Premalignant lesions of the colon

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ABSTRACT: Cancer of the colon and rectum is the second most common cancer in men and women in North America. Early diagnosis results in detection of early stage tumors with a high probability of cure. Several studies document the efficacy of screening for the early detection of colorectal cancer; however, its incidence is so high that screening the entire older adult population is not feasible. Thus, attempts have been made to focus screening on patients at higher than average risk for colorectal carcinoma; these include patients with predisposing conditions or premalignant lesions of the colon. Common predisposing conditions include previous resection of an adenoma or carcinoma, a family history of colorectal carcinoma, and ulcerative colitis of more than 10 years' duration. The most important premalignant lesion is the colonic adenoma. Such lesions must be removed in their entirety and examined histologically to exclude the presence of carcinoma. Approximately 51% of patients with colonic adenomas removed by endoscopic polypectomy will be found to have a carcinoma within the polyp. If a pedunculated adenoma containing invasive carcinoma can be removed with a clear stalk margin, the risk of nodal metastasis is very low, probably less than 2%. In contrast, sessile lesions containing carcinoma already show invasion into the submucosa of the underlying bowel wall with a significant risk of nodal metastasis. Segmental colonic resection is rarely necessary for management of the patient with carcinoma arising in a pedunculated adenoma, but it is often justified for the patient with carcinoma in a sessile lesion. Dysplasia arising in ulcerative colitis is another important premalignant lesion that can be detected by colonoscopy with biopsy. The presence of high grade dysplasia in a patient with longstanding ulcerative colitis is an indication for colectomy. Can J Gastroenterol 1990;4(4):174-178 (pour résumé, voir page 175)

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IN THE UNITED STATES, CANCER ranks second only to cardiovascular disease in terms of cause of death. Colorectal cancer is the second most common type of cancer in both men and women combined, and has an overall mortality rate of approximately 50%. The likelihood of surviving a colorectal cancer is directly related to its stage at the time of diagnosis. Early diagnosis results in the detection of early stage tumours with a high probability of cure. Several studies have documented the efficacy of screening for the early detection of colorectal cancer; however, its incidence in Canada and the United States is so high that screening the entire older adult population would require a massive effort. Thus, attempts have been made to focus screening on patients at higher than average risk for colorectal carcinoma; these include patients with predisposing conditions or premalignant lesions of the colon (1,2).

Risk factors for colorectal cancers identify populations at increased risk. One example is age – the risk of colon cancer increases with age such that the average age at diagnosis is 60 years or more. Other risk factors include geographic location, genetic background and diet. These factors are often
Lésions précancéreuses du côlon

RESUME: En Amérique du nord, le cancer du côlon et du rectum est au second rang des cancers les plus courants chez les hommes et les femmes. Un diagnostic précoce permet de surprendre les tumeurs au premier stade de leur évolution et autorise une probabilité élevée de guérison. Plusieurs études démontrent l'efficacité des examens de surveillance dans la détection du cancer rectocolique; l'incidence de cette affection est cependant si élevée qu'il serait impossible de soumettre toute la population des adultes de plus de 40 ans à des examens de dépistage systématique. Ainsi, on a tenté d'en limiter la pratique aux sujets à risques anormalement élevés, c'est-à-dire aux patients présentant des facteurs prédisposants ou des lésions précancéreuses du côlon, par exemple. Parmi les conditions prédisposantes courantes figurent la résection ancienne d'un adénome ou d'un carcinome, des antécédents familiaux de carcinome recto-colique et une rectocolite ulcéro-hémorragique de plus de dix ans. La lésion précancéreuse la plus importante est l'adénome colique. Les lésions de ce type doivent être totalement excisées et soumises à un examen histologique afin d'exclure toute possibilité de carcinome. Chez près de 51% des patients atteints d'adénomes du côlon et ayant subi une polypectomie par endoscopie, on découvre que le polype renfermait un cancer. S'il est possible d'exercer un polype pédiculé contenant un cancer invasif en sectionnant une marge saine de pédoncle, le risque de nodule métastatique est très bas (probablement inférieur à 2%). Par contre, les lésions sessiles renfermant des cellules cancéreuses ont déjà envahi la sous-muqueuse de la paroi sous-jacente de l'intestin et elles présentent un risque élevé de recrudescence métastatique. Si la résection segmentaire du côlon s'impose rarement chez le patient atteint d'un cancer provenant d'un adénome pédiculé, elle est souvent justifiée chez le malade dont le cancer est situé dans une lésion sessile. La dysplasie résultant de la rectocolite ulcéro-hémorragique est une autre lésion précancéreuse décelable par une colonoscopie avec biopsie. La colectomie est indiquée en présence d'une dysplasie de haut degré chez le patient souffrant d'une rectocolite ulcéro-hémorragique de longue date.

interrelated, and their effects may be difficult to separate. Because risk factors affect large groups of individuals, they have relatively limited value in selecting specific patients for more intensive screening. It is, however, becoming standard practice to perform selected screening flexible sigmoidoscopies on patients over 50 years of age.

Predisposing conditions are diseases or conditions that identify individuals as being at increased risk for the development of colorectal cancer. Some examples of predisposing conditions are shown in Table 1.

Worldwide, schistosomiasis is perhaps the single most important predisposing condition. In parts of China and Africa, where this condition is endemic, the risk of colon cancer is said to be as high as 30% or more. In the United States, a history of previous resection of an adenoma or carcinoma is perhaps the single most important predisposing condition for colorectal carcinoma, connoting a moderately high risk of 10 to 15% over a 10 to 15 year follow-up period (3). A family history of colorectal carcinoma is also important, with the risk being described as low to high in various studies. Extensive ulcerative colitis of more than 10 years' duration also carries a high risk of colorectal carcinoma, but Crohn's disease of the colon of similar duration has a relatively low risk. The other conditions listed in Table 1 are not common and are therefore clinically less important.

Predisposing lesions have the potential to become cancerous. They are often associated with predisposing conditions, and probably represent the final common pathway through which predisposing conditions lead to carcinoma. The three premalignant lesions of the colorectum are epithelial dysplasia, adenomas and familial adenomatous polyposis.

| TABLE 1 |
| Predisposing conditions for colorectal carcinoma |
| Schistosomiasis | High risk |
| Previous adenoma or carcinoma | Moderately high risk |
| Family history of colorectal carcinoma | High risk |
| Ulcerative colitis for more than 10 years | High risk |
| Crohn's disease | Low risk |
| Ureterosigmoidostomy | Moderate risk |
| Therapeutic irradiation | Low risk |
| Peutz-Jeghers syndrome | Low risk |
| Juvenile polyposis | Low risk |

Low 1 to 4%; Moderate 5 to 9%; Moderately high 10 to 15%; High 15%+. Adapted from Haggitt RC. View Dig Dis 1985;17:1

COLONIC ADENOMAS

Adenomas of the colon represent the most common premalignant lesions. They are composed of dysplastic epithelium that has proliferated to form new glands or villi, creating a mass. An adenoma differs from dysplasia in that dysplastic epithelium in the latter remains confined to flat mucosa, whereas in an adenoma the dysplastic epithelium has proliferated to form a visible mass composed of new tubules or villi. The percentage of adenomas that progress to carcinoma is unknown but has been estimated to vary from 10 to 25% (3). In the important study by Stryker and colleagues (4) from the Mayo Clinic, patients with presumed adenomas on x-ray were followed for prolonged periods without treatment. After 15 years of follow-up, approximately 24% of these patients had a carcinoma at the site of the pre-existing lesion, suggesting that as many as 25% of adenomas may ultimately result in carcinoma.

The frequency with which an adenoma progresses to cancer probably depends on the size of the lesion when initially discovered and its histologic type. In general, the larger the adenoma, the more likely it is to be harbouring a carcinoma and, by presumption, the more likely it is to progress to carcinoma if left untreated. Similarly, the more the villous component in an adenoma predominates over the tubular component histologi-
Adenocarcinoma, muscularis propria, submucosa, subserosal connective tissue.

**Pedunculated Adenoma**
- Muscularis propria
- Submucosa
- Subserosal connective tissue

**Sessile Adenoma**
- Muscularis propria
- Submucosa
- Subserosal connective tissue

**Figure 1** Levels of invasion in a pedunculated adenoma (left) and a sessile adenoma (right). The stippled areas represent zones of carcinoma. Note that any invasion below the muscularis mucosae in a sessile lesion represents level 4 invasion, i.e., invasion into the submucosa of the bowel wall. In contrast, invasive carcinoma in a pedunculated adenoma (left) must traverse a considerable distance before it reaches the submucosa of the underlying bowel wall. The dotted line in the head of the pedunculated adenoma represents the zone of level 1 invasion. Although most pedunculated adenomas have a tubular pattern and most sessile adenomas are villous, exceptions to this generalization occur. (Reproduced with permission from Haggit RC, Golzbach RE, Soffer EE, Wurtle LD. Gastroenterology 1985;89:328-36.)

cally, the more likely it contains, or by presumption, will progress to, carcinoma. Because even small adenomas that are purely tubular may contain carcinoma, distinctions about size and villous component are principally of theoretical and not practical interest. If a patient has an adenoma, the only way to rule out the possibility that it contains a focus of carcinoma is to remove it in its entirety and examine it histologically. The third premalignant lesion, familial adenomatous polyposis, is beyond the scope of this discussion.

The most appropriate management for the 5% or so of patients who have a colonic polyp removed by endoscopic polypectomy and who are subsequently found to have a focus of carcinoma within the polyp is an important and somewhat controversial question. Management of endoscopically resected adenomas found to contain carcinoma is based on a balance between the estimated risk of lymph node metastases and their potential cure rate versus the risk of dying from a segmental colonic resection. The mortality and morbidity of surgical resection are related to age, clinical status and type of resection required. The risk of nodal metastasis in early colorectal carcinoma is related to the depth of invasion, with no substantial risk until the carcinoma penetrates into the submucosa of the underlying bowel wall (Figure 1) (5). In a pedunculated adenoma, this means that the carcinoma must extend through the head of the polyp, through the stalk, and into the underlying submucosa of the colonic wall before it acquires a significant risk of metastasis. Thus, if a pedunculated adenoma containing invasive carcinoma can be removed with a clear stalk margin, the risk of nodal metastasis is very low, probably less than 2%. On the other hand, if the lesion is sessile, any invasion below the muscularis mucosae penetrates into the submucosa and is associated with a sig-
significant risk of nodal metastasis (Figure 1). In a study conducted by the present author and colleagues, seven of 28 patients with invasion into the submucosa of the underlying bowel wall had adverse outcomes (5).

Other factors that probably increase the risk of nodal metastasis and which suggest the need for segmental resection include grade of the tumour and lymphatic invasion. High grade or poorly differentiated tumours have a risk of nodal metastasis that is not known with certainty, but which is probably relatively high, on the order of 50% or more. The reason the exact risk is unknown is that such tumours are frequently associated with lymphatic invasion, are deeply invasive, or both, so that the prognostic significance of grade independent of other factors cannot be determined accurately. A similar problem exists with regard to lymphatic invasion, because most tumours with this finding are also poorly differentiated, have invaded deeply, or both. Nevertheless, if a tumour is poorly differentiated or has lymphatic invasion, segmental resection for potential curative removal of positive lymph nodes is usually indicated, because the risk of fatal metastasis usually exceeds the risk of dying from the surgical procedure in such patients.

**DYSPLASIA IN ULCERATIVE COLITIS**

The exact level of the risk of carcinoma in ulcerative colitis is a controversial subject, but there is general agreement that it exceeds the risk in the population without ulcerative colitis. Factors in ulcerative colitis that increase the risk include extent of disease – disease extending proximally to the sigmoid colon indicates a higher risk than more limited disease. Duration is also important, as the risk does not rise to significant levels until after eight to 10 years of disease. It should be emphasized that the degree of activity of the disease does not influence the risk of carcinoma. Patients with remissions of long duration have a risk equal to that of patients who have continuously active disease. In fact, the risk in the former group may be even higher, as patients with longstanding active disease tend to undergo colectomies before they enter the high risk period.

Neoplastic progression in ulcerative colitis is probably a multistep process that begins with inflammation leading to dysplasia and culminating in carcinoma. The exact number of steps required and the length of time necessary for them to evolve is unknown. Although precise data are unavailable, epithelial dysplasia would probably progress to cancer in 50 to 75% of patients with longstanding ulcerative colitis who develop this lesion and who are not treated by colectomy. Neither the inevitability of progression to carcinoma nor the time course required for this progression in ulcerative colitis are known.

Dysplasia in ulcerative colitis can be graded as negative, indefinite, or positive, with the positive group being subdivided into low and high grades. Dysplastic epithelium most often occurs in flat mucosa that appears unremarkable to the endoscopist, apart from the changes of ulcerative colitis. Occasionally, a nodular or villiform mucosal surface may be seen. Biopsies of dysplastic epithelium reveal distortion of crypt architecture and cytologic abnormalities, including enlarged, hyperchromatic nuclei that are crowded and stratified (Figure 2). The presence of active inflammation complicates the interpretation of dysplasia, because reactive changes induced by inflammation can closely mimic dysplastic epithelium. Thus, when searching for dysplasia, one should biopsy the colonic mucosa while the disease is in remission.

The diagnosis of dysplasia is a difficult challenge for the pathologist, and there is a fair amount of interobserver variation in its recognition and grading, particularly when it is less than high grade. For this reason, it is probably appropriate for most pathologists who do not have much experience with this lesion to seek an expert opinion regarding the diagnosis before recommending colectomy.

If neoplastic progression in ulcerative colitis is a multistep process beginning histologically with inflammation and progressing through dysplasia to carcinoma, there should be accompanying genetic abnormalities that can...
be identified objectively. Aneuploidy (abnormal DNA content) measured by flow cytometry is frequent in patients with dysplasia or carcinoma in ulcerative colitis (6). Aneuploidy is most probably a reflection of neoplasia, and it may be present before overt histologic changes. In addition, increased proliferation detected by flow cytometry is frequent in longstanding ulcerative colitis. Such proliferative abnormalities could represent either a response to inflammation or a neoplastic loss of growth control. If this abnormal proliferation can be shown to be a clonal phenomenon, it could be an early step in neoplastic progression that precedes overt histologic evidence of dysplasia. All of the authors' patients whose biopsies have shown dysplasia or carcinoma, or that were indefinite for dysplasia, have had abnormalities detected by flow cytometry.

Maps of the distribution of dysplasia in ulcerative colitis have been created; dysplasia can be quite limited in extent and focal in distribution, meaning that extensive biopsying would be required for its detection (6). In other patients the dysplasia is extensive so that random biopsies would probably detect the lesion.

Table 2 shows the results of a long term, prospective surveillance program for dysplasia and carcinoma in ulcerative colitis that was initiated 15 years ago (7,8).

None of the patients with ulcerative colitis who had carcinoma detected in their colectomy specimens had any clinical evidence of the lesion; thus, these all represent unsuspected carcinomas. The difference in the prevalence of unsuspected carcinoma in the group of patients whose biopsies showed dysplasia on the initial colono-

<table>
<thead>
<tr>
<th>Diagnosis on initial biopsy</th>
<th>Number of patients</th>
<th>Developed dysplasia</th>
<th>Underwent colectomy</th>
<th>Had carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia</td>
<td>18</td>
<td>(18)</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Indefinite</td>
<td>20</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>175</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>213</td>
<td>29</td>
<td>22</td>
<td>8</td>
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REFERENCES