Colorectal cancer

Conference Rapporteur: Keith Bodger

(On 23 June 1999, the Royal College of Physicians of London hosted a conference on colorectal cancer organised by Professor Jonathan Rhodes (University of Liverpool).

Epidemiology and diet

There are wide global variations in mortality from colorectal cancer. For example, in England and Wales the age-standardised mortality rate is high (30.8 and 22.4 per 100,000 for men and women, respectively), whereas much lower mortality rates are found in developing nations such as The Gambia (1.3 and 0.7 per 100,000). Both genetic and environmental factors may explain such geographical variations, but a rising rate of colon cancer in countries adopting an increasingly westernised lifestyle (such as Japan) suggests that environmental factors are particularly important. Estimates of the proportion of all cancers which might be avoidable through dietary changes have varied between 10% and 70%, but measurement of dietary intake is notoriously difficult. Red meat consumption in particular has attracted attention as a potential risk factor, though estimates of relative risk have generally been modest, of the order of 1.5-2.0 fold increase. Furthermore, the effect of dietary components on cancer risk may vary between individuals. For example, in the case of red meat, colorectal cancer risk is independent of meat intake in slow acetylators but rises in a dose-dependent manner in fast acetylators.

Some of the specific mechanisms proposed for the increased risks observed for individual dietary components include the generation during the cooking of meat of heterocyclic amines which are direct mutagens in vitro and are carcinogenic in animals. Increased excretion of N-nitroso compounds and precursors (putative DNA-damaging alkylating agents) has been associated with red meat intake.

Dietary mechanisms

The precise components of diet responsible for altering cancer risk and their mechanisms of action are the subject of Professor Rhodes’ lecture on page 190.

Genetics

The lifetime risk of colon cancer in the general population is about one in 50, but those with a first-degree relative affected have a substantially greater risk – about one in 17 if the relative was over the age of 45 years, one in 10 if under 45 years, and one in 6 if two first-degree relatives have suffered from colon cancer. Germ-line genetic disorders causing familial colorectal cancer account for a relatively small proportion of all cancers, but include familial adenomatous polyposis (FAP) (<1% of all colorectal cancer), hereditary non-polyposis colorectal cancer (HNPCC) (2-5% of all cancers), and other rarer syndromes (<0.1%).

A variety of mutations has been described in the adenomatous polyposis coli (APC) gene associated with different clinical phenotypes of FAP (eg attenuated rs classic forms). The presence of multiple colonic polyps and other clinical features, such as retinal spots, osteomas and desmoid disease, makes identification of families relatively straightforward. Prophylactic colectomy, usually with pouch-anal anastomosis, is recommended for affected individuals as teenagers.

HNPCC also follows an autosomal dominant pattern of inheritance and is characterised by an increased risk of

Conference programme

- Epidemiology and diet
  Dr Sheila Bingham, MRC Dunn Human Nutrition Unit, Cambridge

- Dietary mechanisms
  Professor Jonathan Rhodes, University of Liverpool

- Genetics
  Mr Malcolm Dunlop, University of Edinburgh

- Cellular mechanisms
  Professor Alastair Watson, University of Liverpool

- The potential solutions
  The Rt Hon Tessa Jowell MP, Minister of State for Public Health

- Screening – the theory
  Dr Peter Lance, State University of New York, USA

- Screening – the practice
  Dr Linda Garvican, South East Institute of Public Health, Tunbridge Wells

- Surgery
  Miss Sarah O’Dwyer, Christie Hospital, Manchester

- Chemotherapy
  Dr Matthew Seymour, Cookridge Hospital, Leeds

- COX-2 and aspirin
  Professor Raymond DuBois, Vanderbilt University Medical Center, Nashville, USA
colorectal, gastric and uterine malignancy. Unlike FAP, HNPCC lacks distinctive clinical features. Germ-line mutations have been identified in five DNA mismatch-repair (MMR) genes (MLH1, MSH2, MSH6, PMS1 and PMS2). In a study of 184 kindreds suspected of having HNPCC on the basis of familial clustering of colorectal (and other relevant) cancers, germ-line mutations in MMR genes (MLH1 and MSH2) were found in 26%. Multivariate analysis showed that the following three factors were independent predictors for finding a mutation:

1 younger age at diagnosis of colorectal cancer
2 fulfilment of the strict Amsterdam criteria for HNPCC:
   • at least three family members in two or more successive generations have colorectal cancer, one of whom is a first-degree relative of the other two
   • cancer must be diagnosed before the age of 50 in at least one family member
   • FAP has been ruled out
3 the presence of endometrial cancer in the kindred.

Other studies have confirmed that the likelihood of MMR gene mutations can be predicted by features of the family history, suggesting that detailed and expensive mutational screening could be targeted to appropriate families on the basis of clinical criteria. Potential strategies for managing families in which HNPCC is identified include colonic and gynaecological surveillance, prophylactic surgery, and chemopreventive or dietary interventions.

Cellular mechanisms

The adenoma-carcinoma sequence in sporadic colorectal cancer was initially proposed in the 1960s. It is widely believed that neoplasia in the colon evolves through a series of stages beginning with normal mucosa, progresses through hyperproliferative and adenoma stages and culminates in cancer. The molecular basis of these sequential pathological changes is the accumulation of genetic alterations which include subtle mutational sequence changes, alterations in chromosome number, chromosome translocations and gene amplifications.

A wide variety of genetic changes has been described in colorectal cancer, including mutations affecting the APC, K-ras, DCC (Deleted in Colon Cancer) and p53 genes. Genetic changes may occur in a preferred order during cancer development, but the accumulation of genetic abnormalities is not necessarily a linear process and there appears to be no obligate order for the acquisition of genetic lesions. The clinical significance of a non-linear genetic model is that the identification of any one specific genetic change is unlikely to provide useful prognostic information in an individual patient.

There is some debate as to whether the development of multiple genetic mutations in cancer is the result of either 'normal' rates of mutation, with waves of clonal expansion of cell lineages which have acquired cancer-associated mutations, or of accelerated rates of mutation due to the acquisition of genetic instability per se. Evidence is accumulating that nearly all solid tumours are in fact genetically unstable and that it is this genetic instability which drives both tumour progression and tumour heterogeneity, ensuring that no two tumours are exactly alike and that no single tumour is composed of genetically identical cells.

Genetic instability may be seen at a chromosomal level, in which there is frequent gain or loss of whole chromosomes (chromosomal instability (CIN)), or (less commonly) at the nucleotide level in which abnormalities of MMR result in faulty DNA repair and widespread microsatellite instability (MIN). In colorectal cancers, there is an inverse relationship between CIN and MIN. Cancers exhibiting MMR deficiency are generally diploid and do not have significant chromosomal changes but exhibit normal rates of chromosomal change, whereas tumours with intact MMR are usually aneuploid and accumulate chromosomal abnormalities at an increased rate. The mechanisms of chromosomal instability are largely unknown and are now a major focus of research.

Many of the mutated genes identified in colorectal cancers are involved in apoptosis. In addition to regulating cell number and type, apoptosis is believed to be involved in the disposal of cells with damaged or mutant DNA, although there is no direct evidence of this in vivo. Disruption of this defence mechanism in malignant clones may serve as a survival factor for cancer cells. There is some experimental evidence to support this hypothesis. For example, p53 mutations are frequent in colorectal cancer, and the introduction of wild-type p53 into human cancer cell lines inhibits cell growth and induces apoptosis.

The potential solutions

There are about 20,000 deaths from colorectal cancer and 300,000 newly diagnosed cases in the UK each year. These figures have stimulated public concern and prompted government to identify colorectal cancer as a priority area for measures aimed at encouraging primary prevention, early diagnosis and prompt treatment. The Health Education Authority has endeavoured to promote healthier eating, advocating increased consumption of vegetables and fibre, and a Healthy Schools Programme white paper is imminent.

In an effort to raise public awareness of early symptoms and encourage earlier diagnosis, public information leaflets (eg 'Find out about colon cancer') have been developed. Target standards of care have been set which aim to provide a specialist consultation within two weeks of presentation with alarm symptoms, and risk-stratification of patients will be assisted by recommendations from the Referral Guideline Steering Group. Although the UK does not currently have a national colorectal cancer screening programme, pilot studies of feasibility and acceptability are in progress.

Attempts to improve access and reduce waiting times will require more resources, and some new money (£10 million) has already been specifically allocated to colorectal cancer
services. The ‘Beacons Initiative’ aims to identify eight sites in the UK (1 per region) which provide exceptional examples of service delivery for colorectal cancer. These sites will be allocated extra funding to strengthen their position as specialised regional centres. With these and other measures, the government has set targets for achieving a 25% reduction in all cancer deaths in the under 65 year olds in the next 10 years. Conference delegates welcomed the measures proposed by the Health Minister, though comments both from the Chair and from the audience highlighted the difficulty of achieving improvements in access without consultant expansion in gastroenterology and colorectal surgery.

Screening: the theory

Five-year survival in colorectal cancer is dependent on disease stage at diagnosis, with over 80% surviving with localised tumours (Duke’s stage A), but only 30–70% with evidence of regional spread. Lack of symptoms in early cancer means that by the time most patients are diagnosed their disease is not confined to the bowel wall. Professor Lance told delegates that in the UK only about 10% of colorectal cancers are localised at diagnosis compared to about 30% in the USA. This is reflected in overall five-year survival figures for colorectal cancer (ca 40% in Britain vs 60% in North America). In order to improve these figures, earlier detection of the disease at an asymptomatic stage is desirable.

The practice of searching for and removing adenomatous polyps of the colon is based on the belief that this will prevent cancer. This view was supported by the National Polyp Study in the USA, in which 1,418 subjects underwent colonoscopy and polypectomy with subsequent periodic colonoscopic surveillance for an average of 5.9 years. Compared to a number of reference groups, there was a significant reduction (76–90%) in expected cancers in the screening group.

Screening of patients at particularly high risk of colorectal cancer, such as those with a family history or patients with long-standing pancolitis, is relatively easy to justify. However, the best strategy for screening asymptomatic ‘average risk’ individuals is yet to be defined.

Faecal occult blood test

Faecal occult blood (FOB) testing followed by colonoscopy represents one strategy. In screening studies, positive FOBs are found in 1–16% of individuals, depending on such factors as the age of the person being tested and whether the sample is rehydrated. Reported detection rates for any cancer are 2–17%, and for early (Duke’s A or B) cancers 2–14%. Poor specificity means that the majority (>80%) of asymptomatic average risk individuals undergoing colonoscopic evaluation following a positive FOB screen will not have cancer. Low sensitivity is suggested also because FOB testing was positive in only 26% of recurrent or new cancers in a longitudinal study of 1,217 patients undergoing routine colonic surveillance following curative resection of a colorectal tumour.

Patient acceptability of self-testing by FOB is another limitation. In a randomised controlled trial in general practice in the UK, Hardcastle et al reported that only 36.8% of 10,253 subjects who were invited to complete an FOB test actually did so. Despite these limitations, it has been estimated that FOB testing (followed by colonoscopy) may reduce overall colorectal cancer mortality by about 15–18%, and represents a potential strategy for population screening.

Flexible sigmoidoscopy

An alternative to FOB testing is to undertake screening by flexible sigmoidoscopy, with full colonoscopy for those in whom significant left-sided lesions are detected. Up to 60% of colorectal cancers should be accessible to the fibreoptic sigmoidoscope, and approximately one-third of those with cancer or advanced polyps at a more proximal location will have synchronous marker lesions in the left colon which would prompt full colonoscopic evaluation.

The results of a British multicentre randomised controlled trial of ‘once only’ flexible sigmoidoscopy (the Flexiscope trial) are awaited with interest. In this trial, flexible sigmoidoscopy was offered to subjects aged 55–64 years. In a pilot to this study, up to 61% of invited subjects expressed an interest in screening, of whom three-quarters actually attended. About one in 10 patients had adenomas, seven per 1,000 had cancers (55% Duke’s A), and 6% required colonoscopy.

Screening: the practice

The planning for a national programme of colorectal cancer screening is already under way in the UK. Established rules for the implementation of any screening programme dictate that:

- there should be an established evidence base
- the proposed programme should be reviewed against national screening criteria
- the programme should be sustainable, cost-effective and quality-assurable
- a pilot scheme should be run in the event of any doubt.

It is clear that the present choice lies between FOB testing and flexible sigmoidoscopy. In the case of FOB testing, the test is simple and relatively cheap, while major randomised trials in the USA, UK and Denmark suggest a mortality benefit. The ongoing UK trial of flexible sigmoidoscopy is also likely to show benefit, possibly at greater cost.

A screening strategy based on biennial FOB testing for 50–69 year olds has therefore been considered, a programme which would include around 20% of the UK population. Although FOB tests are relatively cheap (ca £1) and simple to perform, the reading of the tests cannot be
automated at present and is therefore both labour intensive and boring. Present figures for the UK suggest that 10 million people would be eligible for testing so, with biennial testing, about five million people would be invited each year. Assuming a 60% uptake and a 2% recall rate (positive test), about 60,000 subjects would be screened per year with perhaps 6,000 colorectal cancers detected.

Estimated costs have been put at £42 million nationally (including computerised mailing system, radiological and colonoscopic services) which is comparable to the present cost of the national screening programme for breast cancer (£35 million). Such estimates do not include any incentive payment for primary care, actual treatment of screen-detected cancers, follow-up of patients with adenomas, incurred legal costs or initial setting up and training costs.

Quality assurance

Quality assurance (QA) is a major concern in any national screening programme. Measures to ensure adequate QA would include:

- the setting up of regional QA reference centres
- a QA scheme for FOB slides to ensure accurate testing
- regular audit of colonoscopy and barium radiology
- multidisciplinary meetings
- setting up of regional and national specialist groups
- audit of office (administrative) processes and fail-safe procedures
- audit of any interval cancers diagnosed in screened patients
- performance monitoring by the Department of Health.

Two pilot sites in the UK have already been identified (in Coventry and Dundee) taking in a target population of some two million people. These sites will work to an agreed specification ('workbook'); evaluation criteria will be established, such as the definition of routine statistics and quality standards, as well as assessments of impact on primary care and 'symptomatic' patient services.

Surgery

Surgical resection represents the only curative treatment for colorectal cancer, with five-year survival critically dependent on tumour stage. Variable outcomes of surgery between different centres have raised questions as to whether surgery for colorectal cancer should be undertaken only by those with a particular interest in colorectal surgery/oncology. Supporting this view, McArdle and Hole reported rates of postoperative complications, mortality and long-term survival for patients undergoing resection for colorectal cancer at Glasgow Royal Infirmary from 1974-1979. The results for 13 'general' surgeons showed that postoperative mortality varied from 0-20%, local recurrence from 0-21%, anastomotic leak rate 0-25% and 10-year survival for those undergoing apparent curative resection 20-63%. In addition to the human costs of unfavourable outcomes, the direct medical costs of a complication following, for example, anterior resection can be 15-fold higher than successful uncomplicated surgery.

However, a comparison among surgeons of outcomes after colorectal resection is difficult as crude morbidity/mortality rates may be misleading, failing to consider variation in case mix and comorbidity. Sagar et al applied a scoring system which considers a variety of clinical patient variables to allow a risk-adjusted analysis of outcomes between five surgeons. Despite apparent sharp variation in crude outcomes between different surgeons, this variability was largely predictable by patient physiological and operative risk factors, and risk-adjusted surgical performance was remarkably comparable between surgeons.

Advances in surgical techniques have allowed significant improvements in outcomes in recent years. Even in patients requiring radical resection for locally advanced rectal cancer, three-year disease-free survival now approaches 30%. In the UK, an estimated 1,000-1,500 patients per year have potentially resectable metastatic spread confined to the liver. Radical excision of hepatic colorectal metastases prolongs survival time by a median of one year.

Chemotherapy

The proper role for postoperative adjuvant chemotherapy in colorectal cancer remains contentious. In an early randomised placebo-controlled trial which involved 1,296 patients with resected colon cancer that was either locally invasive (stage B2) or had regional nodal involvement (stage C), the combination of fluorouracil (5-FU) and levamisole reduced the risk of cancer recurrence and death in patients with stage C disease by 41% and 33%, respectively, over a median of three years. However, the role of therapy in Duke's stage B was questioned. Recent analysis of the combined results of four trials which included both Duke's B and C stage disease suggested a genuine benefit in stage B, of the order of 30% mortality reduction. In contrast, although the combination of 5-FU and high-dose folinic acid was previously shown to be of overall benefit in resected stage B and C disease, more recent evidence suggests no particular benefit in stage B2 disease. Interest now focuses on identifying biological markers (eg loss of heterozygosity for p53 or APC) in Duke's B disease which may identify a subgroup at higher risk for recurrent disease meriting adjuvant treatment. At the present time, adjuvant chemotherapy in Duke's B disease appears not to be justified in the absence of serosal involvement, poor differentiation or extramural vascular invasion.

Whilst the benefits of 5-FU in advanced disease seem to be established, the optimum treatment regimen remains to be determined. Efforts to improve on the therapeutic index have included altered administration schedules and the addition of biochemical modulators.

Other promising strategies in resected colon cancer include intraperitoneal anti-cancer drug administration.
This offers the prospect of counteracting both microscopic residual disease on peritoneal surfaces and occult liver metastases by achieving high intraportal drug concentrations. Immunocytochemical detection of isolated tumour cells in the peritoneal cavity may have prognostic significance. In a randomised study of adjuvant treatment in resected stage III or high-risk stage II (T4N0MO) colon cancer, the combination of intravenous and intraperitoneal leucovorin and 5-FU produced a 43% mortality reduction at four years in stage III disease compared to 'standard' therapy with 5-FU and levamisole.

Newer agents are also being evaluated in advanced colorectal cancer. The platinum derivative oxaliplatin (trans-1,2-diaminocyclohexane oxaloplatinum) is active and well tolerated, both as monotherapy and in combination with 5-FU/folinic acid as first- or second-line treatment of patients with metastatic colorectal cancer. Irinotecan ('Campto'), a topoisomerase I inhibitor, is another agent showing early promise as a second-line agent in cases of disease progression following initial 5-FU therapy.

**Aspirin and COX-2**

Epidemiological studies have indicated that regular consumption of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) may lower the risk of the development of colon adenomas and carcinomas and reduce mortality from colon cancer.²

Prostaglandins are important mediators of normal physiological processes in the gastrointestinal tract. The cyclooxygenase enzymes (COX) have a central role in the biosynthetic pathway of prostaglandins and are inhibited by NSAIDs. Cyclooxygenases exist in two isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in the gastrointestinal tract, and is thought to be involved in cytoprotection and mucosal integrity. COX-2 is an inducible cyclooxygenase which is absent in normal intestinal mucosa. COX-2 expression is enhanced by pro-inflammatory peptide mediators (cytokines), inhibited by corticosteroids, and (unlike COX-1) over-expressed in about 85% of colorectal cancers. This has stimulated interest in a role for the newer COX-2 selective inhibitors (e.g. meloxicam) as tools in research into colorectal carcinogenesis and as potential chemopreventive agents.

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**Clinical research funding: a priority for the Medical Research Council**

*Conference rapporteur: Richard Holt*

This conference was held on 3 November 1999 at the Royal College of Physicians. Delegates attending the Postgraduate Medical Centre at the Freeman Hospital in Newcastle upon Tyne were able to participate with the aid of live video- and audio-links.

Clinical research has undergone radical changes over the last decade. There has been a shift in the focus of research such that there is no longer a place for a full time clinician dabbling in research. To produce internationally renowned research, resources need to be concentrated in areas of academic strengths. Medical science has moved away from the bedside and into the laboratory where powerful molecular techniques have provided new understandings of human diseases. The changes in training patterns brought about by Calman have resulted in a paucity of new medically qualified researchers who are willing to take on the mantle of academic medicine. The future for the entrepreneurial clinician with a brilliant idea but who works outside a centre of excellence, is problematic. Despite the fall in the numbers of medical graduates wishing to take up a career in academia, those who do so face the prospect of...