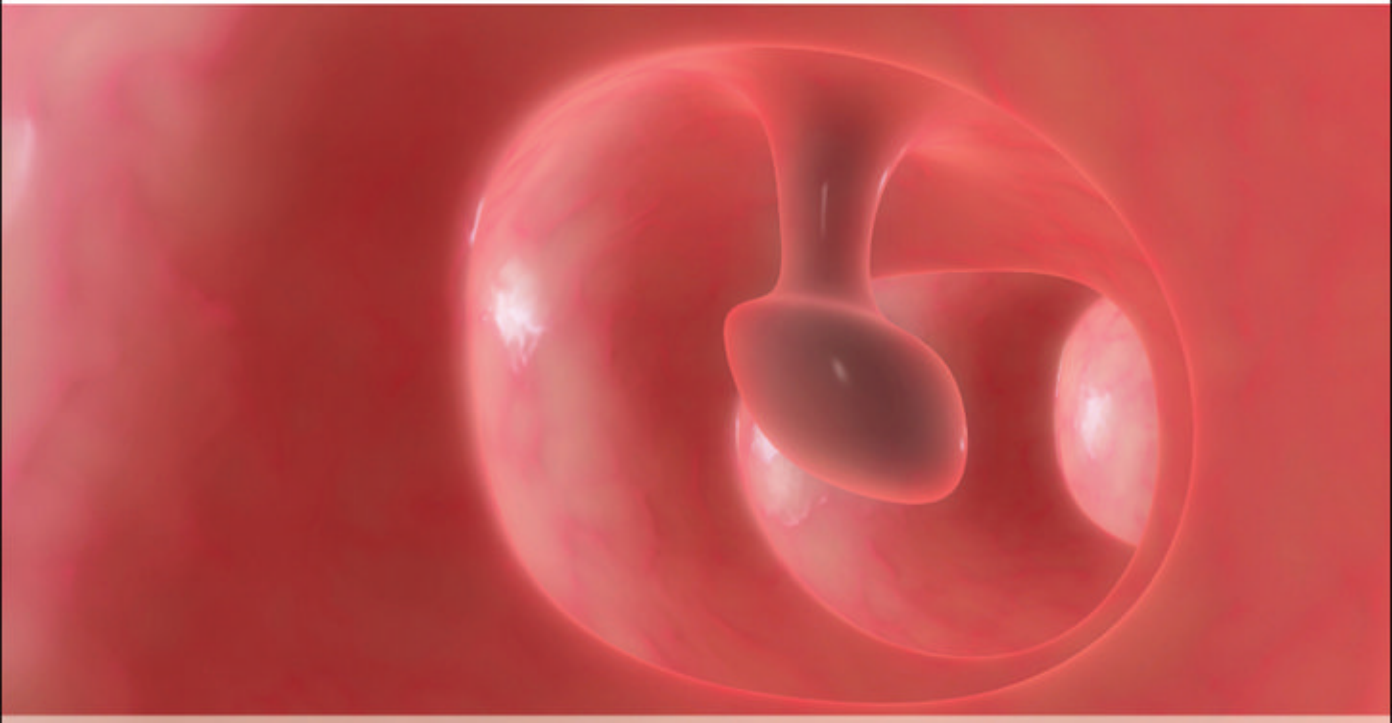
# ABC of Colorectal Cancer

SECOND EDITION

Edited by Annie Young, Richard Hobbs and David Kerr



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ABC of

# Colorectal Cancer

**Second Edition**

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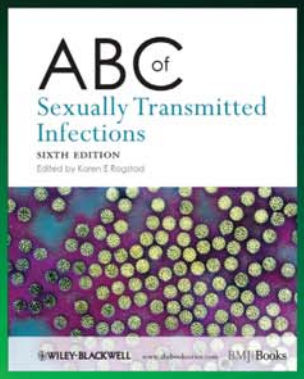


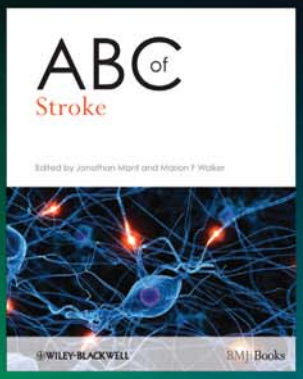


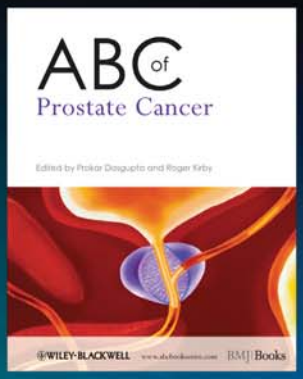


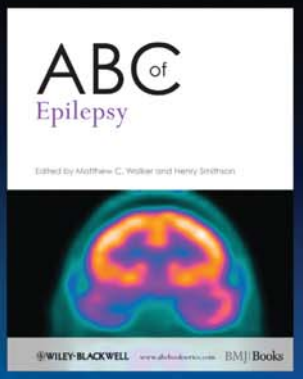


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# Colorectal Cancer

## Second Edition


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# Preface

Colorectal cancer is a common source of morbidity and mortality, with an estimated 1 million incident cases every year, predominantly in Western nations. The truism, 'biology is king' is especially applicable to colorectal cancer as we have come to understand the epidemiological interplay between genetics and the environment, the molecular biology of the progression from benign adenoma to invasive carcinoma and the biomarkers which identify which patients might benefit most from specific therapies. It is a cancer which lends itself to prevention, screening and early detection and which cries out for a multidisciplinary approach, underpinned by the innovative IT and decision support described in Chapter 6. Optimal management extends from population screening, through primary care to secondary and specialist tertiary centres, encapsulating the microcosm of modern cancer care.

We provide updates on important advances in genetics, screening and treatment and include a moving chapter written by a patient who captures the highs and lows, the small indignities and the great kindnesses of his own cancer pathway. We cover the entire spectrum of the disease in a lucid style with an outstanding faculty, each of whom has the capacity for the clarity of communication required to bring the reader up to date with the latest advances which make a real difference to the clinical management of this disease.

You will read, enjoy and reread this book if you are a GP in the front line of cancer care; if you are a medical student who wants to understand the essence of multidisciplinary cancer diagnosis and treatment; if you are a nurse specialist who wants to develop the knowledge base to support your patients at every step of their care pathway; if you are a medical or surgical trainee interested in the management of colorectal cancer.

Remember the patient's (and the endoscopist's!) battle-cry, 'E Tenebris Lux'.

Annie Young
Richard Hobbs
David Kerr

CHAPTER 1

# The Patient Perspective

*Kevin Bond*

Cancer patient, Worcester, UK

**OVERVIEW**

- The family environment and the support it offers hugely influence how the patient deals with a diagnosis of colorectal cancer
- Surveys suggest that colorectal cancer patients seem generally grateful and satisfied with their treatment, including the quality and timeliness of the information they received, the quality of their healthcare, and their level of involvement in decision making
- Nevertheless, despite progress, individual coordination of care still needs addressing, particularly around long-term follow up
- Patients generally have a relatively positive outlook on their illness experience, although those with colostomies have some added difficulty and side effects of treatment often cause anxiety
- Patients need the whole team approach to manage overall care, and to act as a sounding board for ideas and treatment options – not only family and friends and cancer specialists, but GPs and allied healthcare professionals
- Clarity of communication, based on honesty and openness, is key

## Coping with ill-health: family influences

Our views are not shaped through our isolated experience of life alone but also through our upbringing and family influences. The metaphysical poet John Donne said, 'no man is an island unto himself'. I therefore feel that it is appropriate to mention relative family influences which have obviously impacted on how I view the experience of dealing with colorectal cancer. This could be considered a different angle on personalised medicine, in which genetics are trumped by nurture.

My parents came to England from Ireland in the 1930s. My father was a maintenance electrician in a large machine tool manufacturer and my mother was a nursing Sister having qualified in both mental and general nursing. My mother's sister also became a nurse. My paternal grandmother was a midwife, as was my father's sister. I learned of the many advances made in medicine over their careers but also of its limitations and the gentle grace with which this was accepted.

My wife has specialised in elderly care and neuro-physiotherapy and for the past five years has been the physiotherapist at St Richards Hospice, Worcester. This makes life for her at the moment more rather than less difficult; she is more than well acquainted with the prognosis of my illness. Ignorance can sometimes have its blessings, if only in the short term.

## Attitude matters!

I am an Incorporated Engineer and have been a director within several companies since 1976. The one thing I have found is that there is usually more than one view or resolution to any complex problem and there is normally a safe default attitude, bowing to the view of a glass being half empty. My gift lay with a logical appreciation of the technical argument, exploring and exposing possible alternatives and moving the argument and solution to one of a glass half full and getting more full! It is rare to find only one solution and for that solution to be perfect, without ongoing or unforeseen problems that have to be managed or mitigated. Therefore my expectations in expressing a patient's view are conditioned with a sense of reality. I am aware that NHS funds are not limitless and that there are others much worse off than me. This does not, however, stop me from exploring that which is or might still be possible and using every scrap of available information to empower this journey.

## Signs and symptoms: get medical help as soon as possible

The first real noticeable symptoms of my illness manifested themselves in early 2007 and the regularity and severity of these increased as the year progressed. These included:

- increased flatulence
- feeling bloated
- feeling abdominal discomfort within an hour or so of eating
- having to repeatedly go to the toilet

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- blood staining on toilet paper
- actually passing blood with stools
- having to go to the toilet during the night.

At first I was not too concerned as I had irritable bowel syndrome from time to time and had piles, and so to begin with had thought it was just a combination of these two. As the year progressed, my wife became more concerned and badgered me to see my GP but, typical of the male species, I put the matter off; after all, on occasions the symptoms would ease and almost disappear. Besides I had always been very fit and healthy (sporting injuries apart). I was never ill and hardly knew my way to the GP's surgery. Also, I was now in business with another colleague and I could not afford the time to be ill! My wife settled the matter and told me she had made an appointment for me with our GP (I had had the symptoms for 12 months by then) and my subsequent history can be summarised as follows:

- Late November 2007 – Initial consultation at GP surgery.
- Early December 2007 – Blood test appointment.
- January 2008 – Endoscopy appointment with consultant surgeon at Worcestershire Royal at which she informed me there were tumours and they were, from her experience unlikely to be benign. Appointments followed for MRI and CT scans.
- February 2008 – Consultation with surgeon to review results of scans which indicated the colon tumour had metastasised to the liver, then colon resection and referral to the liver unit in Birmingham for possible liver resection
- May to July 2008 – Referred to Cheltenham General Hospital for chemotherapy regime of six fortnightly sessions of Oxaliplatin and 5-Fluorouracil (5-FU)
- 2009 – Liver resection at St James's Hospital, Leeds
- 2010 – One further course of chemotherapy locally at Worcestershire Royal Hospital.

## Good communication throughout the care pathway is the golden key

So breaking bad news was done sensitively and in stages – after the endoscopy and scans with my wife present at each consultation. Although a massive shock, I was grateful for the frankness at each stage which meant there was no false expectation at any of the appointments, which had been in quick succession. I heard 'cancer' and 'secondaries' and little else and was grateful for my wife's attendance and the written, explanatory notes which we could take home to study.

### Good to have a plan of action

I appreciated a plan of action to focus my mind. I became involved – saw the stoma nurse as a colostomy was a possibility at the time of surgery; saw a liver surgeon – to keep that in reserve for after chemotherapy. After my bowel resection (and thankfully, I didn't need a colostomy), I set about self-made plan to get fit for chemotherapy – to eat healthy food, to exercise avidly and to show patience and endurance throughout adversity.

### Telling my sons, mother and three brothers

The worst bit about the diagnosis and pathway was telling my sons, mother and three brothers. As an ex-nurse, my mum was able to be rational and positive. I had to ask my elder son to come back from Iceland early and summon my younger son, who had just started university in Wales, to come home. We had never talked about cancer ever as a family but my son immediately told me that a friend of his had been diagnosed with testicular cancer, which made my problem seem small in comparison.

## Rationalising having cancer

I didn't do the 'Why me?' question that fellow patients speak of, as that seems unresolvable and a waste of my energies. I had had a good life, travelled over the world and been fortunate to raise a lovely family – so felt fortunate. Emotionally, it's tough. I still contemplate all things that I thought I'd do, my dreams and expectations that, for various reasons, are out of reach now; we can no longer afford some of them, my earning capacity has been curtailed as I owned my own business. I have a different focus now, sadly taken up with treatment regimes ahead of me, and am unlikely to be fit enough to realise most of my dreams. So I keep it simple – what else is there other than a return to as reasonable a life as possible within one's own family?

As much as possible, I carry on with work; the stark reality is that the mortgage has to be paid, but we do need more information on what benefits the State might provide.

## My colorectal cancer pathway

Due to the pattern of the care, my cancer pathway has had highs and lows, moments of high drama, low humour, encouragement and disappointment. As I write I find that, despite the best treatment that the NHS could offer and the indefatigable support of my wife and family, the cancer has recurred yet again and that there is no prospect now of cure. In some ways I am glad to be spared further chemotherapy at the moment, as the last session proved tough. My focus now is on keeping as fit and comfortable as possible, supported as I have been throughout by those constant companions, my family and GP. I know that I can access supportive and palliative care services if required, having already been introduced to my palliative care nurse.

I know that I have lived longer than if I had been diagnosed 10 years ago and that I may soon exhaust conventional medical approaches. I may consider complementary therapies but will avoid procedures that might make me feel worse.

Don't believe everything you read on the internet, but feel free to take control of your own life and travel hopefully. This I intend to do.

## Acknowledgement

At a time when criticism of the National Health Service (NHS) still remains politically convenient, I can only report that once I was actively placed with the appropriate consultant, the care I received

for the three and a half years since November 2007 of my illness was generally first class. For the greater part, it would be hard to imagine that even the most expensive of private health care could offer very much more.

I do refer to certain criticisms of the NHS, but I would not want to appear to be churlish or ungrateful – far from it. The criticisms are to be constructive and serve to help others.

May I express my deepest gratitude to all the staff within Worcestershire Royal Hospital, Cheltenham General Hospital, St James' Hospital, Leeds and Queen Elizabeth Hospital, Birmingham, as well as my General Practitioner, Knightwick Surgery, Worcestershire and the Community Nurses for their professional skill and the kindness they have shown me.

## Further reading

Useful websites for both patients and professionals:

American Cancer Society http://www.cancer.org/docroot/MLT/content/MLT_4_1x_Living_With_Uncertainty_-_The_Fear_of_Cancer_Recurrence.asp [accessed 10 April 2011].

Beating Bowel Cancer http://www.beatingbowelcancer.org/ [accessed 10 April 2011].

Bowel Cancer UK http://www.bowelcanceruk.org.uk [accessed 10 April 2011].

The Lance Armstrong Foundation http://www.livestrong.org/site/c.khLXK1PxHmF/b.2660683/k.5BD8/Sadness_and_Depression.htm [accessed 10 April 2010].

MacmillanCancerBackup http://www.macmillan.org.uk/Cancerinformation/Livingwithandaftercancer/Relationshipscommunication/Sexuality/Solutionstosexualproblems.aspx [accessed 10 April 2010].

CHAPTER 2

# Epidemiology and Prevention

*Peter Boyle*[1], *Patrick Mullie*[1], *Maria Paula Curado*[1] *and David Zaridze*[2]

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[2]Institute of Carcinogenesis, Moscow, Russian Federation

**OVERVIEW**

The most important lifestyle changes for colorectal cancer disease prevention are as follows:

- Stop smoking
- Reduce alcohol consumption
- Increase physical activity
- Adopt a healthier diet: low in red/processed meats, high in fruit, vegetables, whole grains and dietary fibre

Further research on gene–diet interactions and identifying protective dietary and lifestyle patterns is required

## Introduction

Colorectal cancer is an important public health problem throughout the world. It is the third most common cancer in men (663,000 cases in 2008: 10% of all cancer cases) and the second in women (570,000 cases: 9.4% of all cancer cases) worldwide. Significant international variations in the distribution of colorectal cancer have been observed for many years. High incidence rates are found in Western Europe and North America, intermediate rates in Eastern Europe with the lowest rates to be found in sub-Saharan Africa (Figure 2.1).

About 608,000 deaths from colorectal cancer are estimated worldwide, accounting for 8% of all cancer deaths, making it the fourth most common cause of death from cancer. As observed for incidence, mortality rates are lower in women than in men; with less variability in mortality rates worldwide (sixfold in men (Figure 2.2) and fivefold in women). Like most solid tumours, the incidence of colorectal cancer increases with age (with the exception of familial colorectal cancer) and, in most regions of the world, the incidence of colorectal cancer is increasing and the mortality rate decreasing (Figures 2.3 and 2.4). The incidence of colon cancer is uniformly higher than rectal cancer in both men and women.

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## Aetiology of colorectal cancer

Ethnic and racial differences in colorectal cancer incidence as well as studies on migrants have suggested for many years that environmental factors play a major role for the aetiology of the disease. In Israel, male Jews born in Europe or America were shown to be at higher risk for colon cancer than those born in Africa or Asia, and a change in risk in the offspring of Japanese having migrated to the United States has taken place, the incidence rates approaching or surpassing those in whites in the same population and being three or four times higher than among Japanese in Japan.

## Risk factors of a non-dietary origin

There is sufficient evidence that cigarette smoking and alcohol consumption are human carcinogens and that both lifestyle habits increases the risk of colorectal cancer. Evidence from observational studies indicates that long-term use of non-steroidal anti-inflammatory drugs (NSAIDS), including aspirin, may reduce the risk of colorectal cancer. Nevertheless, recommendations to general populations on NSAID or aspirin use for cancer prevention are premature given that use of these medications is accompanied by many side effects and may increase the risk of other serious medical conditions, necessitating close medical supervision. Thus, their use as chemopreventive agents may only be practical in those at very high risk of developing colorectal cancer (for example familial adenomatous polyposis (FAP) patients). In women, use of hormone replacement therapy (HRT) has been associated with a reduced risk of colorectal cancer but also with concomitant increases in the risk of breast cancer, and possibly coronary heart disease and thromboembolic events, making its use in any colorectal cancer prevention strategy impractical. Removal of adenomatous polyps has also been found to reduce disease risk, but in practice it is only applicable to those undergoing invasive screening.

## Diet, dietary practices, nutrition and physical activity and colorectal cancer

The evidence of association between diet, dietary practices, nutrition and physical activity and colorectal cancer risk is, surprisingly, at times confusing and unclear.

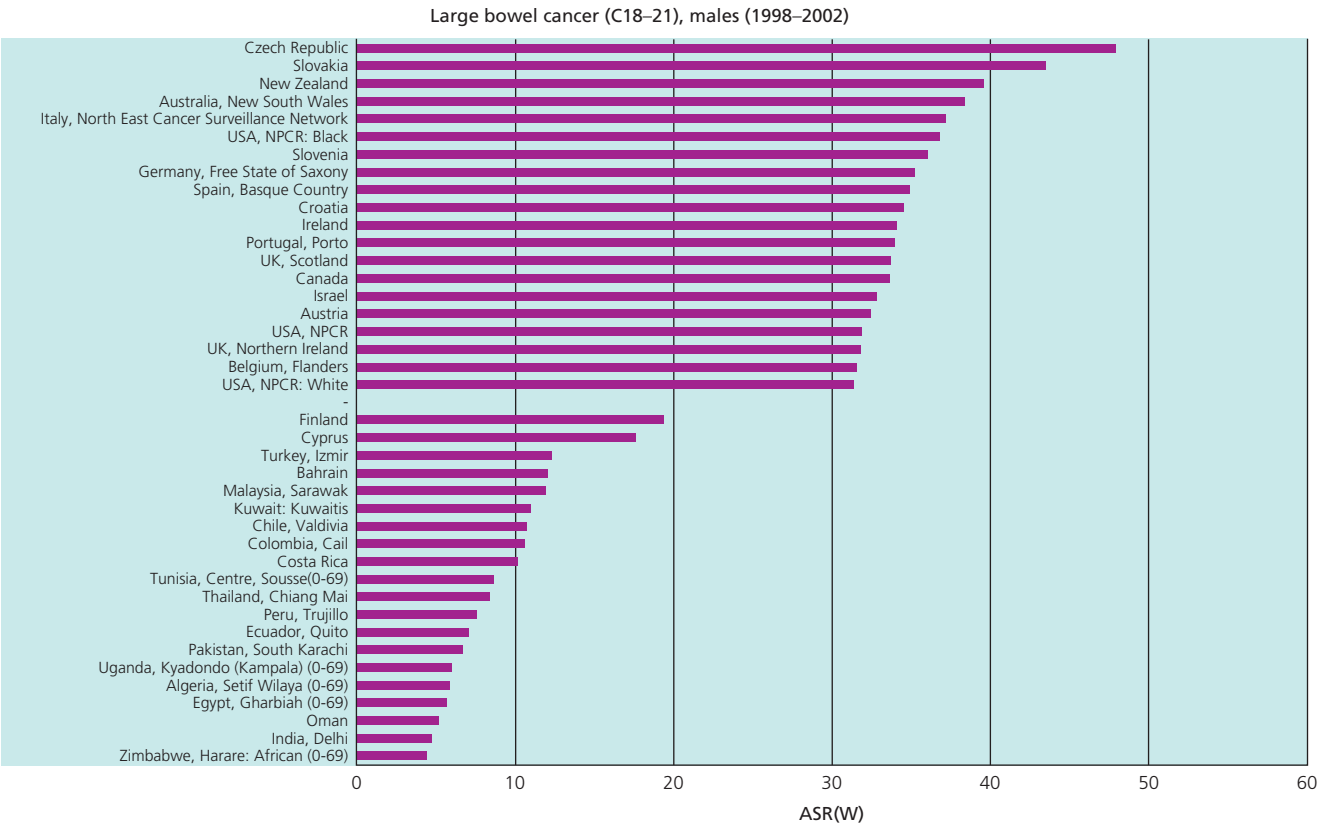


**Figure 2.1** Highest and lowest incidence Age Standardised Rates (adjusted using the World Standard Population) (ASR(W)) for colorectal cancer worldwide for males.

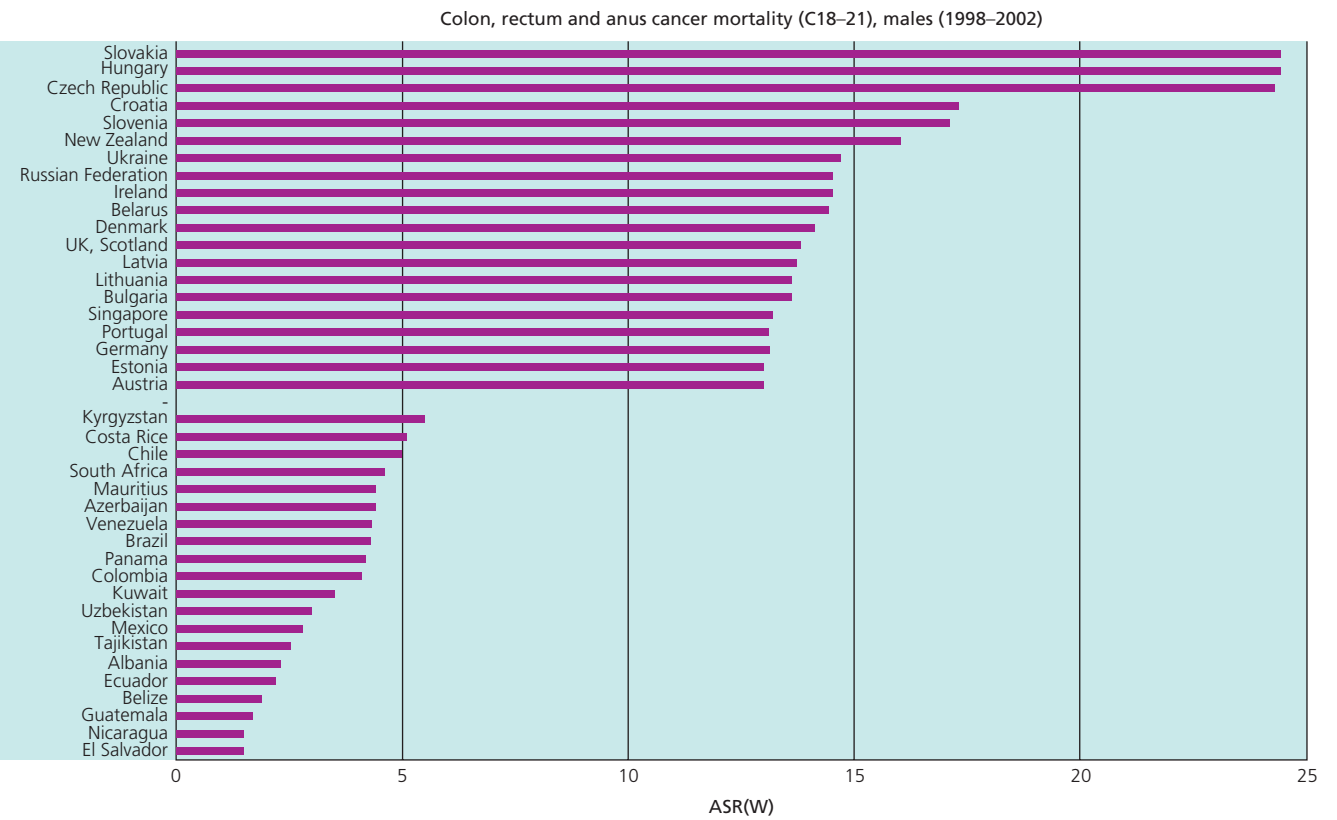


**Figure 2.2** Highest and lowest mortality ASR(W) for colorectal cancer worldwide for males.

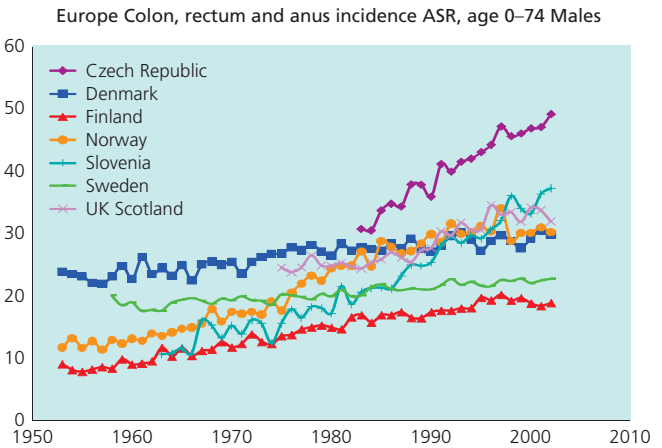


**Figure 2.3** Trends on colorectal cancer incidence in Europe for selected countries (Nordcan; Socrates).

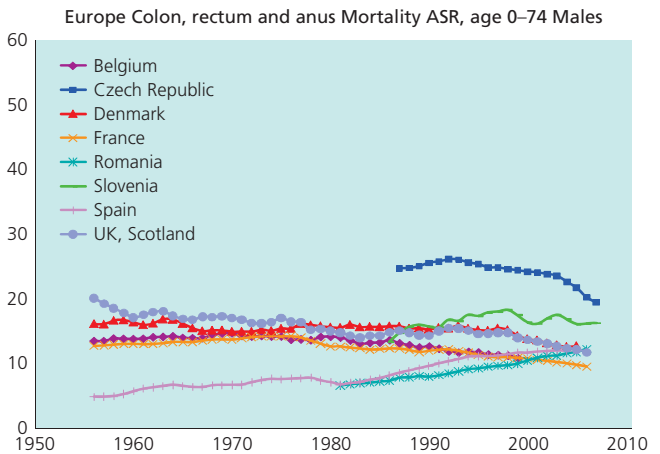


**Figure 2.4** Trends on colorectal cancer mortality in Europe for selected countries (WHO mortality).

## Physical activity

Evidence from epidemiological studies appears consistent that men with high occupational or recreational physical activity appear to be at a lower risk of colon cancer. Such evidence comes from follow-up studies of cohorts who are physically active or who have physically demanding jobs as well as case-control studies which have assessed physical activity by, for example, measurement of resting heart rate, or by questionnaire. Physical activity at a level equivalent to walking four hours per week has been associated with a decreased risk of colon cancer among women when compared to the sedentary group (RR = 0.62, 95% CI = 0.40–0.97).

## Dietary pattern analysis

Dietary pattern analysis, based on the concept that foods eaten together are as important as a more reductive methodology characterised by a single food or nutrient analysis, has emerged as an alternative approach to study the relation between nutrition and diseases and tends to indicate that high consumption of fruits and vegetables and a low consumption of meat and saturated fatty acids are associated with reduced colorectal cancer risk. However, there is some controversy surrounding these findings. For example, a meta-analysis of 13 prospective studies involving 3,635 cases of colorectal cancer and 459,910 participants found no association between total fat, saturated fat, monounsaturated fat and polyunsaturated fat consumption and colorectal cancer.

More than a decennia ago, fruits and vegetables were strongly and widely considered to reduce risk of colorectal cancer, a message strongly supported by the media. Many anticarcinogenic micronutrients, such as vitamin C, beta-carotene, folate, dietary fibre, flavonoids, selenium, phytosterols and other phytochemicals, have been proposed to contribute to this potential anticarcinogenic effect of fruits and vegetables.

In 1997, a World Cancer Research Fund/American Institute for Cancer Research report concluded that there was convincing evidence for a decreasing risk of colorectal cancer associated with increasing fruits and vegetable consumption. A decade later, in an updated report, the same organisation downgraded the protective effect of fruits and vegetables from *convincing* to *probable*. Between these reports, at the same time and using the same scientific evidence, an IARC Working Group declared a lack of association between consumption of fruits and vegetables and colorectal cancer.

Early cohort studies supported a protective effect for fruits and vegetables, which was not the case for more recent prospective research. Variations in results between cohort studies could be due to measurement error and to differences in adjustments. Most prospective studies used a single food frequency questionnaire to assess dietary exposition, which may not satisfactorily represent long-term intake.

In conclusion, the observed risk estimates in prospective studies between fruits, vegetables and colorectal cancer are very modest after adjustment for covariates.

## Dietary fibre intake and colorectal cancer risk

Dietary fibre as an entity is difficult to separate from its dietary sources. Recent meta-analyses and pooled analyses have yielded null findings, that is no association between dietary fibre intake and colorectal cancer risk.

## Red meat, processed meat and colorectal cancer

Prospective cohort and case-control studies have associated a daily intake of red and processed meat with an increased risk of colorectal cancer. The term red meat refers to beef, pork, lamb and goat; processed meat refers to meat preserved by smoking, curing, salting and/or addition of chemical preservatives. The results of meta-analysis support the hypothesis that high consumption of red and processed meat may increase the risk of colorectal cancer. However, the epidemiological association across the prospective studies is relatively weak with a 30% increased risk of colorectal cancer in high meat eaters compared to the lowest group of meat eaters.

Another hypothesis involves the potential role of nitrate and nitrite, commonly used in processed meats as preservation agents, as causes of human cancer. However, exposure is not specific to

processed meat intake, as greater exposure may occur through consumption of other dietary sources such as vegetables or cereal products.

The formation of heterocyclic amines and polycyclic aromatic hydrocarbons in cooked meat has also been cited as a possible mechanism in the development of colorectal cancer. Heterocyclic amines and polycyclic aromatic hydrocarbons are carcinogenic in animal studies although evidence in humans is weak and inconsistent.

Finally, it has been suggested that iron, particularly haem iron, may play a role in colorectal cancer development. Red meat is a primary source of haem iron, which is found naturally in meat as part of haemoglobin and myoglobin, although relatively few studies have evaluated the potential role that this factor may play in cancer risk.

### Vitamins and colorectal cancer

The use of multivitamin, vitamin D and folate supplements has been strongly correlated with healthy lifestyles, which could be associated with a lower risk of colorectal cancer. However, there is no compelling evidence to suggest that dietary supplementation is sufficiently worthwhile to be recommended.

### Summary: lifestyle factors, dietary intakes and their consequences and colorectal cancer risk

Currently the weight of the existing evidence suggests that higher rates of smoking, alcohol consumption, intake of red/processed meats and reduced physical activity are all associated with increased risk of colorectal cancer.

Higher intake of fruits and vegetables may only moderately reduce the risk. A colorectal cancer preventive role of dietary or cereal fibre is debatable, despite recent findings suggesting a negative association with high intakes. Higher intake of calcium and vitamin D has been reported to be colorectal cancer protective, but except for modest findings for calcium supplementation in some intervention studies of adenoma recurrence, evidence is still lacking for any firm conclusions to be drawn. Much further research is required to elucidate the role of other compounds, foods, food components or their derivatives that may have effects that are colorectal cancer protective (folate, antioxidants, vitamins C and E, magnesium, selenium, phytochemicals, phytoestrogens, butyrate, resistant starches, tea/coffee, fish, whole grains, low glycemic index foods) or promotive (insulin, dietary carcinogens, secondary bile acids, iron, heterocyclic amines, refined sugars, high glycemic index foods). In addition, there are many complex interactions between environmental, dietary and genetic factors that may well modify colorectal cancer risk.

Among lifestyle factors, obesity has been suggested to be associated with an increased risk of colorectal cancer, although effects may vary by anatomical sub-site of the intestine and by gender. Physical inactivity has also been associated with an increased risk, although primarily for colon and less clearly for rectal cancer.

Thus, regular physical activity and avoidance of calorie over-consumption may represent two of the most effective ways of preventing this disease. Cigarette smoking is another major modifiable lifestyle factor that recent studies suggest is involved in the colorectal carcinogenesis process, although an induction period of four decades has been suggested.

As with many cancers, early detection of precancerous lesions and rapid, effective treatment of early colorectal tumours appear to be key points of screening and treatment strategies, not only for those at high risk of the disease, but also for general populations at large.

Nonetheless, the primarily sporadic nature of the disease indicates that a reduction in colorectal cancer incidence worldwide can best be achieved by effective primary prevention and changes in modifiable risk factors. Reducing cigarette consumption, decreasing alcohol intake, increasing physical activity and reducing consumption of red and processed meats could reduce the risk of colorectal cancer by more than one quarter.

## Further reading

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CHAPTER 3

# Pathways of Carcinogenesis

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**OVERVIEW**

- Sporadic colorectal carcinogenesis is a multi-step evolutionary process
- Steps reflect advantageous mutations and epigenetic changes in tumour suppressor genes and oncogenes
- The changes that occur and the order in which they occur constitute the genetic pathways of carcinogenesis
- The majority of colorectal cancers develop along the classical histological adenoma-carcinoma sequence, which is associated with mutation of the *APC, KRAS, SMAD4* and *TP53* genes and often the acquisition of chromosomal instability
- A subset of colorectal carcinomas arise via a different genetic pathway characterised by mutation in the *BRAF* gene, CpG island hypermethylation at specific sites and the loss of DNA mismatch repair function resulting in hypermutation at repeat sequences including microsatellites (microsatellite instability); such cancers may arise via the serrated neoplasia sequence
- Genetic and epigenetic changes, individually and in combination, may determine disease prognosis and therapy response

## Introduction

Carcinogenesis is the progressive, stepwise transformation of a normal cell into a malignant cancer cell (see Box 3.1, 'Hallmarks of cancer'). The 'steps' in this multi-step process are represented by genetic mutations or epigenetic changes that activate oncogenes or inactivate tumour suppressor genes and mutator genes (Table 3.1).

In their normal state, tumour suppressor genes inhibit cancer formation, but this inhibition is lost when both alleles (copies) of the gene are inactivated by (epi-) mutations. Given that 'two hits' are required to disrupt gene function, tumour suppressor genes are considered to act in a recessive fashion. Similarly, mutator genes normally maintain genomic integrity, but mutation results in a genome-wide increase in mutation rate (hypermutation), either in the form of specific types of small-scale mutations or large-scale chromosomal changes. In contrast, oncogenes promote cancer formation when activated by mutations in one allele of the gene leading to excessive or inappropriate expression or excessive catalytic activity of the protein. Accordingly, oncogenes are said to act in a dominant fashion. The major tumour suppressor genes, oncogenes and mutator genes involved in colorectal cancer are summarised in Table 3.2.

Box 3.1 **The hallmarks of cancer (Hanahan and Weinberg)**

- Self sufficiency in growth signals
- Insensitivity to growth-inhibitory signals
- Avoidance of apoptosis
- Limitless replicative potential
- Angiogenesis
- Invasion and metastasis

The multi-step process of carcinogenesis is initiated by the occurrence of one or more mutations or epigenetic changes that give a cell a selective growth advantage (Figure 3.1). Analogous to Darwinian evolution, the clone derived from that cell then expands. Further progression to malignancy requires additional advantageous alterations, each of which is followed by a wave of clonal expansion. It is generally accepted that fully malignant behaviour only

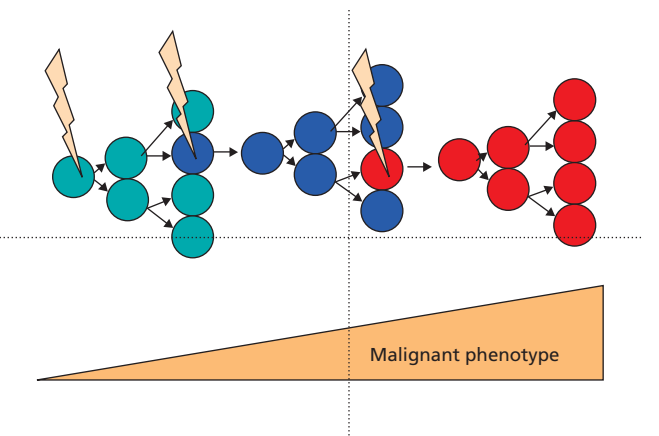


**Figure 3.1** The somatic evolution of cancer. Tumour cells develop an increasingly malignant phenotype as they acquire successive selectively advantageous genetic mutation or epigenetic changes. (Epi-) mutations are followed by waves of clonal expansion.

*ABC of Colorectal Cancer*, Second Edition.
Edited by Annie Young, Richard Hobbs and David Kerr.

**Table 3.1** Types of genetic mutations and epigenetic changes in cancer.

| Type of change | Effect on DNA | Effect on protein |
|---|---|---|
| **Genetic: Small-scale mutation** | | |
| Point mutation | Exchange of a single nucleotide for another | Silent: coding for the same amino-acid<br>Missense: coding for another amino acid<br>Nonsense: creating a stop codon<br>Splice site: removing or creating a splice site |
| Insertion/deletion | Addition/removal of one or more nucleotides | Frameshift: changing the reading frame of the protein<br>In frame: adding/removing one or more amino acids<br>Splice site: removing or creating a splice site |
| **Genetic: Large-scale mutation** | | |
| Duplication/amplification | Gain of one or more copies of a large chromosomal region or a whole chromosome | Increase of dosage for single or multiple genes |
| Deletion | Loss of a large chromosomal region or a whole chromosome | Decrease of dosage for single or multiple genes<br>Creation of novel fusion genes<br>Aberrant gene expression in novel context |
| Translocation | Interchange between nonhomologous chromosomes | Creation of novel fusion genes<br>Aberrant gene expression in novel context |
| Inversion | Reversing the orientation of a chromosomal segment | Creation of novel fusion genes<br>Aberrant gene expression in novel context |
| Loss of heterozygosity | Loss of one allele, either by a deletion or recombination event | Reduction of two alleles to one allele for single or multiple genes |
| **Epigenetic** | | |
| Addition or removal of methyl groups to DNA | At CpG sites, conversion of cytosine to 5-methylcytosine | Silencing or activation of gene expression |
| Modification of histone proteins | Acetylation, methylation, ubiquitylation, phosphorylation, sumoylation | Silencing or activation of gene expression |

**Table 3.2** Oncogenes and tumour suppressor genes commonly involved in sporadic colorectal cancer.

| Gene name | Type of cancer gene | Frequency of mutation or epigenetic silencing | Consequences |
|---|---|---|---|
| *APC* | Tumour suppressor | ~70% | Constitutive activation of the WNT signalling pathway |
| *BRAF, KRAS* | Oncogene | ~10%, ~35% | Constitutive activation of the MAPK pathway |
| *SMAD2, SMAD4, TGFBR2* | Tumour suppressor | ~5%, ~10%, ~15% | Decreased TGF-beta pathway signalling |
| *TP53* | Tumour suppressor | ~50% | Impaired cellular stress and DNA damage response |
| *MLH1* | Mutator gene | ~10% | Defective DNA mismatch repair |

MAPK, mitogen activated protein kinase; TGF-beta, transforming growth factor-beta.

manifests once cells have acquired the capacity of self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, avoidance of apoptosis, limitless replicative potential, angiogenesis, invasion and metastasis. The mutations and epigenetic changes which occur and the order in which they occur constitute the genetic pathways of carcinogenesis. The clonal evolution of colorectal cancer is reflected histologically by a sequence of premalignant lesions showing a progressive increase in atypia and eventually overt malignancy. Current evidence suggests that colorectal tumours develop along a limited number of alternative genetic pathways. The following discussion focuses on sporadic (non-familial) colorectal cancer. Familial colorectal cancer is discussed in Chapter 4.

## The histological development of colorectal adenocarcinoma

### The classical adenoma-carcinoma sequence

The development of most sporadic colorectal cancers from normal epithelium probably follows a relatively consistent histological sequence, the classical adenoma-carcinoma sequence (Figure 3.2). The first stage of this sequence is usually taken to be the onset of dysplasia involving a single crypt (unicryptal adenoma). Single dysplastic crypts develop into clusters of dysplastic crypts which grow to form adenomas that often change from a tubular to a tubulovillous or villous architecture as they increase in size. Similarly, the cells of adenomas show first mild, then moderate, and then severe cytological atypia. Eventually the defining features of malignancy (adenocarcinoma) appear; local invasion and metastasis to distant sites.

For sporadic colorectal tumours the progression from adenoma to carcinoma has been estimated to take approximately 10 to

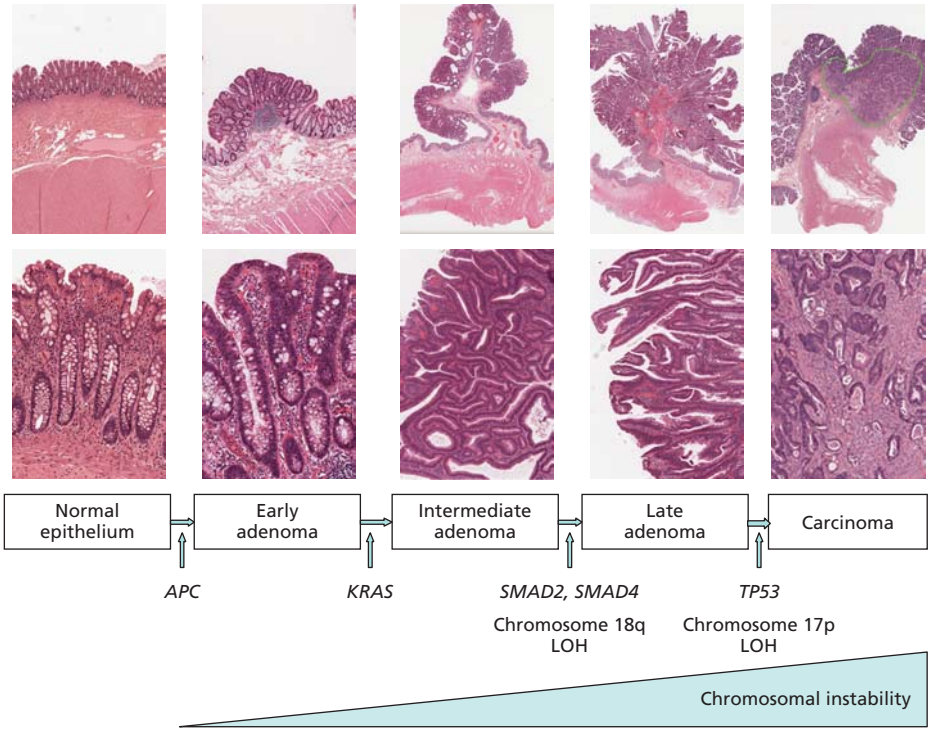


**Figure 3.2** The classical adenoma-carcinoma sequence. Inactivation of the *APC* tumour suppressor gene results in defective Wnt signalling and initiates tumour formation. Subsequent progression towards malignancy is accompanied by mutation in the oncogene *KRAS*, loss of chromosome 18q harbouring the tumour suppressor genes *SMAD2* and *SMAD4*, and loss of chromosome 17p harbouring the tumour suppressor gene *TP53*. The extent of chromosomal instability increases with tumour progression. Villous morphology becomes more prominent as adenomas increase in size. The carcinoma is outlined in green.

40 years. However, there is evidence that not all adenomas undergo malignant transformation. For example, adenomas are considerably more frequent than carcinomas in the general population, taking into account that some patients will die before the adenomas have had sufficient time to progress to carcinoma. More direct evidence comes from long-term endoscopic studies demonstrating that some sporadic adenomas undergo spontaneous regression.

### The serrated neoplasia sequence

In recent years, an alternative sequence of histopathological lesions leading to colorectal carcinoma has been identified, the serrated neoplasia sequence (Figure 3.3). Premalignant lesions in this sequence probably include two distinct types of serrated polyps, traditional serrated adenomas and sessile serrated adenomas, which together may constitute 5–10% of all polyps. However, the true magnitude of risk of progression to adenocarcinoma for these two types of polyps remains unknown and the recommendations on their clinical management continue to evolve. Compared to the classical adenoma-carcinoma sequence, the serrated neoplasia sequence appears to be associated with different sets of genetic and epigenetic changes. In particular, sessile serrated adenomas have been suggested to be possible precursor lesions for DNA mismatch repair deficient sporadic colorectal cancer (see below). The role of the pathologist in reporting such histology is outlined in Chapter 7.

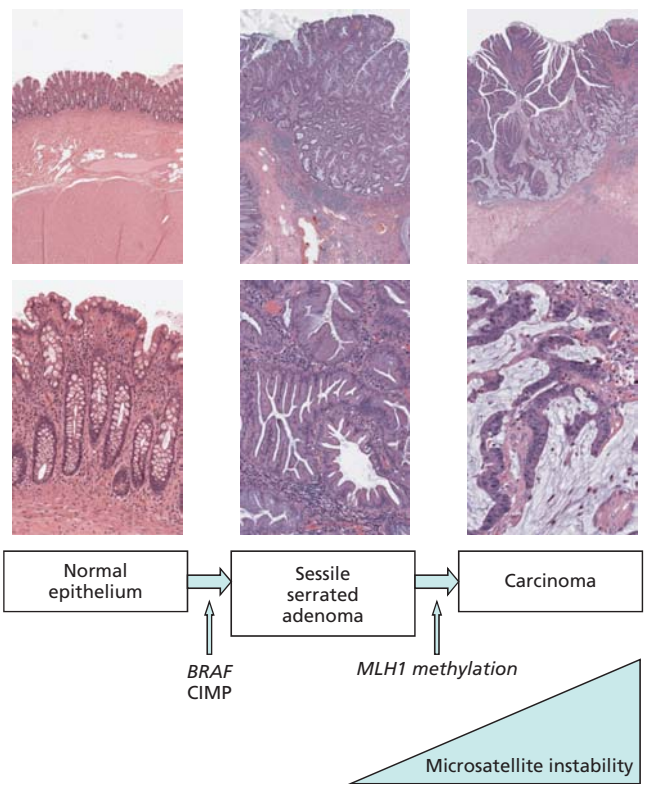


**Figure 3.3** The serrated neoplasia sequence. Sessile serrated adenomas often show *BRAF* mutation and CpG island methylation at specific loci (CIMP). Progression to carcinoma may be associated with *MLH1* promoter hypermethylation and consequent impairment of DNA mismatch repair which manifests as microsatellite instability. Note the serrated luminal outlines in the sessile serrated adenoma, and the mucinous differentiation in the carcinoma.

## Genetic pathways

### The classical genetic pathway for sporadic colorectal cancer

Molecular studies of sporadic lesions from all stages of the classical adenoma-carcinoma sequence have uncovered a common

succession of genetic and epigenetic changes in tumour suppressor genes and oncogenes (Figure 3.2). Tumour growth is probably most commonly initiated by bi-allelic mutation of the adenomatous polyposis coli (*APC*) tumour suppressor gene, with changes detectable in around 70% of microadenomas, early adenomas and carcinomas. *APC* is therefore often referred to as the gatekeeper of colorectal carcinogenesis. One consequence of *APC* mutation is aberrant activation of the Wnt signalling pathway, which plays a key role in controlling stem cell maintenance, proliferation and differentiation of colorectal epithelia.

Although bi-allelic *APC* mutation appears to trigger tumour formation, changes in additional genes are required for further adenoma growth and progression. Activating mutations in the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*), a member of the mitogen activated protein kinase (MAPK) pathway, are found at the transition from an early- to an intermediate-stage adenoma in around 35% of lesions.

Progression from an intermediate- to a late-stage adenoma is associated with loss of chromosome 18q, which is detected in around 60% of large adenomas. The two main tumour suppressor genes which are targeted by this loss are probably the SMAD family members 2 and 4 (*SMAD2* and *SMAD4*), both acting in the transforming growth factor-beta (TGF-beta) signalling pathway. Accordingly, mutations have been identified in *SMAD2* and *SMAD4* in sporadic colorectal cancers, albeit at a lower frequency than the chromosome 18q loss.

The transition from a late-stage adenoma to adenocarcinoma often coincides with loss of chromosome 17q, identifiable in around 50% of cases. The tumour protein p53 (*TP53*), a critical regulator of cellular stress and DNA damage responses, is the most likely target of this change. Chromosome 17q loss strongly correlates with missense and protein truncating mutations in *TP53*.

The cellular and genetic changes that lead to tumour invasion and metastasis are amongst the least understood aspects of colorectal cancer biology. Loss of E-cadherin function, a component of adherens-junctions between cells, is one of the aberrations which have been associated with cancer invasion.

Approximately 80% of colorectal cancers that develop along the classical pathway further appear to acquire some form of chromosomal instability, an increased rate of chromosomal gains, losses and/or rearrangements. However, around 20% of colorectal cancers maintain a relatively normal chromosomal karyotype with some data suggesting an overall better prognosis for patients with such tumours (see below).

## DNA mismatch repair deficient sporadic colorectal cancer

Approximately 10–15% of sporadic colorectal cancers follow an alternative genetic pathway of carcinogenesis characterised by loss of DNA mismatch repair function. This defect is usually caused by hypermethylation of the mutL homolog 1 (MLH1) promoter resulting in silencing of transcription of this DNA mismatch repair gene. DNA mismatch repair deficiency results in genome-wide hypermutation at nucleotide repeat sequences including microsatellites, short tandem repeat sequences of 1–6 base-pairs of DNA.

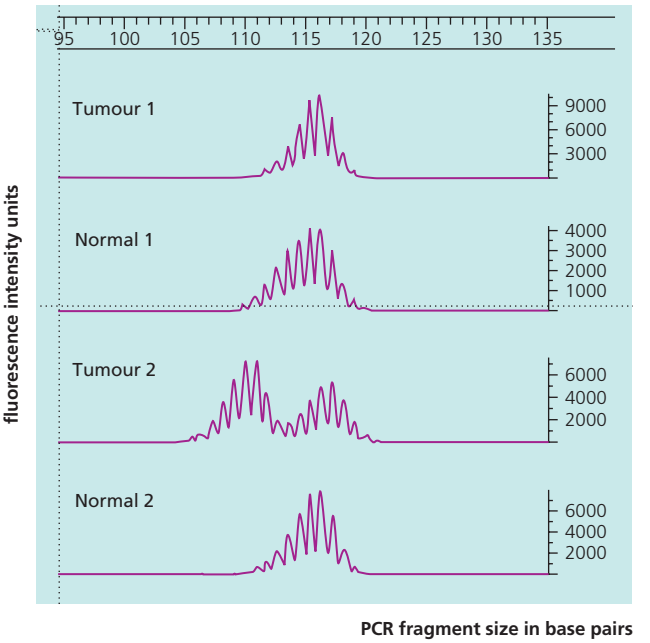


**Figure 3.4** Microsatellite instability in colorectal cancer as indicated by fragment analysis of the mononucleotide repeat marker BAT26. The microsatellite marker BAT26 has been PCR-amplified from tumour and normal DNA from two patients using fluorescently-labelled primers. The PCR-products have been separated according to size. Tumour 2 shows an additional BAT26 peak due to a 6 base-pair deletion within the mononucleotide repeat. In clinical practice, a panel of 5 microsatellite markers, the Bethesda panel (BAT25, BAT26, D5S346 and D17S250), is generally analysed. A tumour is classified as microsatellite unstable if two or more of the five loci show instability.

Microsatellite instability (MSI) detected by polymerase chain reaction (PCR) amplification is a commonly used marker for such tumours (Figure 3.4). In addition, these tumours tend to accumulate frameshift mutations within coding repeats of certain cancer genes including axin 2 (*AXIN2*), transforming growth factor beta receptor II (*TGFBR2*), insulin-like growth factor 2 receptor (*IGF2R*), BCL2-associated X protein (*BAX*) and E2F transcription factor 4 (*E2F4*). Selectively neutral bystander mutations in coding repeats of other genes are also common.

DNA mismatch repair deficient tumours further tend to display activating point mutations in the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), and CpG island hypermethylation at specific loci, a phenomenon referred to as CpG island methylator phenotype (CIMP). The chromosomal karyotype of these tumours tends to be normal, suggesting that microsatellite instability and chromosomal instability are mutually exclusive.

Intriguingly, sporadic cancers with defective DNA mismatch repair show clinicopathological features distinct from other sporadic colorectal cancers. MSI-positive cancers are associated with female gender, older age, right sided location and several histopathological features including mucinous differentation, higher grade (poor differentiation) and a pronounced lymphocytic infiltrate. The presence of MSI has been associated with better disease prognosis and lack of response to fluorouracil (5-FU) based chemotherapy (see below). Notably, sessile serrated adenomas appear to share many of the molecular and clinical characteristics

**Table 3.3** Prognostic and predictive factors in colorectal cancer.

| Marker | Predictive significance | Prognostic significance |
|---|---|---|
| *KRAS* mutation | Confirmed to predict a lack of response to anti-EGFR antibody therapy* | – |
| *BRAF* mutation | May predict a lesser response to anti-EGFR antibody therapy | May indicate a worse prognosis in patients with metastatic disease |
| Microsatellite instability (DNA mismatch repair deficiency) | May predict a lesser response to fluorouracil, and an improved response to irinotecan | May indicate a better prognosis |
| Aneuploidy/Polyploidy (Chromosomal instability) | – | May indicate a worse prognosis |

*Only *KRAS* mutation status is currently recommended as a marker for clinical use. EGFR, epidermal growth factor receptor

of MSI-positive carcinomas, suggesting that these may be the corresponding precursor lesions in a proportion of cases.

## (Epi-) Mutations, disease prognosis and therapy response

There is increasing evidence that certain mutations or epigenetic changes are associated with disease prognosis (prognostic markers) and/or response to therapy (predictive markers) (Table 3.3). Although the use of molecular genetic changes as prognostic or predictive markers for colorectal cancer is currently limited with very few clinical applications, this field is expected to expand in the coming years. See Chapter 4, Clinical Genetics in the Management of Colon Cancer.

The best example of a clinically useful predictive marker is *KRAS* mutation which predicts resistance to anti-epidermal growth factor receptor (EGFR) antibody therapy, mostly used to treat patients with metastatic colorectal cancer. Current recommendations are that all colorectal cancer patients being considered for such therapy should have *KRAS* mutation testing performed on tumour samples, and only patients lacking *KRAS* mutation should receive anti-EGFR antibody therapy. *BRAF* mutation may similarly predict a lack of response to anti-EGFR therapy, but this latter association remains a subject of investigation.

Genomic instability status is also a marker of potential prognostic and predictive value, although it is not yet used in the clinic. Studies indicate that MSI-positive cancers have a better prognosis than MSI-negative cancers, may not benefit from adjuvant 5-FU based therapy, but may show an improved response to irinotecan based therapy. Similarly chromosomal instability (aneuploidy/polyploidy) appears to be associated with a worse prognosis.

Current research aims to further characterise the associations of genetic and epigenetic changes, individually and in combination, with disease prognosis and therapy response. This work may ultimately lead to the development of molecular signatures which may in the future allow more rational planning of treatment and follow-up. As novel therapies targeting mutant proteins in cancer are being developed, mutation testing to select patients for treatment will become more commonplace.

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CHAPTER 4

# Clinical Genetics in the Management of Colon Cancer

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**OVERVIEW**

- The majority of individuals with a family history of colorectal cancer will themselves be at near population risk of developing cancer
- Recognition of a possible familial colorectal cancer syndrome is the key to management
- Treatment includes genetic counselling, genetic testing and screening for cancer
- There is evidence that surveillance programmes are effective in reducing colorectal cancer mortality in dominantly inherited colorectal cancer syndromes
- A carefully designed standard protocol to collect family history information at primary care level facilitates appropriate rapid referral to screening units, genetics services or back to primary care

## Introduction

Before 1990, the role of inherited factors in the aetiology of adult cancer was relatively poorly understood and aroused little interest among doctors and the public alike – although familial adenomatous polyposis (the autosomal dominant colon cancer syndrome referred to in the previous chapter) was an exception in this respect. However, in the last 20 years interest has increased markedly. In the West Midlands (population 5.5 million), for example, familial cancer referrals constituted 1% of all clinical genetic referrals in 1991, whereas now they represent 41% of cases (3,635 cases in 2009) (Figure 4.1).

Despite the estimate that 5–10% of colorectal cancer has an inherited basis, only a small percentage of referred families have mutations in one of the currently identified genes. Furthermore, mutation studies are usually possible only if DNA is available from an affected patient, so molecular investigation will facilitate the management of only a small number of cases. The remaining referrals must be managed with clinically derived strategies. This article discusses the clinical features and management of dominant colon cancer syndromes and provides referral guidelines and screening protocols for more common familial clusters.

Genetic counselling for families with a history of cancer requires a full and accurate family history. When possible, histological confirmation of the reported tumours should be obtained. It should then be possible to recognise the specific cancer syndromes. It is important to emphasise to families that however extensive the family history of cancer, (unless present on both sides), the patient will always have a greater than 50% chance of *not* developing that particular tumour. This simple fact is often overlooked and may surprise but greatly reassure many patients.

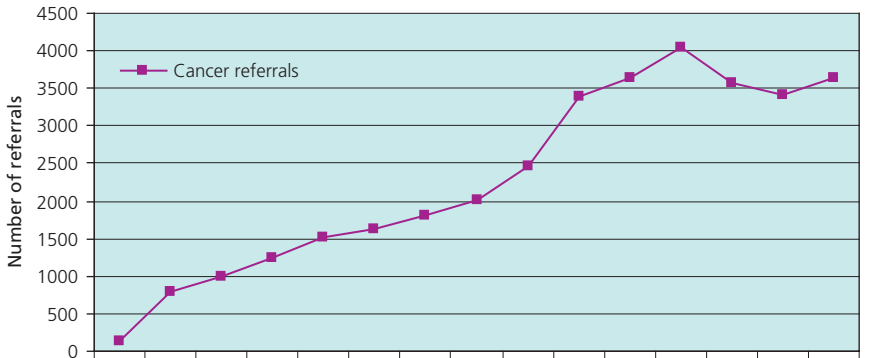
## Familial adenomatous polyposis (FAP)

FAP, previously called polyposis coli (or Gardners syndrome if extra colonic manifestations were present, Figure 4.2 and 4.3), is the best recognised of the colorectal cancer syndromes but accounts for less than 1% of all colorectal cancers and has a prevalence of 1 in 14,000. It is characterised by the presence of 100 or more tubo-villous adenomas in the colon, with intervening micro-adenoma on histological examination. The mean age of diagnosis of polyps is during teenage years, and almost all of gene carriers have polyps by the age of 40. If these are left untreated, malignant transformation is inevitable with a mean age of colorectal cancer occurring during the patient's mid-30s, often with synchronous tumours.

This condition is an autosomal dominant disorder, therefore the offspring of affected individuals are at a 50% risk of being gene carriers. The diagnosis of FAP should always result in a careful and full evaluation of the family history. Wherever possible, parents should have at least one colonoscopy, irrespective of age. In most cases without a family history, parental examination will be negative and the proband (the subject being studied or reported on) will probably be one of 30% of cases that represent new mutations. However the siblings of all probands should be offered annual colonoscopy up to the age of 30, reducing to 3 yearly intervals until aged 60 or until proven to be non-gene carriers.

The cloning of the causative gene (APC) on chromosome 5 in 1991 dramatically changed the management of FAP. If DNA is available from an affected individual, sequencing will detect mutations in 99% of families with classical FAP. In these families first-degree relatives should be offered predictive testing with appropriate genetic

*ABC of Colorectal Cancer*, Second Edition.
Edited by Annie Young, Richard Hobbs and David Kerr.




| | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cancer referrals | 141 | 794 | 994 | 1248 | 1515 | 1629 | 1798 | 2015 | 2475 | 3381 | 3633 | 4055 | 3563 | 3410 | 3635 |

**Figure 4.1** Number of referrals of patients with cancer to West Midlands Regional Clinical Genetics Service, 1995–2009.

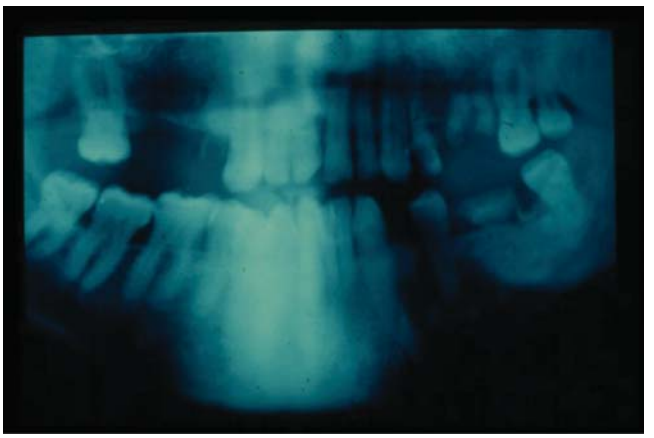


**Figure 4.2** Mandibular cysts in Familial Adenomatous Polyposis.

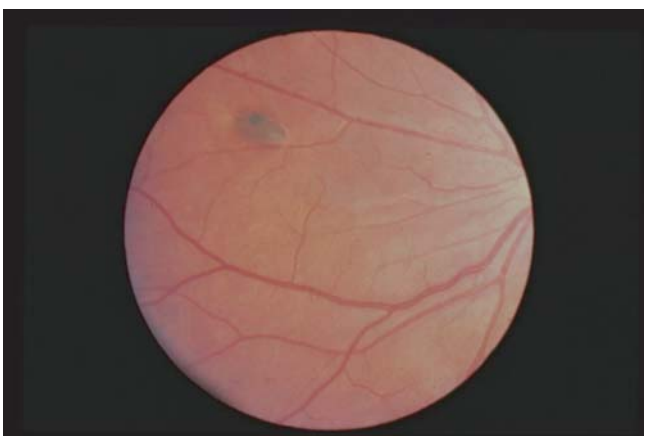


**Figure 4.3** Congenital hypertrophy of the retinal pigment epithelium (CHRPE) in Familial Adenomatous Polyposis.

counselling. In families with no identified mutation, linkage studies to identify the 'high risk' chromosome 5 are possible in many cases. Non-gene carriers should be reassured and surveillance stopped. Gene carriers should be offered annual surveillance from the age of 12. Once a number of polyps are identified, the timing and type of surgery available should be discussed (a sensitive issue in teenagers and young adults). The two most common options are ileal-rectal anastomosis and annual surveillance of the remaining rectal tissue or alternatively an ileal-anal anastomosis and reconstruction of a rectal pouch using terminal small bowel.

Molecular testing is usually offered to 'at risk' children at ages of 10–14 before starting annual sigmoidoscopy. However, parental pressure for earlier testing (prior to the child being able to give consent), is not uncommon and the timing of testing continues to be a subject of debate.

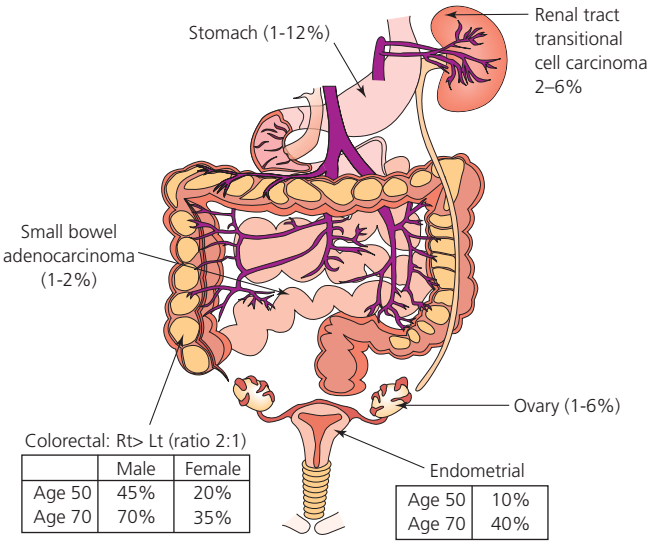
Cloning APC explained several clinical features and aided studies of genotypes and phenotypes. For example the presence of congenital hypertrophy of the retinal pigment epithelium (Figure 4.3), an attenuated phenotype, (that is, fewer than 100 polyps or late onset) and non-malignant but debilitating and potentially lethal desmoid disease each show an association with mutations in specific exon regions. The cloning also confirmed clinical findings that FAP and Gardner's syndrome were different manifestations of the same disease spectrum that could coexist within the same family.

With greater clinical awareness, regular surveillance and the advent of molecular investigation, almost all colorectal cancer deaths in inherited cases of FAP can be avoided. Increased survival has revealed later complications, in particular periampullary or duodenal adenocarcinoma (occurring in 2–12% of individuals post-colectomy). Also important are aggressive desmoid disease and other rarer malignant diseases (Box 4.1).

Box 4.1 **Early and late extracolonic tumours in familial adenomatous polyposis**

Hepatoblastoma (early)
Adrenal adenoma (early or late)
Desmoid disease (early or late)
Papillary thyroid cancer – predominantly females (late)
Periampullary carcinoma (late)

Multi-centre studies of chemoprophylactic approaches to reduce polyp growth (for example, aspirin and non-digestible starch) are in the follow-up phase at present.




| | Male | Female |
|---|---|---|
| Age 50 | 45% | 20% |
| Age 70 | 70% | 35% |

| | |
|---|---|
| Age 50 | 10% |
| Age 70 | 40% |

**Figure 4.4** Tumours in hereditary non-polyposis colorectal cancer (upper figure in ranges may be overestimates due to ascertainment bias).

## Lynch syndrome

Lynch syndrome (LS), also known as hereditary non-polyposis colon cancer (HNPCC), became more widely recognised about 30 years ago in families manifesting mainly colorectal cancer segregating in an autosomal dominant fashion. Many families also exhibit extra-colonic tumours, particularly gynaecological, small bowel or urinary tract carcinomas (Figure 4.4) and these became known as Lynch type 2 to distinguish them from site specific colorectal cancer families, designated Lynch type 1. The subsequent name change to HNPCC was potentially misleading as many gene carriers will develop a small number of tubo-villous adenomas, but not more than 100 as seen in FAP, and Lynch syndrome has become the preferred name again. The proportion of CRC due to LS is controversial and estimates range from 1% to 20%; most observers, however, suggest about 2%.

The diagnosis of LS is suspected on the basis of the family history, as the appearance of the bowel, unlike FAP, is a not diagnostic. To improve the recognition of LS, diagnostic criteria were devised in Amsterdam in 1991 and were subsequently amended to include non-colonic tumours (Box 4.2). Confirmation of the diagnosis is usually through molecular testing.

Mutations in four mismatch repair (MMR) genes, *MLH1, MSH2, MSH6* and *PMS2* have been linked with LS. If both copies of the genes are mutated, as postulated in Knudson's two hit hypothesis, that cell and all its daughter cells are missing a vital mechanism for repair of DNA in somatic tissue. Molecular studies showed that a

Box 4.2 **Modified Amsterdam Criteria**

- At least three relatives affected by an LS-related cancer (colorectal carcinoma, endometrial carcinoma, small intestinal adenocarcinoma, transitional cell carcinoma of renal pelvis)
- At least two successive generations affected
- One case must be diagnosed before the age of 50
- Familial adenomatous polyposis excluded

significant minority (approximately 30%) of early onset CRC (less than 35 years) is due to mutations in the MMR genes. Mutations in the MMR genes lead to microsatellite instability (MSI) (Figure 4.5) and loss of expression of the MMR proteins in the tumour tissue (Figure 4.6). MSI is the presence of additional alleles of certain short tandem-repeat DNA sequences ('microsatellites') – see Chapter 3 Pathways of Carcinogenesis, and is present in more than 90% of LS related colorectal tumours. Loss of MMR protein expression may be detected using immunohistochemistry (IHC). The finding of MSI and MMR protein loss is a strong indicator that a mutation in a MMR gene is present, and MSI and IHC studies on stored tumour tissue are now routinely used to select cases for germline mutation testing.

Risk estimates vary widely across different studies, with lifetime risks of, for example, male bowel cancer ranging from below 50% to almost 100% (Table 4.1). This reflects differences in ascertainment of the families, age at the end of follow-up and methods of statistical analysis. However, consensus approximate lifetime risks of developing the main LS related cancers are shown in Figure 4.4, and these are frequently quoted during the counselling of families.

A review by Lindor *et al.* in 2006 found evidence suggesting that screening for colorectal cancer in LS is beneficial in reducing mortality. Previously, Vasen *et al.* (1999) had reported that screening is cost-effective. The method of choice is colonoscopy rather than flexible sigmoidoscopy as 80% of cancers are proximal to the rectum compared to only 57% in sporadic CRC. Failure to reach the caecum should be followed by barium enema examination, although surveillance using radiological techniques should probably be used sparingly due to the theoretical mutagenic consequences in patients with DNA repair defects. However, the optimal surveillance frequency is controversial. Recent guidelines recommend 2 yearly screening, but interval cancers have been reported, suggesting that screening should perhaps be more frequent than this. Patients should understand that the strategy of colonoscopy is the removal of polyps and prevention of tumours or early diagnosis, but that complete prevention is impossible. Extra-colonic screening guidelines are summarised in Box 4.3 and Table 4.2.

**Table 4.1** Penetrance of colorectal and endometrial cancers in LS in different studies.

| | Colorectal cancer penetrance (%) | | Length of follow-up | Endometrial cancer penetrance (%) | Length of follow-up |
|---|---|---|---|---|---|
| | Males | Females | | | |
| Hampel *et al*. 2005 | 68.7 | 52.2 | Lifetime | 54 | Lifetime |
| Aarnio *et al*. 1999 | 100 | 54 | To 70yr | 60 | To 70yr |
| Quehenberger *et al*. 2005 | 26.7 | 22.4 | To 70yr | 31.5 | To 70yr |

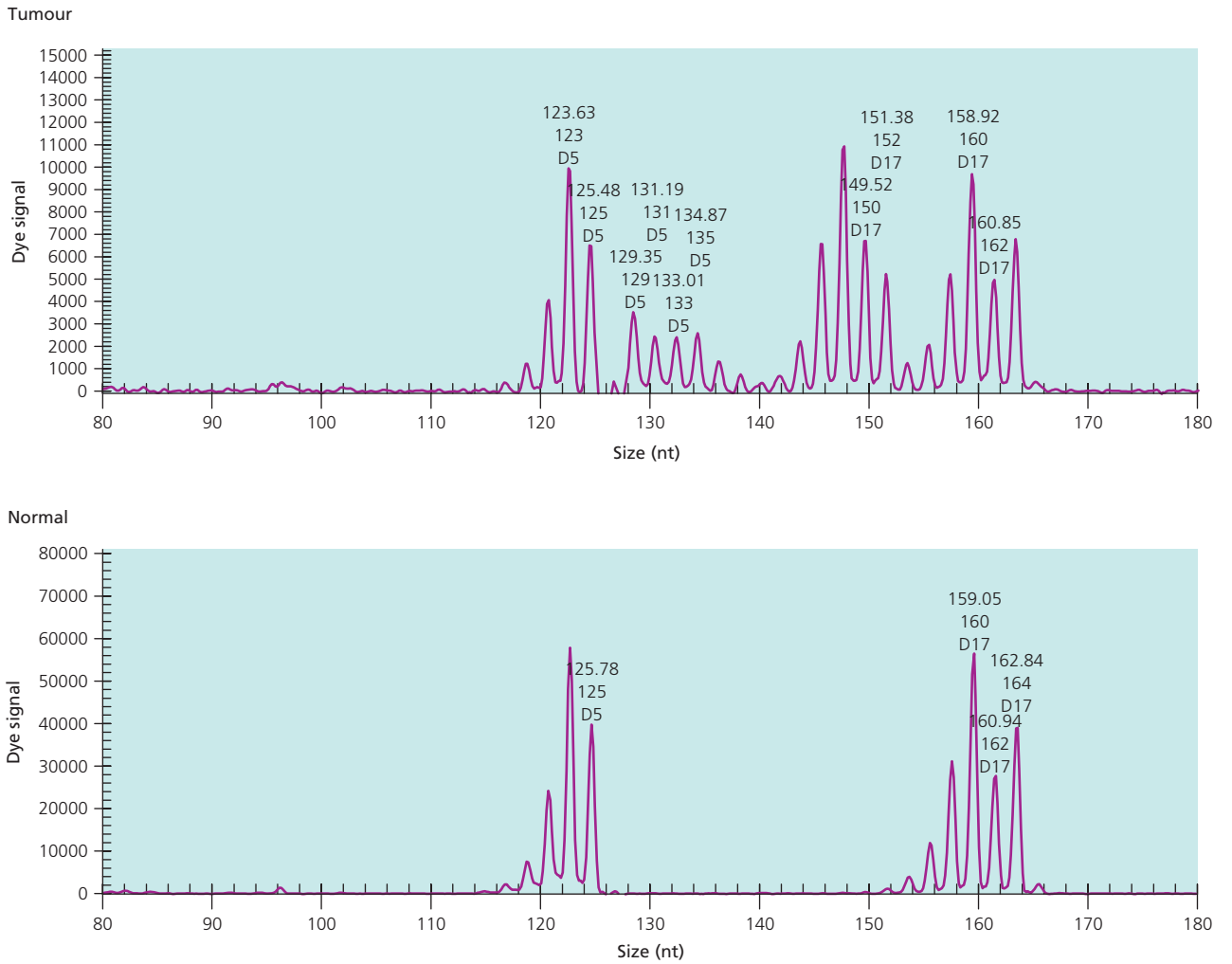



**Figure 4.5** Microsatellite instability. The upper figure shows extra peaks representing additional alleles of the microsatellite marker present in the tumour, which are absent in the patient's normal tissue (lower figure).

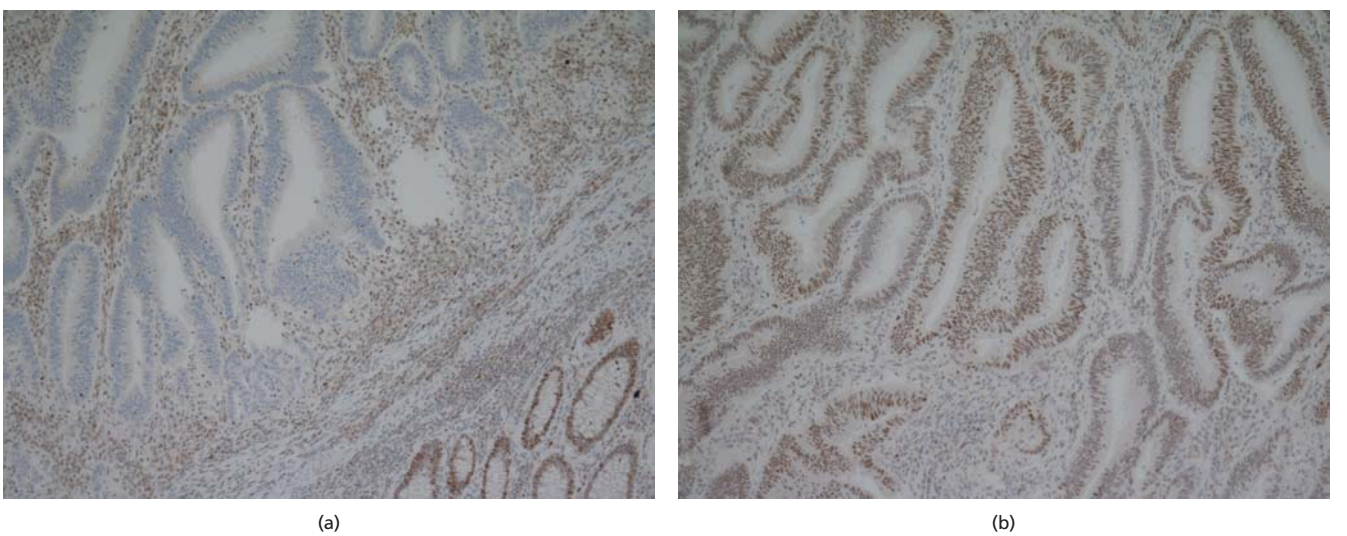



**Figure 4.6** a. Loss of normal brown coloured staining by immunohistochemistry for the MSH2 protein in colon carcinoma cells which are blue in colour. b. Normal preservation of protein staining in colon cancer.

**Table 4.2** Guidelines of the international workshop on surveillance in Lynch Syndrome, convened in 2006 (summarised in Vasen *et al*., *JMG* 2007, 44; 353–362). Evidence of benefit is still not available.

| Site | Screening method | Age at first screen not later than: |
|---|---|---|
| Endometrium | Gynaecological exam, transvaginal ultrasound and aspiration biopsy 1–2 yrly | 30–35yr |
| Ovary | Transvaginal ultrasound 1–2-yrly Measurement of serum Ca 125 | 30–35yr |
| Stomach | Gastroscopy 1–2 yrly in those with a family history of gastric cancer | 30–35yr |
| Urinary tract | Renal ultrasound, cystoscopy, urine analysis and cytology 1–2 yrly in those with a family history of renal or urinary tract cancers | 30–35yr |

Box 4.3 **Screening of other organs in LS**

- Screening of other organ systems has not yet been proven to be beneficial
- However, screening for gynaecological tumours in mutation positive families is widely offered, irrespective of the family history, as 40% of female gene carriers develop endometrial carcinomas
- If tumours have previously been identified within the family in the gynaecological or urinary tract, surveillance also offered

## Familial clusters with no recognisable single gene disorder

Families whose cancers do not meet the diagnostic criteria of FAP, LS or rarer colorectal cancer syndromes (such as syndromes related to the *PTEN* gene, *MYH* gene, Turcot syndrome, Peutz-Jegher syndrome or Juvenile polyposis) make up the largest and most difficult group of patients requesting management. There is rarely any indication of the aetiological basis of the cluster of colorectal cancer and many instances will be coincidental occurrences. Other tumour clusters may be due to common environmental exposures, the effect of multiple low penetrance genes or an interaction of both these elements. The risk of colorectal cancer may be assessed using empiric risk figures (Table 4.3). These figures are estimates, however, and do not take into account factors such as the number of unaffected relatives. Further enquiry is usually justified if features such as multiple relatives with the same tumour or early onset of tumours are present in a family (Box 4.4).

**Table 4.3** Lifetime risk of colorectal cancer in first degree relatives of patient with colorectal cancer (from Houlston *et al*., 1990).

| | |
|---|---|
| Population risk | 1 in 50 |
| One first degree relative affected (any age) | 1 in 17 |
| One first degree and one second degree relative affected | 1 in 12 |
| One first degree relative affected (age <45) | 1 in 10 |
| Two first degree relatives affected | 1 in 6 |
| Autosomal dominant pedigree | 1 in 2 |

Box 4.4 **Four pointers to recognition of familial cancer clusters**

- High frequency of the same tumour in the family
- Early age of onset of tumours
- Multiple primary tumours
- Recognised associations – for example, colorectal and endometrial adenocarcinomas

Concerns that it is often impossible to provide precise risk figures may be misguided, as there is evidence that many patients have difficulty interpreting risk figures and often are only requesting general guidance on risk and a discussion of management options. However, many different screening protocols have been suggested in the past and the lack of consistency and long-term audit in these families is a problem.

To manage familial cancer in the West Midlands, a protocol has been developed which maximises the role of primary care (Figure 4.7). The protocol provides clear inclusion and screening guidelines for cancer units and centres. This has promoted a consistency of management across families as well as between families and is now allowing collection of data for audit. Table 4.4 summarises the recent recommendations for screening commissioned by the British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland. These are useful guidelines but advice from a tertiary genetics unit should be sought for apparently moderate and high risk families, as additional molecular investigations may help to tailor surveillance more appropriately. In particular, some families may benefit from individual clinical or molecular evaluation and modification of the advice given in the guidelines.

The issue of whether primary care should use a reactive or proactive approach is still debated. In the West Midlands, patients requesting advice are asked to complete a family history questionnaire at home. This form and the inclusion criteria are available at http://www.bwhct.nhs.uk/genetics-wmfacs-documents.htm. Completion of the form in the patient's own time, at home, facilitates discussion with relatives to clarify the relevant information and saves time if a referral is required.

After histological confirmation in suspected familial cases, the data are evaluated centrally to identify high risk families requiring specialist investigation or referral to a screening unit. In a pilot study (population 200,000) the protocol reduced referrals from primary care by 50% with a greater reduction in screening due to a fall in low risk referrals to cancer units. This was associated with an increased referral rate for high risk referrals to clinical genetics. Central coordination prevents unnecessary reinvestigations for different branches of any one family.

Reports from local screening units and primary care suggest that the system of triage is beneficial in optimising screening efficiency. Further studies of patient satisfaction and how best to provide reassurance would be valuable.

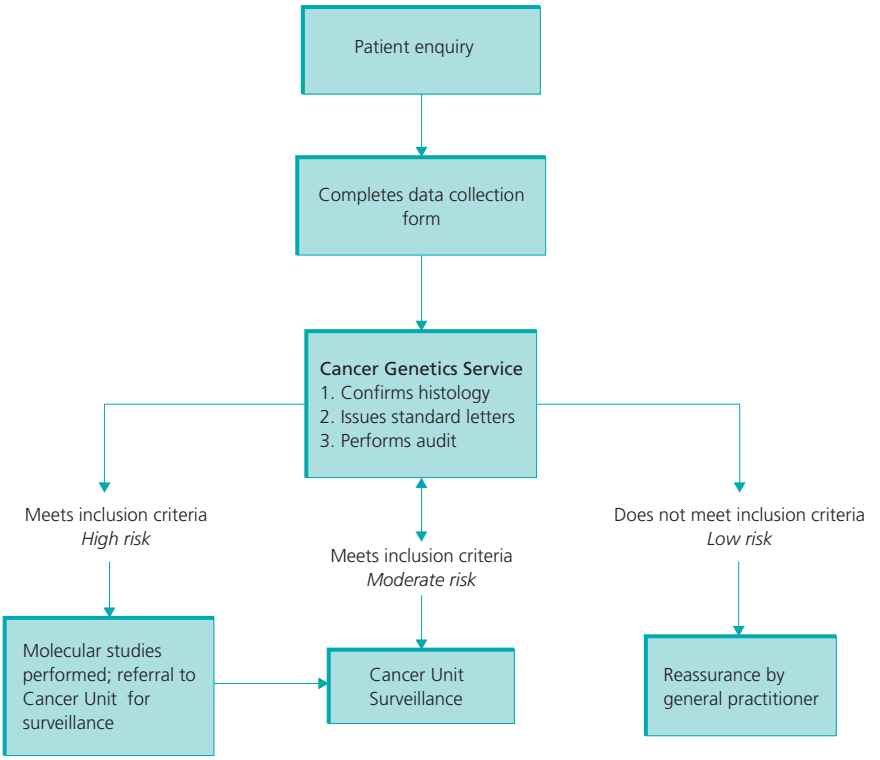



**Figure 4.7** West Midlands protocol for cancer genetics referrals.

**Table 4.4** The guidelines for colorectal screening summarised from Cairns *et al*. *Gut* 2010. Microsatellite instability studies and immunohistochemistry for loss of mismatch repair proteins may aid in the modification of these guidelines for individual families. All individuals should be encouraged to participate in population screening programmes as they are made available.

| Family history | Screening regime |
|---|---|
| FAP – 50% risk no mutation | Colorectal – annual surveillance starting 13–15yrs until 30, then 3–5 yrly from 30–60<br>Upper GI – 3 yrly OGD from 30 |
| FAP – known mutation | Annual surveillance until surgery |
| Lynch Syndrome: family members at 50% risk (where no mutation has been found but family meets Amsterdam criteria) and proven gene carriers | Colonoscopy 2 yearly (discuss 18 monthly) from 25–70/75<br>Upper GI – if family history of gastric cancer, 2 yrly OGD from 50 until 75 |
| Colon cancer family histories* | |
| 3 any age but all >50yrs<br>2 < 60 or mean <60yrs | 'High Moderate' – 5 yrly 50–75 |
| 1 < 50yrs<br>2 between 60–70yrs<br>2 > 70yrs | 'Low Moderate' – one colonoscopy at 55 |

OGD – oesophago-gastro-duodenoscopy
*Relatives should be first degree relatives of each other and of the proband

## Acknowedgements

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## Further reading

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