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ENDGAMES

PICTURE QUIZ

An abnormality at the hepatic flexure

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A 92 year old woman presented to the emergency department after collapsing at home. She recalled standing from her chair, feeling lightheaded, and then collapsing. She had felt generally weak for more than a year, with weight loss of 56 lb (25.2 kg) but no change in bowel habit, dysphagia, or gastrointestinal bleeding. Her medical history included hypertension, hypothyroidism, and anaemia (which was currently being investigated by her general practitioner). Among other drugs, she was taking lisinopril, bendroflumethiazide, and levothyroxine. Her son had died at 60 years of age from large bowel obstruction and perforation secondary to colon cancer.

On examination she appeared cachectic with evidence of conjunctival pallor. Her blood pressure was 117/54 mm Hg when lying and 52/31 mm Hg when standing. No masses were palpable on abdominal examination.

Blood tests showed iron deficiency anaemia and hyponatraemia (haemoglobin 75 g/L (normal range 115-165), mean corpuscular volume 78 fL (80-97), iron 2 µmol/L (12-26), total iron binding capacity 42 µmol/L (45-70; 1 µmol/L=5.59 µg/dL), transferrin saturation (ratio of iron to total iron binding capacity) 4.76% (15-50), sodium 130 mmol/L (135-145; 1 mmol/L=1 mEq/L)). Lisinopril and bendroflumethiazide were stopped and the postural hypotension and hyponatraemia resolved. Oesophagogastroduodenoscopy showed no cause for the anaemia. Computed tomography of the abdomen showed an abnormality at the hepatic flexure (fig 1).

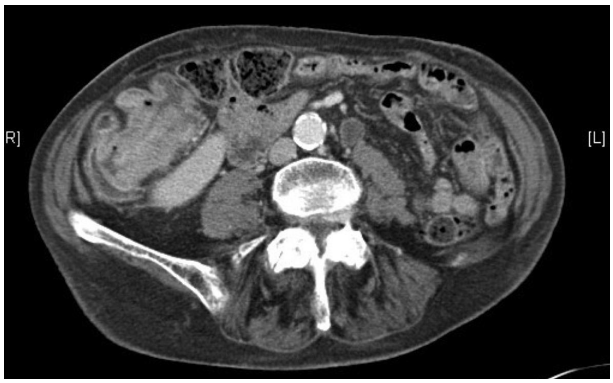

Fig 1 Axial computed tomogram of the abdomen

Questions

1 What does the scan show and what is the most likely underlying diagnosis?

2 What are the causes of this condition?

3 What are the treatment options for this condition?

4 What screening procedures are available to facilitate early diagnosis of this condition in the general population?

Answers

1 What does the scan show and what is the most likely underlying diagnosis?

Short answer

A large bowel stricture with shouldering at the hepatic flexure consistent with colonic carcinoma.

Long answer

The axial abdominal computed tomogram shows a shouldered colonic stricture at the hepatic flexure (fig 2). The stricture has resulted in early subacute bowel obstruction as shown by a mildly dilated caecum with air fluid level and minor fluid

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distension of the terminal ileum, owing to an incompetent ileocaecal valve (fig 3). The proximal small bowel is of normal calibre, with normal bowel content and gas in the distal colon.

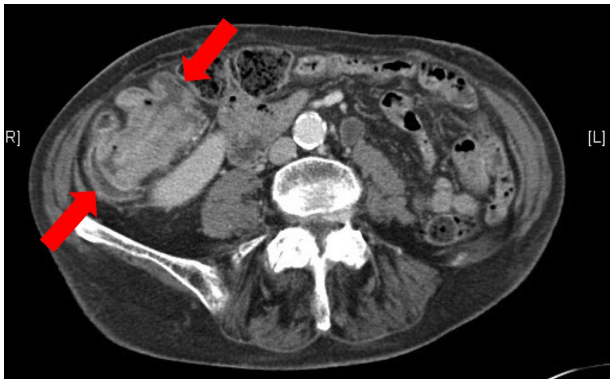

Fig 2 Axial computed tomogram of the abdomen showing an apple core stricture at the hepatic flexure (between red arrows)

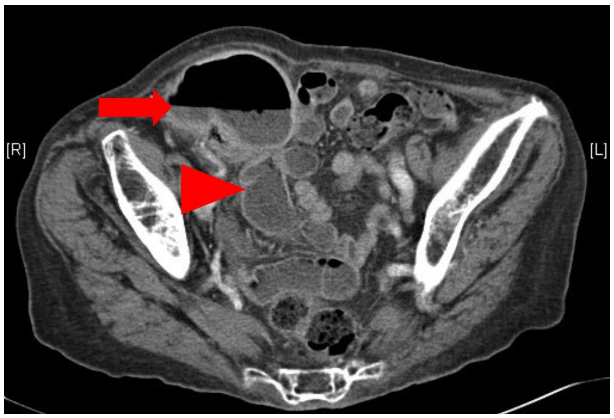

Fig 3 Axial computed tomogram of the abdomen showing a dilated caecum with an air fluid level (red arrow) and mildly dilated fluid filled terminal ileum (red arrowhead)

The stricture affects a short segment of colon and has the classic "apple core" appearance associated with annular-type colorectal cancer.[1 2] (Previously, when barium enema was the initial form of diagnostic imaging, most colorectal cancers detected were described as apple core-type lesions owing to their shouldered margins and strong resemblance to a partially eaten apple core[3]).

There is nodular extramural infiltration into the pericolic fat and small adjacent local lymph nodes but no distant metastatic disease. Hence, this cancer is radiologically staged as T3, N1, and M0 (tables 1⇓ and 2⇓).

Three main morphological subtypes of colorectal cancer are seen on imaging: polypoid lesions arising from adenomatous polyps, annular lesions arising from irregular circumferential masses (as here), and flat broad based lesions.[4 5] Most colorectal cancers detected radiologically are of the annular type, which give rise to the strictured apple core appearance described here.[1 2] On barium enema less than 40% appear as polypoid lesions and less than 10% as flat carpet-like lesions.[4 6]

Computed tomography is used to stage tumours preoperatively, identify metastatic disease, assess recurrence, and detect complications of colorectal cancer.[1 5 7] Preoperative nodal staging in colon cancer is unreliable and does not often alter management. The appearance of colon cancer on computed tomography depends on the degree of spread through the bowel wall (see tables 1 and 2). Typical findings are that of an annular lesion, seen as a soft tissue mass causing luminal narrowing and colonic wall thickening.[1 5]

The differential diagnoses include tumours, inflammatory diseases, infections, and iatrogenic causes (box).[2 5 3 9-12] Annular colorectal carcinoma is the most common cause of colonic apple core lesions.

2 What are the causes of this condition?

Short answer

About 90% of colon cancers are sporadic and 10% are familial. Risk factors include poor intake of fibre, high intake of fat and red meat, obesity, chronic inflammatory bowel disease, and previous colonic cancer. Familial cases relate to hereditary syndromes such as familial adenomatous polyposis coli and hereditary non-polyposis colorectal cancer.

Long answer

In sporadic cases dietary, lifestyle, and medical risk factors that accelerate the multistep process of carcinogenesis have been identified.[13] Recognised risk factors include older age, living in industrialised countries, low fruit and vegetable consumption, obesity, smoking, alcohol consumption, chronic inflammatory bowel disease, and previous colonic cancer.[13 14] Suspected but unconfirmed risk factors include physical inactivity; diets high in fat and red meat; and diets low in calcium, folate, selenium, carotenoid, and fibre.[13 14] The molecular mechanisms involved in the development of chronic inflammatory bowel disease are similar to those for colon cancer.[15] Breast cancer, diabetes, and previous cholecystectomy have a more questionable role in colon cancer pathogenesis.[14]

Hereditary syndromes predisposing to colorectal cancer include familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, Peutz-Jeghers syndrome, juvenile polyposis, Cowden's disease, Bannayan-Riley-Ruvalcaba syndrome, Li-Fraumeni syndrome, and Bloom syndrome.[16] In familial adenomatous polyposis coli, a germline mutation occurs in the adenomatous polyposis coli tumour suppressor gene (*APC*) or in the *MYH* gene.[16] In hereditary non-polyposis colorectal cancer, mutations occur in short repetitive DNA sequences, known as microsatellite sequences, in mismatch repair genes—most commonly the *MLH1* and *MSH2* genes.[13] *APC* mutations are present in 80-85% of cases of sporadic colorectal cancer, and mismatch repair gene mutations are present in 15% of cases.[17] Most colorectal cancers are sporadic, with hereditary cancers accounting for only 5-10% of cases.[13]

In both sporadic and hereditary cases, development of colorectal carcinoma involves the initial formation of neoplastic polyps. Most cases of colorectal cancer develop from tubular and villous adenomatous polyps, with serrated (sessile) adenomatous polyps, previously known as hyperplastic-type polyps, less often implicated.[14] Hence, two main pathways of carcinogenesis are described: the adenoma-carcinoma sequence and serrated adenoma-carcinoma sequence.[14 18]

In both sequences a stepwise accumulation of tumour suppressor gene mutations and activation of oncogenes are needed for cancer to develop.[16] Such genetic alterations may occur at the chromosomal level with allelic losses, known as loss of heterozygosity or chromosomal instability. This form of genetic instability accounts for inactivation of the tumour suppressor genes *P53*, *DCC* (deleted in colorectal carcinoma), *SMAD4*, *SMAD2*, and *APC* and activation of the oncogene *KRAS*.[16 18] In addition, mutation or inactivation of mismatch repair genes, such as *MLH1*, via microsatellite instability or promoter region

Differential diagnosis of colonic "apple core" lesions

Tumours
- Colonic adenocarcinoma
- Lymphoma
- Secondary ovarian cancer
- Villous adenoma

Inflammatory diseases
- Crohn's disease
- Ulcerative colitis
- Diverticulitis

Vascular diseases
- Ischaemic colitis

Infections
- Chlamydia
- Tuberculosis
- *Mycobacterium avium* complex
- *Histoplasma capsulatum*
- Helminthoma
- Amoebiasis
- Cytomegalovirus

Iatrogenic causes
- Stereotactic radiosurgery
- Radiation colitis

hypermethylation, respectively, can lead to colorectal cancer.[13 14 16] Thus there are three main mechanisms in the molecular pathogenesis of colorectal cancer—chromosomal instability, microsatellite instability, and DNA hypermethylation.[15] As evidence on cancer prevention, screening, and treatment based on molecular markers increases, current views of the pathogenesis of colorectal cancer are shifting away from the traditional polyp-carcinoma sequence towards pathways based on the molecular pathogenesis and gene profiles.[18]

3 What are the treatment options for this condition?

Short answer

Localised colon cancers are treated with segmental surgical resection; adjuvant chemotherapy is needed in cases with nodal spread or poor prognostic features on histology. Metastatic disease is treated mainly with combination chemotherapeutic agents—fluoropyramidines and oxaliplatin or irinotecan—and monoclonal antibodies bevacizumab and cetuximab.

Long answer

Management of colon cancer requires a multidisciplinary team comprising the patient, colorectal surgeons, oncologists, radiologists, specialist nurses, and stoma nurses.[19-21] This facilitates well informed evidence based treatment planning, especially in those with metastatic disease, while also ensuring the patient's psychological needs are met and that they are kept fully informed.[19-22]

Treatment options can be considered according to staging and mode of presentation (fig 4). Stage I cancers are confined to the colonic submucosa or muscularis propria, stage II cancers may extend from the colonic subserosa into visceral peritoneum and adjacent organs, stage III cancers have lymph node involvement, and stage IV cancers have metastatic spread (see tables 1 and 3⇓). Treatment of stage I-III disease is curative, whereas in most stage IV cancers a palliative approach is adopted with the aim of improving survival and quality of life.

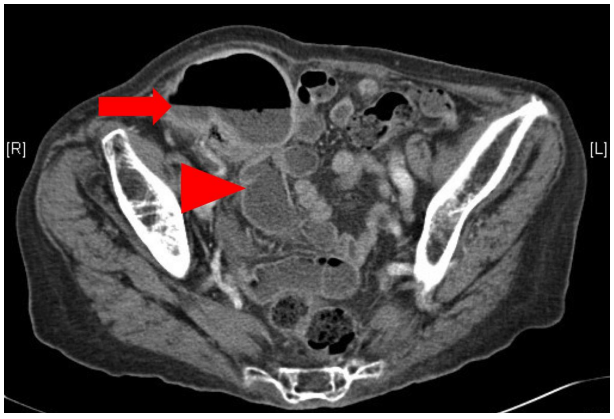

Fig 4 Flow chart for the management of colon cancer. Adapted from the National Institute for Health and Clinical Excellence.[20] Stage II "high risk" includes cancers with pathological extramural vascular or perineural invasion, pathological T4 disease (serosal breach or perforation), bowel obstruction, poorly differentiated or mucinous tumours, or fewer than 10-12 lymph nodes recovered at surgery. CT=computed tomography; MDT=multidisciplinary team

Surgery is indicated in patients with a good performance status in both local (stages I-III) and metastatic (stage IV) disease. For local cancers, operative procedures involve radical segmental mesocolic resection and primary anastomosis, which aim to eradicate disease and remove the regional lymphovascular drainage.[23 24] Metastatic cancers must be assessed by the multidisciplinary team before they can be deemed resectable immediately or after neoadjuvant chemotherapy.[19-21] Surgical options in metastatic disease include colectomy or resection of lung or liver metastases.[15 23] In a retrospective study, immediate colectomy with adjuvant chemotherapy in patients with a good

performance status, well differentiated tumours, and synchronous liver metastases, increased survival compared with chemotherapy alone.[25] Resection of liver metastases is potentially curative for certain patients and may result in disease-free survival of more than 20 years.[26] Radiofrequency ablation is an alternative treatment for liver metastases. A meta-analysis showed that resection of isolated hepatic metastases was superior to radiofrequency ablation in terms of survival and local disease control.[27] It was concluded that radiofrequency ablation should be reserved for patients with solitary liver metastases who are poor surgical candidates. Resection of lung metastases may also improve survival in patients with stage IV cancers, especially those with unilateral lung metastasis and a T1-2 (Dukes's A) primary colon cancer.[28]

For resection of primary colon cancers a laparoscopic rather than open approach may be used depending on the lesion's suitability and the surgeon's experience.[20] Evidence indicates that oncological outcomes and survival are similar for the two approaches, and that laparoscopy may reduce pain, the duration of ileus, and length of hospital stay.[20 29 30]

Emergency presentations of mechanical bowel obstruction caused by colon cancer should be confirmed radiologically and considered for emergency resection or colonic stenting as a bridge to surgery.[19 21] The National Institute for Health and Clinical Excellence (NICE) recommends that people who present with left sided obstruction and no evidence of perforation or peritonitis should undergo colonic stenting.[20] This avoids the morbidity associated with emergency surgery, may prevent the need for stoma formation, and allows planning of elective surgery after optimisation of patient risk factors and full tumour staging.[31] However, the risk of bowel perforation secondary to stenting should be considered while making a treatment decision.[19]

Overall five year survival after radical resection of colon cancers is 60-70%.[32 33] Survival is stage dependent, with five year survival being greater in stage I disease (~100%) than in stage IV disease (~16%).[32] Postoperative complications occur in 18-37% of patients and commonly include wound infections, wound dehiscence, bowel anastomotic dehiscence (~5%), pneumonia, abdominal abscess, and ileus.[32 34] Postoperative mortality at 30 days is 1-4% in elective cases, rising to 10% in emergency cases.[32 35]

Adjuvant chemotherapeutic agents include fluoropyrimidines (fluorouracil (with folinic acid) or capecitabine) and oxaliplatin (see table 4⇓ for mode of action and common side effects).

Adjuvant treatment is recommended in stage III disease (nodal spread) and in "high risk" stage II disease to prevent disease recurrence and improve survival.[20 36] Several pathological features are used to identify high risk disease, including extramural vascular or perineural invasion, pathological T4 disease (serosal breach or perforation), bowel obstruction, poorly differentiated or mucinous tumours, and less than 10-12 lymph nodes recovered at surgery.[15 20 21]

The patient's age is important when considering adjuvant treatment. In the QUASAR study, involving mainly stage II patients randomised to adjuvant fluorouracil and folinic acid or observation, the survival benefit for adjuvant treatment was restricted to those aged less than 70 years.[37] In addition, the MOSAIC trial, which compared oxaliplatin with fluorouracil and folinic acid with standard treatment (fluorouracil and folinic acid) mainly in patients with stage III disease, found no significant survival benefit in the intervention group in those over 65 years.[38] This suggests that patients with stage III disease aged over 65 should be offered fluorouracil only.

Most patients with stage IV cancer are not surgical candidates and treatment is palliative with chemotherapy. Chemotherapeutic agents used in metastatic disease that have been shown to increase survival and downstage cancer to a resectable status include combinations of intravenous fluorouracil with folinic acid and oxaliplatin or irinotecan.[15 19 20 23] Alternative treatments to fluorouracil include the oral fluorouracil prodrugs, capecitabine or tegafur with uracil, or raltitrexed (for those intolerant to fluorouracil treatment).[20 39] Table 4 provides a review of the various classes of chemotherapeutic agent used in colon cancer.

The decision to start chemotherapy should always be made after an informed discussion between the treating oncologist and patient while considering adverse effects of chemotherapy agents, the patient's performance status, and personal preferences.[20 21]

Asymptomatic patients with stage IV disease and non-obstructing tumours may be treated conservatively. If obstruction occurs, palliative stenting may be considered for left sided tumours.[23]

Biological agents, including the vascular endothelial growth factor antibody bevacizumab and epidermal growth factor receptor antibody cetuximab, also play a role in the management of stage IV disease as adjuncts to chemotherapeutic agents or in chemorefractory patients.[15 19 20] Bevacizumab is associated with improved survival when used alongside combinations of fluoropyramidine and irinotecan.[43] Cetuximab may help to improve the treatment response rate when added to combination chemotherapy and increase survival in tumours with an unmutated (wild-type) *KRAS* gene.[44]

4 What screening procedures are available to facilitate early diagnosis of this condition in the general population?

Short answer

In the UK, the NHS bowel screening programme offers biennial faecal occult blood testing for those aged 60-74 years, followed by colonoscopy if the test is positive. People at high risk may be offered colonoscopy surveillance.

Long answer

Screening of colorectal cancer can be divided into that for the general population and that for those at high risk.[23]

The NHS bowel screening programme involves biennial screening for those aged 60-74 years with the faecal occult blood test and subsequent colonoscopy if the test is positive.[45] Randomised controlled trials of this test in the United States, Denmark, and the UK have shown a significant decrease in deaths caused by colorectal cancer, with a meta-analysis showing a 16% reduction.[46] This reduction is attributed mainly to early detection and treatment of colorectal cancer rather than precancerous adenomas because follow-up is unlikely to have been long enough in the trials.[47 48] However, the robustness of this evidence for population based screening has been questioned because total mortality was not reduced in the trials, as would have been expected, and the number needed to treat was high, ranging from 600 to 1200.[48] Furthermore, the reduction in death from colorectal cancer was confined to the first 10 years, with no evidence for benefit after the initial six rounds of biennial screening.[49]

Because of potential complications of screening through invasive investigation with colonoscopy,[47] and the unsuitability of certain frail and elderly patients for endoscopy, computed tomography

colonography may be considered as an alternative test after a positive faecal occult blood test.[50]

Those with affected first degree family members, a family history of specific hereditary syndromes, or a history of inflammatory bowel disease may be at increased risk of developing colorectal cancer. The British Society of Gastroenterology and the Association of Coloproctology of Great Britain and Ireland have issued detailed guidance in this area (summarised in table 5⇓).[21 51]

Patient outcome

The patient underwent a right hemicolectomy and primary anastomosis for the right sided colorectal cancer. Macroscopically, the cancer had a polypoid and ulcerating appearance, with circumferential involvement of the large bowel. Histological evaluation showed a moderately differentiated adenocarcinoma extending into the muscularis propria, with extramural vascular invasion but no spread to the lymph nodes. The tumour was pathologically staged as T3 N0 Mx (Dukes's B) and required no adjuvant treatment. She made a good recovery and had no symptoms at one month follow-up. Screening guidelines recommend that any first degree relatives should undergo colonoscopy at 55 years of age because both she and her son developed colon cancer with mean age greater than 60 years.[51]

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Patient consent obtained.

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Tables

Table 1| The American Joint Committee on Cancer (AJCC) TNM staging system for colorectal cancer8

Characteristic	Description
Primary tumour	
T0	No evidence of primary tumour
Tis	Carcinoma in situ; intraepithelial or lamina propria invasion
T1	Submucosal invasion
T2	Muscularis propria invasion
T3	Subserosal/pericolorectal invasion
T4a-b	a: Invasion through serosa to surface of visceral peritoneum; b: Invasion or adherence to other organs and structures
Regional lymph nodes	
N0	No regional lymph node metastases
N1	1-3 regional lymph nodes affected
N2a-b	a: 4-6; b: >6 regional lymph nodes affected
Distant metastases	
M0	No distant metastases
M1a-b	a: Distant metastases in 1 site or organ; b: metastases in >1 site or organ or peritoneum

Table 2| **Staging of colorectal cancer with computed tomography7**

Stage	Appearance on computed tomography
T1	Intraluminal mass; no thickening
T2	Thickened wall (>0.6 cm) or pelvic mass; no invasion or extension to pelvic side walls or abdominal wall
T3a	Thickened wall (>0.6 cm) or pelvic mass; invasion of adjacent structures but not to pelvic side walls or abdominal wall
T3b	Thickened wall or pelvic mass with extension to pelvic side wall or abdominal wall
T4	Distant metastases with or without local abnormality

Table 3 | **The American Joint Committee on Cancer staging of colorectal cancer8**

Stage	T	N	M	Dukes	Modified Astler-Coller classification
0	T0-Tis	N0	M0	—	—
I	T1-2	N0	M0	A	A-B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-2	N1-2a	M0	C	C1
IIIB	T1-4a	N1-2b	M0	C	C1-2
IIIC	T3-4b	N1-2b	M0	C	C2-3
IV	Any T	Any N	M1	-	D

Table 4| **Chemotherapeutic agents used in colorectal cancer40 41**

Class	Examples	Mode of action	Side-effects
Antimetabolite: fluoropyramidines	Fluorouracil (with folinic acid); oral fluorouracil prodrugs: capecitabine, tegafur (with uracil)	Inhibit tumour growth by inhibiting RNA synthesis and function and inhibiting thymidylate synthase (which helps DNA synthesis and repair through catalysing production of the pyrimidine, thymidine).[42] These drugs are incorporated into DNA leading to DNA strand breaks. Folinic acid augments the action of fluorouracil	Anorexia, headache, gastrointestinal disturbance, oral mucositis, myelosuppression, alopecia, cerebellar syndrome (rare), desquamative hand-foot syndrome (prolonged infusions)
Antimetabolite: thymidylate synthase inhibitor	Raltitrexed	Inhibits thymidylate synthase, thereby disrupting DNA and RNA synthesis and tumour growth	Gastrointestinal disturbance, asthenia, myelosuppression
Platinum based alkylating agent	Oxaliplatin	Forms cross links with DNA, thereby inhibiting DNA replication and transcription	Neurotoxicity (including peripheral neuropathy) gastrointestinal disturbance, ototoxicity, myelosuppression, interstitial lung disease, pulmonary fibrosis
Topoisomerase I inhibitor	Irinotecan	Inhibits topoisomerase I, thereby disrupting DNA replication by preventing the repair of DNA double strand breaks	Myelosuppression, gastrointestinal disturbance, acute cholinergic syndrome with early diarrhoea and delayed diarrhoea, asthenia, alopecia, anorexia, interstitial lung disease

Table 5| **Screening for colorectal cancer in higher risk individuals21 51**

Risk factor	Risk of cancer	Colonic surveillance
First degree family member <45 years old or 2 first degree family members	Moderate	Single colonoscopy at 55 years age*
≥3 first degree relatives affected (none <50 years old)	Moderate to high	Colonoscopy 5 yearly from 55-75 years of age*
A family history of hereditary non-polyposis colorectal cancer and positive mismatch repair gene mutation	Very high	Colonoscopy 2 yearly from 25 years of age (or from 5 years younger than age of diagnosis of family member) to 75 years of age
A family history of familial adenomatous polyposis coli and positive *APC* mutation†	Very high	Prophylactic colectomy at 16-20 years of age. If surgery is deferred, 6 monthly flexible sigmoidoscopy + annual colonoscopy are necessary, but surgery is strongly recommended before 25 years age
Inflammatory bowel disease	Higher risk than general population	Colonoscopy 10 years after onset of symptoms to assess endoscopic risk factors,‡ with pancolic dye spray and biopsy of abnormal areas. Colonoscopy should be carried out yearly, 3 yearly, or 5 yearly, depending on family history and endoscopy risk factors‡

*If 3-4 adenomas or 1 adenoma ≥1 cm found then 3 yearly colonoscopy, if ≥5 adenomas or ≥3 adenomas with 1 adenoma ≥1 cm then annual colonoscopy.
†If no *APC* mutation is identified, flexible sigmoidoscopy is recommended yearly between 13 and 30 years of age and 3-5 yearly between 30 and 60 years of age.
‡Endoscopic risk factors include: active inflammation, extent of inflammation (surface area, proximal extension), postinflammatory polyps, strictures, and confirmed dysplasia.