Q J Med 2000; **93**:131–134

Editorial

QJM

Colorectal cancer: still a major killer despite progress on many fronts

Progress was all right. Only it went on too long James Thurber

Colorectal cancer is the second leading cause of cancer-related death in much of the developed world. Cumulative lifetime risk of developing large-bowel cancer is estimated at 6%, of whom half will die of the disease despite optimal therapy.[1] In contrast to many other commonly occurring cancers, where there has been little impact on prevalence and survival, spectacular advances in the understanding of large-bowel cancer have been achieved. Such is the level of optimism that one might predict eradication of colorectal cancer as a realistic public health objective within the present century. Grounds for this include improvements in primary and secondary prevention, effective screening, endoscopic accessibility for diagnosis and elimination of premalignant lesions, feasibility of radical excision with minimal disruption to physiology and sphincters, and more effective adjuvant therapies. Advances in understanding the molecular genetics of colorectal cancer have already been translated to clinical utility in screening and prevention, and have future implications for prognostication and therapy.

Colorectal carcinogenesis is a multi-step process, arising from a progressive accumulation of genetic abnormalities that underlie its progression along an adenoma–dysplasia–carcinoma–metastases sequence.[2] The time sequence of these events provides an opportunity to screen for and resect premalignant lesions. When targeting at risk groups, nothing takes precedence over an accurate family history and pedigree distribution for all malignancies. Approximately one quarter of colorectal cancers occur in young individuals with a family history of the disease. Familial adenomatous polyposis (FAP) is an autosomal dominant disorder, caused by a germline mutation of the tumour suppressor APC gene on chromosome 5q21. This accounts for 1% of colorectal cancers and is the prototype for prophylactic cancer surgery.[3] Hereditary nonpolyposis colorectal cancer (HNPCC) is responsible for about 3% of colorectal cancers, and is due to a germ-line mutation in one of a growing list of DNA mismatch repair (MMR) genes.[4] Extracolonic cancers in individuals with mutations of MMR genes occur at higher than expected rates, may be predominant in the pedigree, and underscore the importance of vigilance and accuracy in obtaining a family history. These two syndromes are now amenable to genetic diagnosis and screening, and there is a high expectation that a genetic basis for many of the remaining cases of familial colorectal cancer will be defined.

There is persuasive evidence for the effectiveness of screening and surveillance in early detection of colorectal polyps and cancer.[1] Endoscopic resection of adenomatous polyps reduces risk of cancer, and detection of early-stage cancers is associated with significantly improved 5-year survival in the range of 80–90%.[5] Population-based studies have shown reductions in colorectal cancer mortality by screening for either faecal occult blood or with sigmoidoscopy.[1,6,7] Although the cost-effectiveness of screening colonoscopy in the average-risk population has not been formally demonstrated, there is indirect evidence for its efficacy, and it has the advantage of resection of premalignant lesions from all parts of the colon. Furthermore, the value of a negative colonoscopy exceeds that of other tests and may permit wider screening intervals. Double-contrast barium enema and virtual colonoscopy are potential alternatives in the same risk population, but their role remains to be determined.[8] Choice of screening modality and surveillance interval depends on the degree and nature of risk within the population. Current recommendations for average-risk individuals indicate that screening commence at 50 years of age; patients with a negative colonoscopy do not warrant further surveillance for at least 5 years.[1,6,7] For the high-risk individual, colonoscopy is the preferred surveillance

examination. High risk includes a history of colorectal adenomas, family history of colorectal cancer or adenoma, history of inflammatory bowel disease, personal history of colorectal cancer and hereditary colorectal cancer syndromes. For individuals with a history of colonic adenomas or cancer, surveillance intervals can be extended beyond 3 years once the colon is confidently deemed to be clear of lesions. Surveillance of patients with ulcerative colitis is controversial, but most clinicians favour annual colonoscopy with multiple biopsies in patients with pancolitis of at least 7–10 years duration.[9] For syndromic colorectal cancer, genetic screening, where available, can identify family members for whom intensive surveillance is indicated.[3] Colonoscopic screening in FAP should commence in the second decade of life, and once the diagnosis is confirmed, proctocolectomy should be performed. For other familial syndromes such as Peutz-Jeghers and Familial Juvenile Polyposis syndrome, there is an increased risk of colon cancer, small bowel and foregut malignancies, and endoscopic surveillance of upper and lower bowel is recommended at 3–5 year intervals. Patients with HNPCC should undergo colonoscopy at 1–2 year intervals starting at age 20. In addition, special screening for extracolonic malignancies is recommended.[1]

Since a Western diet and other lifestyle factors have been implicated in the aetiology of colorectal cancer, it seems obvious that adjustments to these might form the basis of an effective preventive strategy.[10] Excess caloric intake, obesity, and a high-fat, high-red-meat, low-vegetable diet are associated with enhanced risk of colorectal carcinogenesis. Unfortunately, community policies of education on healthy lifestyles are difficult to establish and monitor, and impact and compliance are difficult to confirm objectively. They are also confounded by cultural and economic pressures.

A more exciting strategy has emerged with the discovery that cyclo-oxygenase (COX) enzyme activity is linked to colorectal carcinogenesis. Evidence that COX inhibition by non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the incidence of colonic cancer by 40–50% has prompted vigorous research into pharmacological chemopreventive strategies.[11,12] An early indicator of the effectiveness of NSAIDs was the demonstration that they could reduce both the size and number of polyps in patients with FAP, and in experimental models of carcinogenesis.[13] The development of selective inhibitors of the inducible isoform, COX-2, has been particularly exciting because they have fewer side-effects than traditional NSAIDs and are, therefore, potentially more suitable for large-scale trials of primary prevention in average-risk populations. Mechanisms for the anti-cancer effect of NSAIDs include altered cell proliferation, increased frequency of apoptosis, reduced invasiveness and angiogenic potential.[11] Even more exciting is the recognition that NSAIDs may have an anti-tumourigenic effect by mechanisms other than COX inhibition. This has led to pursuit of alternative molecular targets for chemoprevention. Peroxisome proliferator-activated receptor δ (PPARδ) belongs to the nuclear receptor superfamily, which includes steroid hormones, thyroid hormone and retinoids, and functions as a ligand-dependent transcription activator. An important finding is that both NSAIDs and the gene product of APC downregulate the transcriptional activity of PPARδ, and this common link may underlie the tumour supprssor effects of APC and NSAIDs.[14] The intriguing possibility arises that chemopreventive drugs may be designed to target specific genetic alterations that underlie tumour development.

The principal modality of treatment remains radical surgical excision of the tumour with a generous margin of surrounding bowel and attached mesentery.[15] Where relevant, en-bloc excision of attached viscera or abdominal wall should be performed; this provides a global 5-year survival of over 60%, in contrast to approximately 15% where tumour lines are violated, or macroscopic disease is left at surgery.[16] In rectal cancer, recognition that tumours do not spread distally has allowed preservation of the distal rectum to within 2 cm of the cancer and sphincter conservation, without compromise of cancer cure. Mesorectum must be totally excised en-bloc with the tumour to guarantee lateral clearance of tumour margins and excision of lymph node metastases in the distal mesentery.[17] Because the lymphatic drainage of the distal rectum has both lateral and axial flow routes, some surgeons advocate an extended lateral pelvic lymphadenectomy. This technique has not been subjected to randomized trial, and the added morbidity of bladder dysfunction and impotence currently precludes its routine use without confirmation of therapeutic advantage for local control and survival. Stapling techniques permit restoration of colorectal continuity in all except those where the sphincter complex is involved and, as a result, abdominoperineal resection of rectum and permanent colostomy is seldom required.[15] Laparoscopic techniques have been developed to a level where comparable radical surgery may be performed without the need for a major abdominal wall incision. Nevertheless, this technique has not found widespread application, due to its demanding technical nature, fears of increased incidence of port site incisional recurrence, and failure to demonstrate advantage in patient recovery. Local transanal microsurgery may be adequate for small distal rectal tumours selected by endorectal ultrasound.

Local recurrence of rectal cancer is a major cause of therapeutic failure, but controversy surrounds its prevention.[15,18] While there are variables in surgical technique that influence this, it is humbling to note

that recurrence rates published in the context of controlled trials have been in the range of 30%, despite optimal surgery, suggesting intrinsic tumour variables such as increased invasiveness and metastatic potential. From controlled studies, there is now a consensus emerging for the use of neoadjuvant radiotherapy, and concomitant systemic chemotherapy may further improve local control and survival.[18] However, improvement in local control has not always been accompanied by improved survival, emphasizing that many of these patients have disseminated tumours *ab initio* and require systemic therapy. Post-operative radiotherapy is less effective than neoadjuvant radiotherapy in preventing local recurrence, and is reserved for those patients with positive tumour margins or for symptom control.

The efficacy of adjuvant chemotherapy in colorectal cancer has been well established in the past decade.[19–21] Relapse rates can be reduced by 40% and mortality by one third with fluorouracil and levamisole, or fluorouracil and folinic acid in patients with node-positive (Dukes' stage C) disease. Whether adjuvant chemotherapy has a role in patients with earlier stage disease (Dukes' B) is less certain. Because of associated toxicity, albeit generally mild, selection of such patients for chemotherapy on the basis of evidence for residual disease following surgical resection of the primary tumour, would be desirable. Genotypic and phenotypic features of the primary tumour are of some predictive value, and serum levels of tumour markers have been used to reflect residual disease, but lack sufficient sensitivity and specificity. Therefore, molecular, immunochemical, and other methods have been used recently to identify micrometastatic residual disease within lymph nodes and bone marrow.[22,23] Direct demonstration of disseminated residual disease by these techniques supports the view that cancer should be managed as a systemic disease. Clearance of disseminated micrometastases by monoclonal antibody adjuvant therapy in patients with resected Dukes' C colorectal cancer has been associated with prolonged survival.[24] The value of this approach for Dukes' B disease remains to be demonstrated, although it is sobering to note that bone-marrow micrometastases have been detected in up to a quarter of these patients.[23]

What of the future? Unravelling the molecular pathogenesis of colorectal cancer offers opportunities for improvements in genetic testing, targeted intervention including gene therapy, chemotherapy, immunotherapy and patient selection for different therapeutic strategies based on tumour genotype-phenotype correlations. The current pace of discovery in the molecular basis of colorectal carcinogenesis suggests that prospects for eradication of this Western world scourge are unlikely to be constrained by science. Rather, the challenge will be the integration of molecular medicine, epidemiology and public health policy. A comprehensive policy for colorectal cancer will include screening programmes that incorporate advances in molecular genetic testing, coupled with primary and secondary chemoprevention strategies and public health education. This will require consensus in difficult areas that include ethical concerns, logistical dilemmas, fiscal constraints, and ultimately political will. Therein lie the real limits to rapid progress.

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