
- Subramanian V, Bisschops R. Image-enhanced endoscopy is critical in the surveillance of patients with colonic IBD. *Gastrointest Endosc Clin N Am.* 2014;24:393-403.
- Baars JE, Kuipers EJ, van Haastert M, Nicolai JJ, Poen AC, van der Woude CJ. Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. *J Gastroenterol.* 2012;47:1308-22.
- Hutchison J, Cohen Z, Onyeagucha BC, Funk J, Nelson MA. How microRNAs influence both hereditary and

- inflammatory-mediated colon cancers. *Cancer Genet.* 2013;206:309-16.
38. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med.* 2009;361:2066-78.
  39. Han Z, Li C, Han S, Han Y, Qiu J, Shi Y, et al. Meta-analysis: polymorphisms in TNF-alpha gene promoter and Crohn's disease. *Aliment Pharmacol Ther.* 2010;159-70.
  40. Nagpal N, Kulshreshtha R. miR-191: an emerging player in disease biology. *Front Genet.* 2014;5:99.
  41. Zhu QC, Gao RY, Wu W, Qin HL. Epithelial-mesenchymal transition and its role in the pathogenesis of colorectal cancer. *Asian Pac J Cancer Prev.* 2013;14:2689-98.
  42. Hemminki K, Li X, Sundquist J, Sundquist K. Cancer risks in Crohn disease patients. *Ann Oncol.* 2009;20:574-80.
  43. Múzes G, Molnár B, Sipos F. Regulatory T Cells in inflammatory bowel diseases and colorectal cancer. *World J Gastroenterol.* 2012;18:5688-94.
  44. Caruso R, Warner N, Inohara N, Núñez G. NOD1 and NOD2: signaling, host defense, and inflammatory disease. *Immunity.* 2014;41:898-908.
  45. Rubio CA, Kapraali M, Befrits R. Further studies on the frequency of colorectal cancer in Crohn's colitis: an 11-year survey in the Northwest Stockholm County. *Anticancer Res.* 2009;29:4291-5.
  46. Cabral P, Barbosa E. Dissertação (Mestrado) O tabaco e a doença inflamatória intestinal. Faculdade de Medicina Universidade do Porto; 2014.
  47. Reenaers C, Belaiche J, Louis E. Impact of medical therapies on inflammatory bowel disease complication rate. *World J Gastroenterol.* 2012;18:3823-7.
  48. Egea-Valenzuela J, Belchí-Segura E, Essouri N, Sánchez-Torres A, Carballo-Alvarez F. Adenocarcinoma of the rectum and anus in a patient with Crohn's disease treated with infliximab. *Rev Esp Enferm Dig.* 2010;102:501-4.
  49. Gong J, Zhu L, Guo Z, Li Y, Zhu W, Li N, et al. Use of thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel diseases: a meta-analysis. *PLoS One.* 2013;8:e81487.