

*Ministry of Defence*

## **Synopsis of Causation**

### **Colorectal Cancer**

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## **Disclaimer**

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This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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# 1. Definition

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- 1.1. Cancer of the colon and cancer of the rectum share many common features with regard to aetiology, treatment, and prognosis. Consequently, published reports often refer to combined data from these two sites, using the titles of either colorectal or large bowel cancer.
- 1.2. Worldwide, an estimated 1 million new cases of colorectal cancer are diagnosed per year. According to WHO mortality estimates, around 622,000 people died as a result of the disease in 2002. On this basis, colorectal cancer is the third highest cause of death from cancer worldwide, exceeded only by lung cancer and stomach cancer.<sup>1</sup>
- 1.3. In the UK, 35,969 new cases of colorectal cancer were diagnosed in 2002 making it the third most common site for cancer diagnosis, following breast and lung cancer. Despite an increase in incidence over the last 20 years, deaths from colorectal cancer have been falling and the estimated prevalence of the condition in the UK for the year 2000 reached 77,000. The five-year relative age-standardised survival rate for patients diagnosed with colorectal cancer between 1996 and 1999 was just under 50%. Nonetheless, the disease remains the second most common cause of cancer mortality in the UK, responsible for 16,107 deaths in 2003. The incidence rises with age in both sexes, and nearly 85% of cases in the UK arise in people who are aged over 60 years. The lifetime risk for developing colorectal cancer is 1 in 18 for men and 1 in 20 for women.<sup>2,3</sup>
- 1.4. In the UK, around 63% of cases of large bowel cancer arise in the colon, with the remaining 37% in the rectum (i.e. the distal 15cm of the large intestine). Tumours in the [sigmoid colon](#), rectosigmoid junction and the rectum together account for over half of all cases. The proximal colon (right side) is less often affected, although the [caecum](#) is a relatively common site.
- 1.5. The text of this synopsis focuses on [adenocarcinoma](#), which constitutes around 98% of colonic cancers. However, other malignancies can affect the large bowel, albeit rarely. These include:
  - colorectal [lymphomas](#) (most commonly associated with immunosuppression, including HIV infection)<sup>4</sup>
  - [carcinoid](#) tumours
  - gastrointestinal stromal tumours (mural sarcomas)
  - squamous cell carcinomas (at the anus or anorectal junction only)
  - direct invasion from cancers arising in adjacent organs (e.g. ovary, uterus, bladder, or prostate)
  - [metastatic](#) tumours that exhibit an affinity for the gastrointestinal tract (e.g. malignant melanoma)
  - tumours of the appendix that extend into the caecum<sup>5</sup>
- 1.6. More than 90% of colorectal cancers develop from [adenomatous polyps](#).<sup>6</sup> These polyps grow slowly and can gradually become malignant. A polyp is generally considered a cancer risk when it reaches a size more than 1cm. Villous adenomas have a stronger malignant potential than either the tubular or tubulovillous types (see section 3.2). The development of invasive carcinoma is preceded by progressive cellular atypia (dysplasia).

## 2. Clinical Features

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- 2.1. Colorectal cancer is often symptomless in the early stages of the disease. The range of presenting symptoms includes the following:
- Bleeding, manifested by dark, tarry stools (melaena) or red blood in the stool
  - Persistent change in the bowel habit (includes diarrhoea, constipation or change in stool consistency)
  - Abdominal discomfort, pain, sensation of incomplete evacuation ([tenesmus](#))
  - Unexplained anaemia and/or weight loss
  - Surgical emergency ([peritonitis](#) due to bowel perforation or acute intestinal obstruction)
- 2.2. There may be no abnormal physical findings. Where physical signs are present, they may include the following:
- Abdominal mass or tenderness
  - Palpable mass, blood or mucus on rectal examination
  - Pallor secondary to anaemia
  - Advanced cases may display [cachexia](#), enlarged liver due to [metastases](#), or [ascites](#) secondary to [peritoneal](#) deposits
- 2.3. Screening and investigative techniques include the following:
- Digital rectal examination
  - Faecal occult blood (FOB) testing
  - [Sigmoidoscopy](#), both rigid and flexible, which allows inspection of the rectum and [sigmoid colon](#)
  - [Colonoscopy](#), which is generally the investigation of choice as it allows the entire bowel to be visualised, [polyps](#) to be removed and [biopsy](#) samples to be taken
  - Double-contrast barium enema
  - Genetic testing is recommended for individuals with a family history suggestive of hereditary colon cancer
  - Ultrasound scan, computed tomography (CT) and magnetic resonance imaging (MRI) are used to stage the tumour and plan treatment
  - Plasma levels of carcinoembryonic antigen (CEA) can prove useful in monitoring the course of the disease
  - Faecal testing for cancer-specific mutations in DNA is currently being evaluated
  - Computed tomography colonography (CTC), a new minimally-invasive technique that generates a “virtual colonoscopy”, is also undergoing evaluation
- 2.4. The **staging** of the tumour guides the choice of therapy and the evaluation of prognosis. Several staging systems have been described, the most common of which are as follows:<sup>5</sup>
- 2.4.1. The **TNM** method of classification has become the recommended standard for staging colorectal cancer. In this system:
- the depth of penetration of the primary tumour into the underlying [submucosa](#) and muscle coat of the intestine is allocated a **T** grade

- the status of spread into the regional lymph nodes is allocated an **N** grade
- the presence or absence of detectable distant metastases is allocated an **M** grade

The combination of T, N, and M scores provides the basis of the staging which ranges from stage 0 (carcinoma in situ) through stages I, IIA, IIB, IIIA, IIIB, and IIIC to stage IV (presence of distant metastases).

2.4.2. **Dukes' classification**, dating from 1932, divides tumours into stages A-C according to the degree of penetration of the bowel wall and the presence or absence of lymph node deposits.

2.4.3. The Astler-Coller modification of Dukes' classification divides tumours into stages A-D, roughly approximating to stages I-IV as defined by the TNM classification.

2.5. The regional lymph nodes and liver constitute the main sites for [metastases](#).

### 3. Aetiology

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- 3.1. The risk of developing colorectal cancer increases with advancing age. Geographically, incidence rates vary considerably, with the highest rates in the developed world and the lowest in Africa and Asia. The incidence of colorectal cancer rises rapidly in migrants moving from low to high risk countries. The rates for second generation migrants can be double that of the first. Conversely, the incidence of colorectal cancer falls in migrants moving from high to low risk countries.<sup>7</sup>
- 3.2. More than 90% of colorectal cancers begin as small, non-cancerous [adenomatous polyps](#) which, over time, have the potential to undergo stepwise transformation to malignant change. This process is known as the **adenoma-carcinoma sequence**. Adenomatous polyps are usually asymptomatic and may be found in over 30% of the middle-aged and elderly population. The propensity to become malignant multiplies with increasing adenoma size. Tubular adenomas carry the least risk, followed by tubulovillous and then villous adenomas. Thus the risk of cancer in a tubular adenoma smaller than 1 cm in diameter is less than 5%, whereas the risk of cancer in a villous adenoma larger than 2 cm is 50%. It has been estimated that a polyp larger than 1 cm carries a cancer risk of 2.5% in 5 years, 8% in 10 years, and 24% in 20 years.<sup>8</sup> A small proportion of cancers develop from sessile adenomas.
- 3.3. Colorectal cancer is a multifactorial condition and most cases are [sporadic](#). Genetic and environmental factors both play a part and interact closely. Certain individuals appear more prone than others to develop colorectal cancer due to their genetic background. Over the course of many years, environmental factors interact with individual susceptibility, and the outcome defines the fraction of the population who will become affected. Diet and lifestyle have received particular attention as likely environmental influences, although the results of studies have at times been contradictory. Consequently, the main aetiological determinants that have been identified involve genetic factors, diet, physical activity, and inflammatory bowel disease. Other factors that may contribute include alcohol, tobacco, drugs, radiation, and occupational exposures.
- 3.4. **Genetic factors.** The genetic factors that are involved in colorectal cancer have yet to be fully elucidated and appear to include complex gene-gene and gene-environment interactions.
  - 3.4.1. **Chromosomal instability** is detected in around 85% of colorectal tumours and leads to a sequential accumulation of mutations in [oncogenes](#) and tumour suppressor genes. These genes exercise crucial roles, with activation of oncogenes (e.g. *K-ras*) linked to the **initiation** of tumours, whilst inactivation of tumour suppressor genes (e.g. *p53* and *APC*) is associated with **progression** of tumours. The genetic changes may be inherited or acquired through exposure to environmental factors. For example, inactivation of the *p53* tumour suppressor gene, present in 75% of colorectal cancers, has been linked to elements of a Western-style diet such as high consumption of red meat and foods that increase [glycaemic](#) load.<sup>9</sup>
  - 3.4.2. **Microsatellite instability (MSI)** is found in 15% of sporadic colorectal cancers and over 90% of cases of hereditary nonpolyposis colorectal cancer (see section 3.5.7). MSI is caused by a defect in the DNA mismatch repair pathway. The

mismatch repair genes (predominantly *MLH1* and *MSH2*, also *MSH6*, *PMS1*, and *PMS2*) are integral components of the DNA mismatch repair pathway, whereby errors that have occurred during DNA replication are recognised and corrected. Pathogenic mutations in the mismatch repair genes result in MSI, in which microsatellites (repetitive DNA sequences, found throughout the genome) are replicated incorrectly and not repaired. This situation leads to a rapid accumulation of mutations in [oncogenes](#) and tumour suppressor genes.<sup>10</sup> The presence of MSI may be associated with a more favourable prognosis in colorectal cancer and may also influence the response to chemotherapy.<sup>11</sup>

3.4.3. **Familial risk.** About 10-20% of patients diagnosed with colorectal cancer have some familial risk without fulfilling the strict criteria for the hereditary syndromes described in section 3.5.<sup>12</sup> The risk is highest for individuals with two or more affected first-degree relatives, and for the relatives of patients whose cancer was diagnosed before the age of 45 years. These considerations translate into a 2- to 4-fold increased risk of colorectal cancer for the first-degree relatives of patients who have developed the disease.<sup>13</sup> In addition to genetic factors, the occurrence of family clusters may also have some basis in the tendency of family members to adopt similar dietary habits.

3.5. Around 5-10% of cases of colorectal cancer develop in the setting of a defined **hereditary cancer syndrome**, i.e. an inherited mutation in a cancer predisposition gene. Hereditary nonpolyposis colorectal cancer is the most common of these conditions, followed by familial adenomatous polyposis. Genetic counselling and testing is available for individuals who are at increased risk from these syndromes. The hereditary colorectal cancer syndromes may be classified according to their propensity to form [polyps](#) as follows:<sup>14</sup>

- **[Adenomatous](#) polyp syndromes**
  - ◇ Familial adenomatous polyposis
  - ◇ Attenuated familial adenomatous polyposis
  - ◇ MYH polyposis
  - ◇ Turcot syndrome
  
- **[Hamartomatous](#) polyp syndromes**
  - ◇ Peutz-Jeghers syndrome
  - ◇ Juvenile polyposis syndrome
  - ◇ Cowden syndrome.
  
- **Hereditary nonpolyposis syndromes**
  - ◇ Hereditary nonpolyposis colorectal cancer (HNPCC)
  - ◇ Muir-Torre syndrome
  - ◇ APC variant

3.5.1. **Familial adenomatous polyposis (FAP)** is an [autosomal dominant](#) disease characterised by the development of hundreds to thousands of adenomatous polyps along the colon and rectum, typically commencing in the second or third decade of life. If left untreated, colorectal cancer develops in nearly all patients by age 40 years. Patients also have an increased risk of gastroduodenal polyps and cancers, including duodenal and periampullary cancer, as well as malignant tumours of the thyroid and brain.<sup>15</sup> In a subtype of FAP known as **Gardner's**

**syndrome**, extracolonic features are also present, including congenital hypertrophy of the retinal pigment epithelium, [desmoid tumours](#), osteomas, and epidermoid cysts. In another variant of FAP, known as **attenuated familial adenomatous polyposis (AFAP)**, patients develop fewer polyps (<100) and have a tendency towards later onset of polyp formation and colorectal cancer. A mutation in the adenomatous polyposis coli (*APC*) gene, which acts as a tumour suppressor gene, has been linked to both FAP and AFAP. A mutation in this gene can be identified in around 80% of FAP cases.<sup>16</sup>

- 3.5.2. **MYH polyposis.** In 5-30% of FAP patients no *APC* mutation is identifiable, and mutations in a different gene, the Mut Y homolog (*MYH*) gene, have been implicated.<sup>12</sup> An [autosomal recessive](#) mode of inheritance has been suggested.
- 3.5.3. **Turcot Syndrome** incorporates some cases that have been linked to mutations in the *APC* gene and other cases linked to mutations in the mismatch repair genes. [Adenomatous](#) polyps occur and the condition is also characterised by a high incidence of brain tumours. Medulloblastoma is common in those families that demonstrate mutations within the *APC* gene, whilst glioblastoma multiforme is associated with mutations in the mismatch repair genes.<sup>14</sup>
- 3.5.4. In a small proportion of cases, the predisposing condition is one of the several [hamartomatous polyposis](#) syndromes. **Peutz-Jeghers Syndrome (PJS)** is inherited as an [autosomal dominant](#) disorder, although [sporadic](#) cases are also described. The *STK11* gene, which acts as a tumour suppressor, is responsible. Patients with PJS typically develop dozens to thousands of benign hamartomatous polyps in the stomach and intestines, primarily in the proximal small intestine. Patients are at increased risk for tumours at several gastrointestinal and extra-intestinal sites including the colon, rectum, stomach, oesophagus, ovaries, and pancreas. However, studies have varied widely in their estimates of the risk of malignant change, ranging from no increased risk to 50% risk.
- 3.5.5. **Juvenile polyposis syndrome** is an autosomal dominant condition linked to the *SMAD4*, *PTEN*, and *BMPRIA* genes and is associated with gastrointestinal polyps and both gastrointestinal and pancreatic malignancies.<sup>14</sup>
- 3.5.6. **Cowden syndrome** is an autosomal dominant disorder associated with the *PTEN* gene. In addition to hamartomatous polyps, the condition has been linked to multiple trichilemmomas (benign tumours derived from hair follicles), unusual mucocutaneous papillomas, mental retardation, and both benign and malignant breast and thyroid disease.<sup>14</sup>
- 3.5.7. **Hereditary nonpolyposis colorectal cancer (HNPCC – also known as Lynch syndrome)** is an autosomal dominant disorder and the most common form of heritable colorectal cancer. Diagnosis is guided by the Amsterdam II criteria, a set of conditions relating to family history. HNPCC is a syndrome that places people at high risk of developing various forms of cancer. For an individual, a diagnosis of HNPCC does not necessarily imply that a cancer has already developed, but it invariably indicates the presence of gene mutations that markedly increase the risk of developing early-onset, [metachronous](#) colorectal cancers. A few polyps usually develop, although large numbers are not seen. The lifetime risk of developing colorectal cancer is around 80% with an average



age at diagnosis of 44 years. Patients with HNPCC are also at increased risk of various other tumours, including cancer of the [endometrium](#), ovary, renal pelvis, ureter, bladder, stomach, pancreas, biliary system, and small bowel. Women with HNPCC have a lifetime risk of 40-60% for endometrial cancer and 10-12% for ovarian cancer.<sup>14</sup> The condition is caused by pathogenic mutations in the mismatch repair genes, giving rise to microsatellite instability (see section 3.4.2).

3.5.8. **Muir-Torre syndrome** is a subtype of HNPCC demonstrating [autosomal dominant](#) transmission and featuring sebaceous skin tumours and urological malignancies as well as colorectal cancers. A second type of Muir-Torre syndrome arises in individuals without a family history and does not exhibit deficiency in mismatch repair.<sup>17</sup>

3.5.9. A variant of the APC gene termed I1307K is found in 6-7% of the Ashkenazi Jewish population and has been linked to nonpolyposis colon cancer. The inheritance is autosomal dominant, and carriers have a 10-20% lifetime risk of colorectal cancer.<sup>14</sup>

3.6. **Diet.** The finding of geographical variation in the incidence of colorectal cancer has fuelled speculation that dietary factors may be relevant. In 1997, The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) published an expert report entitled “Food, Nutrition and the Prevention of Cancer: a global perspective.” A second report is scheduled for publication in 2006.<sup>18</sup> Recently, evidence has started to accumulate from the European Prospective Investigation into Cancer and Nutrition (EPIC – a large pan-European study involving around ½ million subjects). The current position is that, although diet appears to play a significant role in the development of colorectal cancer, uncertainty remains over the degree to which individual macronutrients and micronutrients contribute.<sup>6</sup>

3.6.1. **Fibre.** The finding that many communities with low bowel cancer rates have diets that are rich in fibre has led to speculation that an increase in the level of dietary fibre in the diet in industrialised countries might help to reduce the rate of bowel cancer. The EPIC project has demonstrated a protective effect of dietary fibre, which is greatest for the left side of the colon and least for the rectum. A significant reduction in the incidence of colorectal cancer was found on comparing the highest fifth of the population in terms of dietary fibre intake (mean daily intake 33.1g fibre) to the lowest fifth (mean daily intake 12.6g fibre). The researchers estimated that in populations with low average intake of dietary fibre, an approximate doubling of total fibre intake from foods could reduce the risk of colorectal cancer by 40%.<sup>19</sup> Another large study has reported that high intakes of dietary fibre were associated with a reduced risk of adenoma of the colon (but not the rectum), the association being strongest for fibre derived from grains, cereals, and fruits.<sup>20</sup> In contrast, a long-term US study of two large prospective cohorts did not demonstrate an important association between fibre intake and colorectal cancer.<sup>21</sup> Moreover, a review of five randomised controlled studies found that increasing fibre in a western diet for two to four years did not lower the risk of bowel cancer.<sup>22</sup>

3.6.2. **Vegetables and fruit.** The initial WCRF report published in 1997 concluded that high consumption of vegetables (but not fruit) was probably associated with a reduced risk of colorectal cancer. However, a more recent prospective study of

two large cohorts in the USA concluded that the frequent consumption of fruits and vegetables did not appear to offer protection from either colon or rectal cancer.<sup>23</sup> It should be noted that the protective effect of vegetable and fruit consumption, if any, may be mediated through the fibre content and/or the presence of various micronutrients.

- 3.6.3. **Red and processed meat.** Prolonged high consumption of red and processed meat has been linked to colorectal cancer in many but not all published studies. The EPIC project has reported an increased risk of colorectal cancer associated with high consumption of red and processed meat at a level in excess of 160 g/day, as compared to consumption of less than 20 g/day. Conversely, a reduced risk was demonstrated for fish consumption in excess of 80 g/day as compared to intake of less than 10 g/day. No relationship to poultry intake was detected.<sup>24</sup>
- 3.6.4. **Fats.** Saturated animal fats have been implicated as a risk factor for colorectal cancer, although the evidence is not entirely convincing.<sup>7</sup> Fat and fibre may promote or inhibit carcinogenesis in part by altering the bacterial flora of the large bowel. Limited evidence suggests a protective effect of **total dairy products** and **milk intake**.<sup>25,26</sup> The EPIC project has investigated the possibility of a reduced risk of colorectal cancer associated with intake of unsaturated fatty acids or phytonutrients, as found in **nuts** and **seeds**. The study found a reduced risk for colon cancer in women for the highest level of nut and seed intake (>6.2 g/day) as compared with non-consumers. However, no effect was observed for rectal cancer in women, or for colon or rectal cancer in men.<sup>27</sup>
- 3.6.5. **Micronutrients, vitamins and minerals.** Suggestions have been made that a number of antioxidant vitamins and minerals may be protective against colorectal cancer including vitamins A, C and E, minerals (e.g. selenium), [flavonoids](#) and methionine (a dietary essential amino acid).<sup>6,7</sup>
- 3.6.6. Experimental and epidemiological evidence has been suggestive but not conclusive for a protective role for high dietary **calcium** intake. A review of two randomised controlled trials concluded that calcium supplementation might contribute to a moderate degree to the prevention of colorectal adenomatous [polyps](#) and, therefore by implication, of colorectal cancer.<sup>28</sup> No convincing evidence has emerged for a Vitamin D effect.<sup>26</sup>
- 3.6.7. **Folic acid** intake may confer protection against colorectal cancer, either directly or indirectly. However, the evidence from a large number of studies has proved inconsistent and the precise nature of the association is beyond our present knowledge.<sup>29</sup>
- 3.6.8. High levels of consumption of dietary **heterocyclic aromatic amines (HAAs)** may increase the risk of the subset of colon cancers that are associated with microsatellite instability. HAAs are carcinogens, and a high intake is related to a preference for well-done red meat and high frequencies of certain cooking practices e.g. frying, barbecuing, grilling, and the use of meat drippings.<sup>30</sup>

### 3.7. **Physical activity, obesity and energy imbalance**

- 3.7.1. Regular **physical activity** (recreational and/or occupational) reduces the risk of colon cancer, but does not affect rectal cancer risk. The protective effect appears

to be most conspicuous where high levels of physical activity are maintained throughout life.<sup>31</sup> In quantifiable terms, crude estimates only are available of the dose required for a protective effect, the current indication being that somewhere between 3.5 and 4 hours of vigorous activity per week may be needed to optimise protection.<sup>32</sup>

- 3.7.2. **Obesity.** Central obesity (as measured by waist circumference) has been linked to an increased risk of colon cancer.<sup>33</sup> On current evidence, a direct association between obesity (as measured by [body mass index](#)) and rectal cancer appears less likely.<sup>34</sup>
- 3.7.3. Laboratory studies have shown that hyperinsulinaemia and hyperglycaemia promote the growth of colorectal cancer; both insulin and insulin-like growth factor-1 (IGF-1) receptors are found on these tumours. An analysis of responses from nearly ¼ million subjects who participated in the National Health Interview Survey (NHIS) in the USA showed an increased risk for individuals with **diabetes**. After controlling for potential confounding factors, diabetics were 1.4 times more likely to develop colorectal cancer.<sup>35</sup>
- 3.7.4. A state of **energy imbalance** could provide a link for the observations that colorectal cancer risk appears to be associated with each of sedentary lifestyle, obesity, and diabetes.

### 3.8. **Smoking and alcohol consumption**

- 3.8.1. A weak association between **smoking** and colorectal cancer has been proposed, although the evidence is inconsistent. It has been postulated that the effects of cigarette smoking may be confined to the 15% of tumours that are characterised by microsatellite instability. One study reported an association between MSI positive tumours and cigarette smoking that was strongest in those subjects who started to smoke at a young age, smoked for 35 or more years, and were either current smokers or had stopped fewer than 15 years before diagnosis.<sup>36</sup> Another study reported an increased risk of rectal cancer in male smokers, especially those who had smoked more than 20 [pack-years](#) of cigarettes, although no such association was detected in women.<sup>37</sup>
- 3.8.2. An increased risk of colorectal cancer has been linked to **alcohol consumption** of 30g per day or more. The risk did not appear to vary according to the type of alcoholic beverage consumed.<sup>38</sup> (N.B. One unit is approximately equivalent to 8g of alcohol.)

### 3.9. **Drugs**

- 3.9.1. Certain non-steroidal anti-inflammatory drugs appear to exert a protective effect (see section 4.5.1).
- 3.9.2. A number of reports have suggested a reduced risk of colorectal cancer for patients who are taking statins (lipid-lowering drugs).<sup>39</sup>
- 3.9.3. A number of studies have reported an association between hormone replacement therapy and colorectal cancer, with the majority providing evidence

in favour of a protective effect. Oral contraceptive use and later age at menarche have also been linked to a decreased risk.<sup>6</sup>

### 3.10. Radiation exposure

- 3.10.1. Several studies have suggested an increased risk of development of secondary malignancies following radiation therapy to the pelvis. A significant increase in the development of rectal cancer has been reported following radiation for prostate cancer, although no effect was observed in areas of the colon that had not been directly irradiated.<sup>40</sup> An elevated risk of cancer of the colon has been reported in men who have been treated for testicular cancer,<sup>41</sup> and in patients who have received radioiodine for thyroid cancer.<sup>42</sup>
- 3.10.2. There is no evidence of either an increased incidence of colorectal cancer or of increased mortality attributable to this condition in service personnel who participated in the UK's atmospheric nuclear weapons tests.<sup>43</sup>
- 3.10.3. It is important to consider the potential risks from diagnostic radiography. Most recently, computed tomography colonography (CTC) has been assessed, and its benefits as a screening tool are considered to outweigh the cancer risk from radiation exposure. Using typical current scanner techniques, the estimated absolute lifetime cancer risk for radiation exposure from paired CTC scans is about 0.14% for a 50-year-old, and about half that for a 70-year-old. The main organs at risk for cancer are the colon, stomach and bladder.<sup>44</sup>
- 3.10.4. Uncertainty remains concerning the effect of magnetic fields from high voltage power lines on people living in close proximity. One study demonstrated a significant increase in the risk of cancer of the colon in women, but others have found no evidence of an excess risk.<sup>45</sup>

3.11. **Occupation.** Limited evidence has been published to suggest an increased risk of colorectal cancer in certain occupations, e.g. among workers in the synthetic textile industry.<sup>46</sup> In epidemiological studies, various occupational exposures have been implicated, including polymers, asbestos, fibres, metals, dyes, solvents and mineral oils. In view of the multiple exposures that arise in many occupations and the time lag involved between exposure and onset of disease, the effect of individual agents has yet to be established.<sup>47,48</sup>

### 3.12. Associated medical conditions

- 3.12.1. Patients with **inflammatory bowel disease** (both ulcerative colitis and Crohn's disease) have an increased risk of colorectal cancer, although the magnitude of reported risk has varied widely in different studies. The cumulative risk of colorectal cancer for patients with **ulcerative colitis** has been estimated at 2% after 10 years, 8% after 20 years, and 18% after 30 years of disease.<sup>49</sup> Cancer in ulcerative colitis probably evolves from microscopic [dysplasia](#) rather than from [adenomas](#).<sup>15</sup> Patients whose **Crohn's disease** is confined to the terminal [ileum](#) have no increased risk of colorectal cancer, but the risk for those with disease confined to the colon is increased more than five-fold.<sup>50</sup>
- 3.12.2. The risk of colorectal cancer in patients with inflammatory bowel disease is greatest for those with prolonged duration of disease, early age at onset,

extensive disease, [primary sclerosing cholangitis](#) and a family history of colorectal cancer. Cancer may develop in a residual rectal stump following partial colonic [resection](#).<sup>51</sup> Recent reports have suggested that active medical and surgical intervention may serve to mitigate the increased risk of colorectal cancer in both ulcerative colitis and Crohn's disease.<sup>52,53</sup>

- 3.12.3. A **previous history of colorectal cancer** predisposes individuals to fresh occurrences of the disease. The risk of development of a second colorectal cancer is 1.5-3% in the first five years following diagnosis.<sup>12</sup> In a Danish study of patients who were aged under 40 years at diagnosis and who were subsequently observed for up to 41 years, the cumulative risk of a [metachronous](#) colorectal cancer was found to be 30%.<sup>54</sup> Thus surveillance of the remaining colon is indicated after surgical resection, and a case can be made for more extensive colectomy in younger patients.

## 4. Prognosis

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- 4.1. There has been significant improvement in 5-year survival for colorectal cancer over the past 30 years. This progress is attributable to earlier diagnosis and advances in treatment. The overall 5-year survival rate exceeds 60% in the USA, is just under 50% in the UK, and is less than 40% in less developed countries.
- 4.2. Prognosis depends on factors related to the patient, tumour, and treatment. **Staging** is the strongest predictor of survival. Five-year survival rates by stage are reported as follows:<sup>12</sup>

Stage I	80-95%
Stage II	65-75%
Stage III	25-60%
Stage IV	0-7%

Other prognostic considerations include the following:

- The expertise of the treatment team, both surgeons and oncologists, is a major determinant of outcome<sup>12</sup>
- Colorectal cancer usually has a poor prognosis in patients under the age of 40 years (constituting about 2-6% of cases)<sup>55</sup>
- Some studies have suggested that the prognosis for patients with colorectal cancer due to HNPCC is more favourable than that for patients with sporadic colorectal cancer<sup>56</sup>

### 4.3. Treatment

- 4.3.1. “Invasive carcinoma” describes the situation in which malignant cells have penetrated the [muscularis mucosae](#). A [polyp](#) that does not show evidence of invasive carcinoma can be treated adequately by complete excision, usually by colonoscopy. For invasive colorectal cancer, the mainstay of treatment is surgical [resection](#) of the tumour with adequate margins, plus removal of the regional lymph nodes, and restoration of the continuity of the gastrointestinal tract by [anastomosis](#). A permanent [colostomy](#) is required for cases of low rectal cancer, while temporary defunctioning colostomy may protect against leakage of a low colorectal anastomosis.<sup>8</sup> Treatment may be directed at either cure or palliation, the latter being carried out to alleviate pain, obstruction and blood loss. Resection of solitary hepatic and pulmonary metastases may be undertaken in certain circumstances.
- 4.3.2. Prophylactic colectomy is advocated for patients with familial adenomatous polyposis as, in the absence of surgical intervention, these individuals have virtually a 100% risk of developing colorectal cancer. Operation usually entails resection of the colon and rectum with the formation of an anastomosis between an [ileal](#) pouch and the anus.
- 4.3.3. Depending on the site and stage of the tumour, surgical treatment may be supplemented by adjuvant chemotherapy and/or radiotherapy (the latter is primarily indicated for cancer of the rectum). A number of chemotherapeutic

options are available for the treatment of colorectal cancer, including fluorouracil, irinotecan, capecitabine, oxaliplatin, and cetuximab. Several novel drugs are under development.

#### 4.4. Secondary prevention

- 4.4.1. **Screening** programmes are vitally important and have been credited with producing an increase in survival rates due to the capacity to identify and treat premalignant [polyps](#) and early cancerous lesions.
- 4.4.2. Debate continues over the optimum screening procedure, given consideration of such factors as effectiveness, cost, and acceptability. [Colonoscopy](#) is the most thorough screening method, as it allows the entire large bowel to be visualised. The most commonly advocated alternative of faecal occult blood testing plus flexible [sigmoidoscopy](#) is simpler but rather less successful in identifying lesions.<sup>57,58</sup> In the USA, regular colorectal screening is actively encouraged for everyone aged over 50 years. In the UK, the Government has announced a national colorectal cancer screening campaign to commence in April 2006. Unfortunately, patient participation in screening initiatives can prove problematic, due to a number of factors including discomfort.
- 4.4.3. Screening programmes for individuals who are identified as having **additional risk factors** differ from the recommendations for the general population, with regard to the age of onset of screening, preferred method, and frequency. Guidance is stratified according to the degree of risk, and enhanced surveillance is recommended for patients with a hereditary cancer syndrome, inflammatory bowel disease or a family history of colorectal cancer in one or more first-degree relatives.<sup>8</sup>
- 4.4.4. In view of the increased risk of [metachronous tumours](#), regular follow-up and colonoscopy is essential following treatment for colorectal cancer.

#### 4.5. Chemoprevention

- 4.5.1. A number of studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the development of colorectal adenomas and cancer. Aspirin, sulindac, and the COX-2 selective inhibitor, celecoxib are among the agents that have been credited with this preventative action. A review of randomised controlled trials has provided evidence that aspirin significantly reduces the recurrence of [sporadic](#) adenomatous polyps after one to three years. Sulindac and celecoxib are associated with regression (but not elimination or prevention) of colorectal adenomas in familial adenomatous polyposis.<sup>59</sup> However, it should be noted that the use of COX-2 inhibitors such as celecoxib is now restricted following reports of an increased risk of cardiovascular events (heart attack and stroke).
- 4.5.2. The potential for chemoprevention with supplements containing micronutrients, such as vitamins C, D and E, calcium and selenium, has been studied in clinical trials. As yet, this concept remains in experimental development.<sup>6</sup>

## 5. Summary

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- 5.1. In the UK, the large bowel is the third most common site for cancer diagnosis. Colorectal cancer is the second most common cause of cancer mortality in the UK, responsible for over 16,000 deaths in 2003.
- 5.2. Most colorectal cancers begin as small, non-cancerous adenomatous polyps, which over time have the potential to undergo stepwise transformation to malignant change. This process is known as the adenoma-carcinoma sequence.
- 5.3. Colorectal cancer is a multifactorial condition and most cases are sporadic. Genetic and environmental factors both play a part and interact closely. However, 5-10% of cases of colorectal cancer develop in the setting of a defined hereditary cancer syndrome. A further 10-20% of the patients who are diagnosed with colorectal cancer have some familial risk without fulfilling the strict criteria for the diagnosis of a hereditary syndrome.
- 5.4. Current evidence suggests that the risk of colorectal cancer is increased by a variety of factors including high meat consumption, smoking, alcohol, sedentary lifestyle, obesity and inflammatory bowel disease. Conversely, dietary fibre, various micronutrients, physical activity and non-steroidal anti-inflammatory drugs may reduce the risk.
- 5.5. Staging is the strongest predictor of survival for patients who have been diagnosed with colorectal cancer.
- 5.6. Screening programmes are vitally important and have been credited with producing an increase in survival rates due to the capacity to identify and treat premalignant polyps and early cancerous lesions.



## **6. Related Synopses**

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Cancer of the Stomach

## 7. Glossary

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adenocarcinoma	A form of cancer that develops in the mucous lining or inner surface of an organ.
adenoma	A benign tumour in which the cells form recognisable glandular structures or in which the cells are clearly derived from the glandular surface lining. Hence: <i>adenomatous</i> .
anastomosis	Surgical union of two ends of bowel (or other hollow structures).
ascites	Accumulation of fluid in the abdominal cavity.
autosomal dominant	A gene that expresses its effects when one copy is present; therefore only one parent need have the characteristic in order to pass it to the offspring.
autosomal recessive	A gene that is required in two copies to be active, and therefore can be inherited only when both parents carry the gene.
biopsy	A procedure that involves obtaining a tissue specimen for microscopic analysis to establish a precise diagnosis.
body-mass index (BMI)	A measure which correlates with the amount of fat in the body. BMI = body weight in kilograms/square of height in metres.
cachexia	The appearance of widespread wasting of the body.
caecum	The commencement of the colon in the right lower quadrant of the abdomen at the end of the small intestine; the appendix arises from the caecum.
carcinoid	A tumour of neuroendocrine origin, which may be benign or malignant, and which usually arises from the gastrointestinal tract, especially the ileum ( <i>q.v.</i> ) and the appendix. It is generally slow-growing.
colonoscopy	The visual inspection of the inside of the entire length of the colon by means of a flexible fiberoptic viewing instrument, inserted through the anus under sedation.
colostomy	The surgical construction of an artificial outlet between the colon and the surface of the abdomen.
desmoid tumour	A fibrous tissue tumour that has features of both a benign growth (fibroma) and a cancerous growth (fibrosarcoma). Desmoids can occur in patients with familial adenomatous polyposis.
dysplasia	Alteration in size, shape, and organisation of adult cells.

endometrium	The lining of the uterus.
flavonoids	A group of plant substances that includes anthocyanins, which are water-soluble pigments that impart colour to flowers and other plant parts.
glycaemic	Glucose content in blood.
hamartoma	A tumour that is made up of tissues normally found in the area in which it is sited, but in an unusual mixture. Hence: <i>hamartomatous</i> .
ileum	The lower part of the small intestine, leading to the large intestine. Hence: <i>ileal</i> .
lymphoma	Tumour of the lymphatic system and lymph nodes.
metachronous	Occurring at a later time: c.f. <i>synchronous</i> .
metastasis (-es)	A deposit of malignant tumour at a distant site of the body, spread through the blood vessels, lymph channels or abdominal cavity. Hence: <i>metastatic</i> .
muscularis mucosae	A thin layer of smooth muscle found in most parts of the digestive tract.
oncogene	A gene that causes normal cells to convert into cancerous cells.
peritoneum	The smooth membrane that lines the cavity of the abdomen and surrounds the interior organs. Hence: <i>peritoneal</i> pertaining to the peritoneum, <i>peritonitis</i> inflammation of the peritoneum.
polyp	Growth that protrudes, usually on a stalk, from a mucous membrane (membrane that lines cavities within the body).
primary sclerosing cholangitis	An inflammatory disease of the bile ducts, which leads to liver cell damage. Around 70% of patients with the condition also have an inflammatory bowel disease.
resection	Excision of part or all of an organ or other structure.
sigmoid colon	The final portion of the colon, connecting to the descending colon above and the rectum below.
sigmoidoscopy	The visual inspection of the inside of the rectum and sigmoid colon ( <i>q.v.</i> ) by means of an instrument inserted through the anus.
smoking pack-years	Derived by multiplying the number of packs of cigarettes smoked per day by the number of years smoked.
sporadic	Occurring in a random or isolated manner.

submucosa	The layer of tissue beneath the mucous membrane lining the intestinal cavity.
tenesmus	Ineffectual and painful straining on defaecation.

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