ELSEVIER

Seminars in
ROENTGENOLOGY

Colorectal Cancer Screening

Andrew A. Plumb, BM BCh, MRCP, FRCR, and Steve Halligan, MBBS, MD, FRCP, FRCR

Introduction

Colorectal cancer (CRC) is well suited to screening. It is a common disease, affecting approximately 1 in 20 adults in the United States and Europe, ultimately proving fatal in almost 50% of cases. Symptoms are frequently nonspecific and are often common (eg, change in bowel habit and abdominal pain), leading many patients to ignore the condition until a relatively late (and hence incurable) stage. As for most cancers, prognosis is strongly related to disease stage at presentation, with early tumors (confined to the bowel wall) having nearly 95% 5-year survival compared with less than 50% if there is nodal involvement.[1] Therefore, detection of early-stage cancer can reduce mortality by curing the patient of a disease that would likely be fatal if detected later.

However, cure is not the only potential benefit of CRC screening; cancer can also be prevented. Most CRC is believed to develop from benign, but potentially premalignant, precursor lesions—adenomatous polyps. Although the natural history of colonic adenomas is not fully understood, a proportion of them undergo malignant transformation to carcinoma (the "adenoma-carcinoma sequence," Fig. 1). In most cases, this transformation occurs slowly, averaging approximately 10 years.[2] Hence, there is a window of opportunity during which adenomas can be removed, potentially preventing carcinoma from ever developing. The key target is the so-called advanced adenoma—one that is either large (≥10-mm maximal diameter) or shows significant dysplastic or villous components histologically, as these have the highest risk of malignant transformation. Accordingly, effective CRC screening programs can reduce both disease incidence and mortality, which may prove cost saving as well as clinically beneficial. Depending on the particular test used, screening programs combine the 2 approaches to varying degrees—prevention of cancer by removal of its precursor, or improved cure rates for established cancer via early detection.

Division of Medicine, Centre for Medical Imaging, University College London, London, UK.

Address reprint requests to Steve Halligan, University College London, Centre for Medical Imaging, 3rd Floor East, 250 Euston Rd, London NW1 2PG, UK. E-mail: s.halligan@ucl.ac.uk, heather.fitzke@uclh.nhs.uk

Large-scale national screening programs are expensive, particularly for CRC as (unlike breast, cervical, or prostate cancer) both the sexes need to be screened. Furthermore, most CRCs develop in patients with no known specific risk factors, and adenomas are similarly sporadic, meaning that we do not know in advance which individuals to target (unlike lung cancer screening, which can be restricted to smokers). Overall, the strongest risk factor is age, which increases the prevalence of CRC exponentially. Hence, the most sensible option is to offer screening to all individuals above a certain age threshold. Adenomas are also extremely common (approximately 30% of screened individuals older than 50 years will have at least one adenoma), and any of these might potentially develop into CRC. As the only practical method to distinguish which adenomas will ultimately become a CRC is via maximal diameter, all require either removal (especially if ≥10 mm) or close surveillance. This is expensive because techniques to resect adenomas by polypectomy or measure their size (which requires direct visualization) are inherently expensive. Polypectomy also carries small but significant risks of bleeding, colonic perforation, and even death. Despite all of these barriers, CRC screening has been proven in large-scale randomized trials to reduce disease-specific mortality,[3,4] level-1 evidence that underpins implementation of CRC screening.

Options for Testing

The variety of tests available for CRC screening perhaps underlines the fact that none is perfect. Each has strengths and weaknesses, and this has generated disagreement among both clinicians and policy-makers about which strategy to implement. As the development of adenomas (particularly in the distal colon) rises sharply in patients older than 50 years, if the goal is to reduce cancer incidence by prophylactic polypectomy, intuitively we must use a test that detects both polyps and CRC from approximately this age. These relatively young individuals will derive the most benefit from reduction in incidence, as (on average) they will have fewer comorbidities and are likely to live longer if their CRC is prevented by polypectomy. They are also less at risk from adverse events,

http://dx.doi.org/10.1053/j.ro.2014.10.007

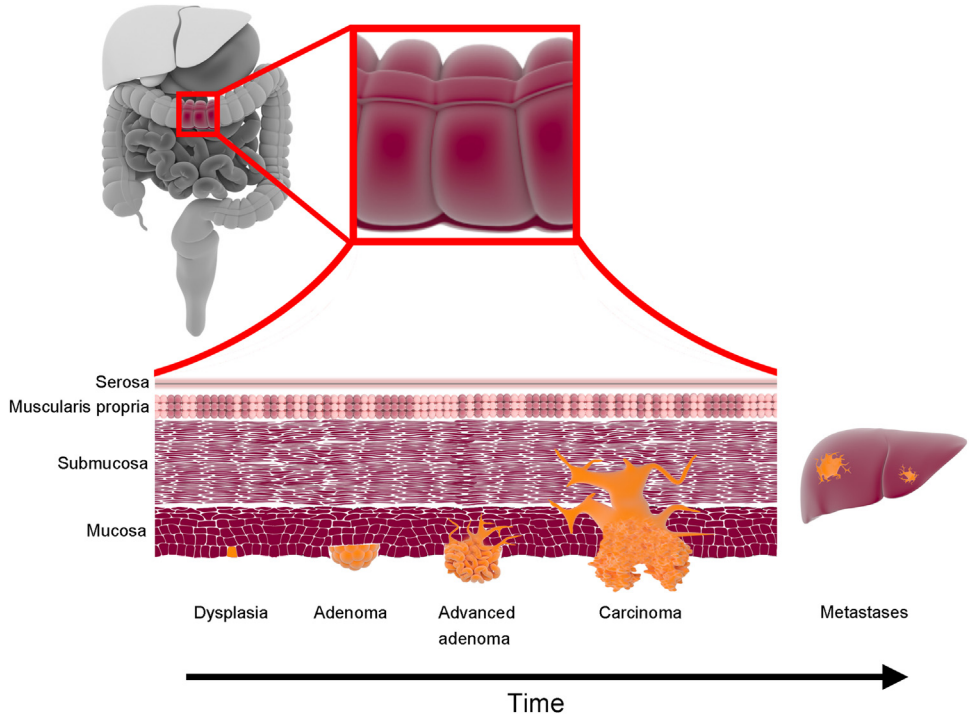

Fig. 1 The "adenoma-carcinoma sequence." Over time, progressive accumulation of genetic damage in colonic epithelium leads to development of carcinoma from premalignant precursors. This process is believed to take many years, meaning disease can be prevented by timely polypectomy. Image constructed using elements available from www.somersault1824.com. (Color version of figure is available online.)

with the result that more aggressive interventions can be used safely.

Conversely, as CRC incidence lags behind adenoma development by 10-15 years, if the goal is to improve CRC mortality by detecting early cancers, older individuals must also be screened. Less invasive options should be considered at this point, as the hazards of invasive testing increase with age. Such individuals are less likely to benefit from polypectomy, as (on average) they have a greater chance of dying sooner of other pathologies. The detection of asymptomatic established cancer remains important owing to significant short-term mortality if not identified.

Fecal Blood Testing

CRC often bleeds, resulting in detectable blood products in the feces. Unfortunately, such bleeding is often intermittent, and early cancers may not bleed at all. Similarly, most adenomas do not bleed. As a result fecal blood tests primarily detect CRC rather than polyps and affect prevalence more than incidence. The most extensively studied technique for fecal blood testing is based on a wood resin derived from Guaiacum trees, and hence is termed the "guaiac fecal occult blood test" (gFOBt). The heme component of hemoglobin catalyzes the oxidation of colorless alpha-guaiaconic acid to a blue quinone and so a positive test can be identified by this color change. Unfortunately, various foods also catalyze the reaction, notably red meat and some uncooked vegetables, causing false-positive results. Conversely, vitamin C and citrus fruits can inhibit the oxidative reaction and cause false-negatives results. Even when used correctly and 3 samples are completed (as generally recommended), sensitivity for cancer varies widely in the published literature, with so-called highly sensitive gFOBt kits reaching perhaps 70%.[5] Furthermore, of those who have positive results, only approximately 10% will actually have cancer and 40%-50% will have adenomas,[6] so the test also has limited positive predictive value. Importantly, the test is indirect—it does not visualize polyps or cancers directly, but instead detects them via a secondary phenomenon, that is, bleeding. A positive result, therefore, mandates a further test to confirm or refute the diagnosis and either biopsy cancer or treat polyps via excision biopsy; a costly addition, as half of these subsequent tests will be normal. Positive tests also cause anxiety and subject individuals who are screened to risks from endoscopy that may not be necessary. This additional step also introduces the potential for attrition from the screening pathway, if screened individuals do not attend their follow-up test.

Despite all of these problems, gFOBt has several key advantages. It is relatively cheap to administer (it can be posted to the screened individual, completed at home, and then posted back for interpretation), widely available, completely safe if used correctly, and causes minimal discomfort. Furthermore, it can be repeated on multiple occasions, which improves sensitivity. Most crucially, there is undoubted evidence that such screening is effective. Several large randomized trials, each with thousands of screened individuals, have shown a reduction in disease-specific mortality (Table 1). Meta-analysis of data from 327,043 screened individuals from 4 countries (Denmark, Sweden, the United States, and the United Kingdom) showed mortality reduction of approximately 16% overall (23% for those who actually adhered to screening).[3]