Preventing bowel cancer: an insight for clinicians

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Abstract: Worldwide, colorectal cancer causes 610,000 deaths annually with 38,000 new cases diagnosed in the UK and 16,000 deaths each year. The prognosis is directly related to the staging of the cancer at diagnosis, with an overall 5-year survival rate of approximately 50%. However, for localized disease the figure is much higher at 90%, although unfortunately many cancers present at an advanced stage. Importantly, there is the potential to reduce the incidence because most tumours arise from premalignant adenomatous polyps, which if detected and removed interrupts the adenoma–adenocarcinoma sequence. In addition, identifying colorectal cancer at an early stage can impact on the mortality rates for this neoplasm. The current screening options for bowel cancer include analysis of stool for occult blood and endoscopic assessments of the colorectum, including flexible sigmoidoscopy and full colonoscopy. The aim of this review is to present information on the natural history of colorectal cancer, the evaluation of the different screening modalities and the current faecal occult blood screening program within the UK National Health Service, and to discuss how dietary factors and aspirin may affect aetiology.

Keywords: colorectal cancer, prevention

Introduction

Worldwide, colorectal cancer causes 610,000 deaths annually [World Health Organization, 2010] with 38,000 new cases diagnosed in the UK and 16,000 deaths each year [Cancer Research UK, 2008]. The prognosis is directly related to the staging of the cancer at diagnosis, with an overall 5-year survival rate of approximately 50%. However, for localized disease the figure is much higher at 90%, although unfortunately many cancers present at an advanced stage. Importantly, there is the potential to reduce the incidence because most tumours arise from premalignant adenomatous polyps, which if detected and removed interrupts the adenoma–adenocarcinoma sequence. In addition, identifying colorectal cancer at an early stage can impact on the mortality rates for this neoplasm. The current screening options for bowel cancer include analysis of stool for occult blood and endoscopic assessments of the colorectum, including flexible sigmoidoscopy and full colonoscopy. The aim of this review is to present information on the natural history of colorectal cancer, the evaluation of the different screening modalities and the current faecal occult blood

screening program within the UK National Health Service, and to discuss how dietary factors and aspirin may affect aetiology.

The adenoma–adenocarcinoma sequence

There is consistent evidence that colorectal cancer arises from initially benign adenomatous polyps, which progress histologically through an adenoma–adenocarcinoma sequence. Detecting and removing adenomas will interrupt this sequence and may actually reduce the development and incidence of colorectal cancer. The data supporting this progression come from histological, radiological and genetic studies, and more recently trial data of polypectomy. Polyps, which look endoscopically benign, may indeed contain carcinoma cells and it is reasonable to assume that malignant spread can subsequently occur. In 2500 polyps reported from St Mark's Hospital, London [Muto and Morson, 1975; Morson, 1974], the frequency with which malignant tissue was present in the adenoma depended on the polyp size, histology and degree of dysplasia. Only 1% of polyps less than 1 cm in diameter contained malignant cells, but this increased to 46% in those greater than 2 cm.

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Polyps containing villous adenomatous tissue and severe dysplasia were more likely to contain malignancy. The American National Polyp Study analysed polyp characteristics in patients referred for colonoscopy [Winawer *et al.* 1993, 1992; O'Brien *et al.* 1990]. In total, 2362 patients had 5066 polyps, 66.5% of which were adenomas, 11.2% hyperplastic and the rest were classified as 'other', such as juvenile polyps. Of the adenomas removed, 86% showed mild dysplasia, 7.7% moderate dysplasia and 6.2% either severe dysplasia or carcinoma *in situ*. The number of adenomas containing malignant tissue increased with size and the presence of villous histology. The adenoma–adenocarcinoma sequence is also supported by genetic studies demonstrating *in vitro* transformation of benign cell lines to malignant cells [Manning *et al.* 1991; Williams *et al.* 1990], which can occur when exogenous carcinogens such as nitrosoguanidines are applied [Williams *et al.* 1990]. Radiological data reported that 8% of polyps left *in situ* (because of medical contraindications to polypectomy) became malignant over 10 years and 24% of adenomas became malignant at 20 years [Stryker *et al.* 1987]. Finally, and most importantly, there is now evidence from randomized controlled trials that endoscopic polypectomy reduces cancer incidence [Atkin *et al.* 2010; Hoff *et al.* 2009]. Therefore, for a screening programme to impact on actually lowering the incidence of cancer, compared with reducing mortality by detecting cancers at an early stage, the screening test must have a high sensitivity for colorectal adenomas. The two screening modalities most thoroughly investigated are faecal occult blood testing and flexible sigmoidoscopy, both forms of secondary prevention, which aim to detect precancerous lesions or tumours at an early stage of development.

Faecal occult blood testing

The current colorectal cancer screening program in the UK uses faecal occult blood tests (FOBTs), the principle of which is to detect small and hidden amounts of blood from asymptomatic cancers. Patients with positive tests are invited to undergo a colonoscopy with the aim of detecting cancers and polyps. Hypothetically, these tumours are at an earlier stage of development than by the time they have become more advanced and symptomatic. The detection of early lesions should lead to improved survival following treatment. FOBTs were developed by Gregor in 1967 and consist of

guaiac-impregnated cardboard slides on which small samples of stool are smeared [Gregor, 1971]. Hydrogen peroxide developer solution is added to the stool samples and if blood is present a blue colour appears. Hydrogen peroxide activates pseudo-peroxidase in haem and converts the phenol guaiaconic acid in the slide to a quinone, guaiacum blue. As cancers bleed intermittently, slides are completed over 3 days, which leads to a detection rate of colorectal cancers of up to 82%. More frequent testing would lead to further cancer diagnosis but at the expense of reducing compliance. FOBTs have a low sensitivity for colorectal adenomas, most of which go undetected. Consequently the impact of FOBTs on reducing incidence through adenoma detection and removal will be much less than that on mortality through early cancer identification.

The efficacy of FOBTs every 2 years has been well established in three randomized controlled clinical trials of screening, with mortality from colorectal cancer being reduced by 15% [relative risk (RR) 0.85, 95% confidence interval (CI) 0.78 to 0.92] [Hewitson *et al.* 2008]. When adjusted for screening attendance there was a 25% reduction (RR 0.75, 95% CI 0.66 to 0.84), although there was no difference in all-cause mortality (RR 1.00, 95% CI 0.99 to 1.02). The largest trial was conducted in Nottingham in the UK, where 152,850 men and women aged 45–74 years were randomized to the screening or control arms of the study [Hardcastle *et al.* 1996]. The compliance was 54%, the positive test rate 2.1%, with a favourable staging of the cancers detected in those completing FOBTs. In the screened group, there were four times as many cancers classified as Dukes' A (52% *versus* 13%, $p < 0.001$) and less Dukes' D (5% *versus* 22%, $p < 0.001$). Similar favourable cancer staging was reported in comparable studies from Sweden [Kewenter *et al.* 1994] and Denmark [Kronborg *et al.* 1996]. In a further study, the US Minnesota trial, 46,551 participants aged 50–80 years were randomly allocated to screening with FOBTs every year, screening once every 2 years or the control arm [Mandel *et al.* 1993]. Most slides were rehydrated, which resulted in a high positive rate of 9.8%, whereas the figure without rehydration, as in the other trials, was expected to be much less at about 2%. The 13-year cumulative mortality from colorectal cancer was statistically significantly lower in the annually screened group compared with the control group (5.88/1000 *versus*

8.83/1000), but not in those tested every 2 years (8.33/1000). The high positive FOBT rate resulted in 38% of those in the annually screened group having at least one colonoscopy during the trial period. Part of the improved mortality benefit may therefore be due to colonoscopy, rather than FOBTs, with the former detecting non-bleeding cancers and a beneficial effect of polyp removal.

The consistency of the trial results for the benefit of FOBTs prompted several countries to introduce a screening programme using this modality of early detection [Benson *et al.* 2008]. In the UK, the Department of Health commissioned successful pilot screening rounds for men and women aged 50–69 years in Coventry and Warwickshire in England and in Tayside, Grampian and Fife in Scotland. Currently, the NHS Bowel Cancer Screening Programme (NHS BCSP) comprises five programme hubs and approximately 100 local screening centres, each serving populations of between 500,000 and 2 million people. The programme hubs perform the mailing and analysis of FOBTs and arrange nurse-led clinic appointments to explain the significance and follow up to people with positive test results. At the appointment, the nurse explains the nature of a colonoscopy, inherent risks and an assessment of the person's health and fitness for endoscopy.

The development of the national FOBT screening programme, together with advances in endoscopic techniques, has led to advances in the endoscopic management of patients in whom adenomas are detected, particularly large sessile lesions. Previously, these adenomas were managed surgically because the risk of perforation following endoscopic excision of broad-based lesions was relatively high. However, screening endoscopists are now becoming skilled in excising such lesions, including those in the right colon, where the wall is thinner than the wall on the left. Removal of such lesions by screening accredited colonoscopists involves saline or other solutions being injected under the base of the lesion to elevate it, followed by whole or piecemeal snaring of the adenoma with a hot snare wire (endoscopic mucosal resection). The technique of endoscopic submucosal dissection again involves raising the base of the polyp and using a heated knife to dissect and remove the lesion under endoscopic vision. Retrieval of the tissue is essential to determine the precise histology,

exclude malignancy and to ensure excision is complete.

In summary, the trials have demonstrated the efficacy of FOBTs in reducing mortality from colorectal cancer. However, the relatively low sensitivity of FOBTs for adenomas and hence the potential low impact on future cancer incidence has led to the evaluation of other modalities such as flexible sigmoidoscopy, which has a greater sensitivity for polyps.

Preventing bowel cancer by flexible sigmoidoscopy

Flexible sigmoidoscopy is an endoscopic procedure, taking between 10 and 15 min to perform, and examines the left side of the colorectum to the splenic flexure. The investigation has the potential, first, to reduce the incidence of cancer by polyp detection and removal, and second, to decrease cancer mortality by diagnosing asymptomatic colorectal cancers at an early stage. Importantly, approximately two-thirds of polyps and cancers occur in the left colon [Shinya and Wolf, 1979] within reach of the sigmoidoscope [Gillespie *et al.* 1979; Snyder *et al.* 1977]. People with distal adenomas displaying histological and morphological features with a high risk of becoming malignant are advised to undergo colonoscopy because such lesions are predictive of proximal cancer [Atkin *et al.* 1992]. People are at high risk when they have lesions that are at least 1 cm in size, they have three or more lesions or they have lesions with severe dysplasia or villous histology. People with a normal distal colon, or with adenomas of low malignant potential, are less likely to have proximal pathology and can be discharged. An advantage of flexible sigmoidoscopy is that it only needs to be performed once to identify people with polyps, rather than repeat testing with FOBTs to detect evolving cancers. At the initial flexible sigmoidoscopy, small polyps (<1 cm) may be removed if the bowel is clean and the views are good, although larger lesions require full oral bowel preparation. Such a requirement for a single test may enhance compliance rather than if there was the need for repeat endoscopy. As the peak polyp incidence occurs around the age of 60 years, trials have assessed endoscopic screening 5 years below and above this age.

The efficacy of screening is being assessed in four randomized controlled trials [Atkin *et al.* 2010; Hoff *et al.* 2009; Weissfeld *et al.* 2005; Segnan

et al. 2002], two of which have reported their results [Atkin *et al.* 2010; Hoff *et al.* 2009] and the other two will shortly [Weissfeld *et al.* 2005; Segnan *et al.* 2002]. The largest trial was from the UK and involved approximately 170,000 participants aged 55–64 years. A total of 40,674 people underwent screening with flexible sigmoidoscopy (71% of those expressing an interest and invited to attend) with a median follow up of 11.2 years [interquartile range (IQR) 10.7 to 11.9] [Atkin *et al.* 2010]. In the intervention group, the incidence of colorectal cancer was reduced by 33% [hazard ratio (HR) 0.67, 95% CI 0.60 to 0.76], mortality from colorectal cancer decreased by 43% (HR 0.57, 95% CI 0.45 to 0.72) and the incidence of distal colorectal cancer reduced by 50% (HR 0.50, 95% CI 0.42 to 0.59). There was no impact on the incidence of proximal cancers (HR 0.98, 95% CI 0.85 to 1.12) and there was a 3% reduction in all-cause mortality (HR 0.97, 95% CI 0.94 to 1.00, $p=0.0519$). The number needed to be screened to prevent one colorectal cancer diagnosis was 191 (95% CI 145 to 277). The Norwegian Colorectal Cancer Prevention Screening Study (NORCCAP) trial [Hoff *et al.* 2009], a study of 13,823 men and women aged 55–64 years, offered once-only flexible sigmoidoscopy, with or without one FOBT, and compared outcomes with 41,913 controls. No difference was found in the 7-year cumulative incidence of colorectal cancer between the whole screening group (attenders and nonattenders) and controls (134.5 *versus* 131.9 cases/100,000 person years), but the cohort continues to be monitored. For participants who actually attended, compared with controls, there was a statistically significant reduction in mortality for both total colorectal cancer (HR 0.41, 95% CI 0.21 to 0.82, $p=0.011$) and rectosigmoid cancer (HR 0.24, 95% CI 0.08 to 0.76, $p=0.016$). The investigators will in the future report cancer incidence at 10 and 15 years after recruitment, when the benefits of polypectomy may become apparent. Two other similar trials will report soon, namely The Italian Multicentre Randomized Controlled Trial of “Once-Only Sigmoidoscopy” (SCORE) trial [Segnan *et al.* 2002], based on the UK protocol, and the US Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO) study [Weissfeld *et al.* 2005], assessing screening every 3–5 years between the ages of 55 and 74 years. The emerging evidence showed a benefit of flexible

sigmoidoscopy for preventing bowel cancer and led to the initiation of pilot schemes in the UK in 2010 for a potential national screening programme of this screening modality.

Future developments

Newer screening methods are being developed, including faecal immunochemical testing and computed tomographic (CT) colonography, although neither of these has been assessed in randomized controlled clinical trials. The faecal immunochemical tests use an antibody to detect haemoglobin present in occult stool blood and they have a higher sensitivity for colorectal cancer than standard guaiac tests (37% *versus* 69%) [Allison *et al.* 1996]. Faecal DNA screening studies involve testing stool for multiple mutations in the *K-ras*, *APC* and *p53* genes, plus markers for microsatellite instability. A single faecal DNA test was more sensitive for adenocarcinoma (51%, 95% CI 35% to 68%) than a standard guaiac test (13%, 95% CI 5% to 29%) [Imperiale *et al.* 2004], although both had a low sensitivity for advanced cancers. CT colonography is a rapidly developing technique that is less invasive than conventional colonoscopy, in which a CT scanner produces two and three-dimensional images of the entire colon and rectum. Bowel preparation is required and the colon is distended by insufflations with air or carbon dioxide, via a rectal tube. Antispasmodic agents and contrast agents may be administered intravenously before the scan and the subsequent images are interpreted by a radiologist. For CT colonography, two larger studies [Johnson *et al.* 2008; Pickhardt *et al.* 2003] reported this was comparable to colonoscopy for detecting adenomas of at least 10 mm, but not for those smaller than 6 mm. One of seven colorectal cancers was missed on CT colonography in one study [Johnson *et al.* 2008], whereas in the other investigation both cancers were detected [Pickhardt *et al.* 2003]. The disadvantages of this radiological modality are that it is purely diagnostic not therapeutic, and removal of any polyps requires a colonoscopy. Furthermore, there is uncertainty about the radiation risk and the implications of finding extracolonic lesions.

There are two areas which will be relevant to the future success of screening programmes. The clinical skill of endoscopists to detect pathology at both initial sigmoidoscopies and any subsequent colonoscopies is important. The obvious factors which determine detection rates for

adenomas and cancers include the skill of endoscopists and the quality of bowel preparation. Even for experienced colonoscopists, pathology detection rates differ and small polyps can be easily missed. In a US study, two consecutive same-day colonoscopies on the same patients were performed in 183 people by practitioners who had previously done at least 500 colonoscopies. Patients were randomized to undergo the second procedure with the same or a different colonoscopist [Rex *et al.* 1997a]. The overall rate for missed adenomas was 24%, which varied according to the size of the adenoma. The miss rate for adenomas up to 5 mm was 27%, for adenomas 6–9 mm it was 13% and for adenomas at least 1 cm it was 6%. Right-sided adenomas were missed more than distal ones, although the difference was not statistically significant (27% *versus* 21%). Furthermore, cancers may also be undetected, as a retrospective survey reported that 3% of patients with colorectal cancer had undergone a diagnostic colonoscopy in the previous 3 years [Rex *et al.* 1997b]. A second issue which may be relevant to screening programmes of flexible sigmoidoscopy is the potential ‘proximal shift’ of colorectal cancers reported from certain regions. For example, between 1970 and 2000, the data from the US Department of Veterans Affairs, which reports hospitalizations associated with colorectal cancer from 172 hospitals throughout the country, reported a 16% increase in the proportion of proximal lesions in white men and women and a 22% increase in black men [Cucino *et al.* 2002]. Similarly, for the time period 1973–1997, data from the US Surveillance, Epidemiology, and End Result Programme, which covers approximately 10% of the US population, documented a 6% rise in the proportion of proximal cancers amongst whites and blacks of both genders [Cucino *et al.* 2002]. If these trends continue and are consistent in other countries, then this will decrease the efficacy of flexible sigmoidoscopy.

Prevention of cancer in high-risk groups

Certain people are at a higher risk of developing colorectal cancer than the general population and can be offered regular colonoscopic screening. These people are predominantly those with a family history of bowel cancer, but also those with inflammatory bowel disease, acromegaly or post-ureterosigmoidostomy. The minority of patients with a family history of bowel cancer will have genetic conditions, including familial

adenomatous polyposis, hereditary nonpolyposis colorectal cancer, Peutz-Jegher’s syndrome and juvenile polyposis. Bowel cancer developing in these genetic syndromes probably only accounts for about 2–3% of all colorectal cancers. In people with a family history of bowel cancer, without an obvious genetic condition, the British Society of Gastroenterology and the Association of Coloproctology of Great Britain and Ireland recommends a pragmatic approach to screening those with a ‘high to moderate risk’ by colonoscopy between the ages of 50 and 75 years [British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland, 2010]. This category comprises people with three or more affected first-degree relatives (none younger than 50 years, otherwise they fulfil high-risk criteria); two affected first-degree relatives younger than 60 years, or two affected first-degree relatives with a mean age at diagnosis less than 60 years. If polyps are identified, then patients are offered specific surveillance according to the characteristics of the adenomas.

Patients with inflammatory bowel disease, either ulcerative colitis or Crohn’s colitis, have an increased risk of colorectal cancer [Eaden, 2004; Eaden *et al.* 2001]. For all these patients, an index screening colonoscopy is recommended approximately 10 years after the onset of symptoms to reassess disease extent [Mowat *et al.* 2011]. This colonoscopy, performed when the patient is in remission, identifies mucosa which may be dysplastic, a risk factor for future cancer. Previously, biopsies were taken throughout the whole of the colon, but now pancolonic dye spraying allows target biopsies of abnormal areas, likely to be dysplastic. The index colonoscopy allows the identification of patients with extensive colonic disease, that is, ulcerative colitis extending proximal to the splenic flexure or Crohn’s colitis affecting at least 50% of the surface area of the large bowel. These patients are then classed into three groups: lower, intermediate or higher risk for colorectal cancer, and have further colonoscopies at 5 years, 3 years or yearly intervals respectively. The higher-risk group comprises patients with moderate or severe disease activity on the previous examination, those with a stricture or dysplasia who have declined surgery within the previous 5 years, those with primary sclerosing cholangitis, and those with a family history of colorectal cancer in a first-degree relative younger than 50 years. In patients with acromegaly, better treatment of the disease

and its complications means patients are now surviving to develop malignancies. Patients with acromegaly have an increased prevalence of both colorectal adenomas and cancer [Jenkins, 2001] and should be offered colonoscopic screening starting at 40 years and repeat testing depending on the baseline findings and activity of the underlying condition [British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland, 2010]. Finally, following ureterosigmoidostomy, cancer occurs in about a quarter of patients at 20 years of follow up and they should be offered annual flexible sigmoidoscopy [British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland, 2010].

Primary prevention of colorectal cancer

Primary prevention encourages the population to adopt lifestyle measures which inhibit the development of cancer. The aetiology of colorectal cancer is uncertain, but dietary factors and aspirin may be involved. To investigate diet, randomized controlled trials of sustainable interventions would be the preferred methodology, but such an approach is often pragmatically difficult or has ethical problems. Therefore, observational epidemiological studies are required, namely retrospective case-control or prospective cohort investigations. The latter have many advantages in nutritional epidemiological work because this design eliminates both recall and selection biases, which are inherent in case-control studies. In a cohort investigation, many thousands of initially healthy participants record their habitual diet. They are then followed up over subsequent years and ultimately nutritional factors, recorded at baseline, are compared between those with and without cancer. As the dietary information is collected at recruitment, that is current diet, these studies are less prone to error than case-control studies, in which people with cancer are asked to recall their diet before the development of symptoms.

Important information on diet and colorectal cancer risk is emerging from the European Prospective Investigation into Cancer and Nutrition (EPIC) study [Gonzalez and Riboli, 2010]. EPIC is a multicentre prospective cohort study in 23 centres in 10 European countries, namely Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the UK. A total of 519,978 men and women,

aged 35–70 years completed information at baseline and were followed up over subsequent years to identify those who developed cancer, including colorectal cancer (maximum number of cases for individual analyses = 2819). The main findings related to the risk of colorectal cancer were a 42% decrease with high dietary fibre [Bingham *et al.* 2005], a halving with greater fish consumption [Norat *et al.* 2005], a 50% increase with higher red meat intake [Norat *et al.* 2005] and a 31% reduction with increased dietary calcium [Jenab *et al.* 2010]. There was also a positive association between a high alcohol consumption and cancer risk, with a 15 g/day increase associated with an elevation of the risk by 8% [Ferrari *et al.* 2007]. The advantages of the EPIC study are that there are large variations in diets across participating countries, hence differences are more likely to be detected. However, data from many cohort studies are required to confirm consistency of findings which then implies causality. A pooled analysis of 13 cohort studies assessed 725,628 participants with follow up of 6–20 years and accrued 8081 cases of colorectal cancer [Park *et al.* 2005]. There was an inverse association between dietary fibre and the risk of colorectal cancer in the age-adjusted model (RR 0.84, 95% CI 0.77 to 0.92), although this was attenuated and not statistically significant after adjusting for other factors, including red meat and alcohol (RR 0.94, 95% CI 0.86 to 1.03). Therefore, the evidence suggests fibre-containing foods are inversely associated with cancer, but the precise nutrient which may be protective in such foods needs to be clarified. The data on red meat consumption are consistent with a meta-analysis of 15 prospective investigations, involving 7367 cases, reporting an estimated summary RR of 1.28 (95% CI 1.18 to 1.39) per 120 g red meat increase consumed per day [Larsson and Wolk, 2006].

There is emerging evidence that aspirin may prevent colorectal cancer, for which there are plausible biological mechanisms. Four randomized controlled multicentre trials, including two larger studies from the USA [Cook *et al.* 2005; Gann *et al.* 1993] and two from the UK [Farrell *et al.* 1991; Peto *et al.* 1988] assessed aspirin for a potential reduction in incidence of colorectal cancer as the outcome. The two larger studies prescribed aspirin at a relatively low dose of 100 mg every other day for 10 years [Cook *et al.* 2005] or 325 mg every other day for 5 years [Gann *et al.* 1993]. Antioxidants were also

given to 50% of the aspirin and placebo groups in a factorial design. The two smaller studies prescribed aspirin at higher doses of 300–500 mg/day for 1–7 years [Farrell *et al.* 1991] and 300–1500 mg/day for 1–7 years [Peto *et al.* 1988]. The follow-up periods ranged between 5 and 23 years in the different trials. A meta-analysis of the data from the four trials reported no effect on incidence after 10 years of follow up or less (RR 1.01, 95% CI 0.84 to 1.21) [Cooper *et al.* 2010]. However, when the results from the two smaller trials were analysed, although again there was no effect over 10 years, after 23 years, there was a statistically significant 26% reduction in the relative risk of colorectal cancer in aspirin users (RR 0.74, 95% CI 0.57 to 0.97, $p=0.03$) [Cooper *et al.* 2010]. When this analysis was restricted to the second 10-year follow-up period the risk reduction was 39% (RR 0.61, 95% CI 0.43 to 0.88, $p=0.008$). Therefore, in this report higher doses of aspirin seemed to confer a protective benefit after relatively longer periods of time. In another combined analysis of four trials, of which 391 of 14,033 participants developed colorectal cancer, aspirin reduced the 20-year risk of colon cancer (incidence HR 0.76, 95% CI 0.60 to 0.96), but not rectal cancer (HR 0.90, 95% CI 0.63 to 1.30) [Rothwell *et al.* 2010]. There was no greater benefit with doses of aspirin greater than 75 mg daily, with an absolute reduction of 1.76% (95% CI 0.61 to 2.91) in 20-year risk of fatal colorectal cancer with more than 5 years' treatment with 75–300 mg daily. Finally, for aspirin in the secondary prevention of colorectal adenomas, a meta-analysis of four clinical trials involved 2967 randomly assigned patients following removal of an adenoma [Cole *et al.* 2009]. A total of 2698 patients had colonoscopic follow up and were included in the analysis of both adenoma and advanced lesion recurrence. The pooled risk ratio for adenoma recurrence for any dose of aspirin *versus* placebo was 0.83 (95% CI 0.72 to 0.96), equivalent to an absolute risk reduction of 6.7% (95% CI 3.2% to 10.2%). For any advanced lesion, the pooled risk ratio was 0.72 (95% CI 0.57 to 0.90). The decision as to whether to recommend prescribing aspirin to the general population would need to include an assessment of the potential harmful effects of the drug, including gastrointestinal bleeding, although the precise dose still needs to be clarified.

Conclusions

In summary, colorectal cancer is a major public health problem with significant morbidity and mortality, with many cancers developing from adenomas. Screening with FOBTs has been shown in randomized controlled trials to reduce mortality and consequently such programmes now operate in several countries, including the UK. Examination of the left colon with flexible sigmoidoscopy to detect and remove adenomas reduces the incidence of the disease. Consequently, there is a debate as to the relative merits and the place of these modalities in national programmes. People with a family history and inflammatory bowel disease are at increased risk of colorectal cancer and screening with colonoscopy is recommended. There is emerging aetiological epidemiological evidence from prospective cohort studies and randomized trials which should guide public health recommendations, including those on dietary factors and treatment with aspirin. In the near future, a combination of both these primary and secondary prevention measures may dramatically reduce the incidence and mortality of the commonest cancer of the gastrointestinal tract.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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