Clinical Biochemistry 47 (2014) 921–939

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Tests and investigations for colorectal cancer screening

Magdalen R.R. Carroll [a,b], Helen E. Seaman [a,b,c], Stephen P. Halloran [a,b,c,*]

[a] NHS Bowel Cancer Screening Programme Southern Hub, 20 Priestley Road, Surrey Research Park, Guildford, Surrey GU2 7YS, UK
[b] Royal Surrey County Hospital Foundation Trust, Egerton Road, Guildford, Surrey, GU2 7XX, UK
[c] University of Surrey, Guildford, GU2 7XH, UK

ARTICLE INFO

Article history:
Received 4 February 2014
Received in revised form 11 April 2014
Accepted 15 April 2014
Available online 24 April 2014

Keywords:
Screening
Cancer
Colorectal
Bowel
FOBT
FIT
Faecal occult blood
Faecal immunochemical test

ABSTRACT

Worldwide, colorectal (CRC) is the third most common form of cancer, after lung and breast cancer, and the fourth most common cause of cancer death, although in developed countries CRC incidence is higher and it accounts for an even higher proportion of cancer deaths. Successful treatment of early-stage CRC confers substantial survival advantage, and there is now overwhelming evidence that screening average-risk individuals for CRC reduces the incidence and disease-specific mortality. In spite of considerable research for new biomarkers for CRC, the detection of blood in faeces remains the most effective screening tool. The best evidence to date for population-based CRC screening comes from randomised-controlled trials that used a guaiac-based faecal occult blood test (gFOBt) as the first-line screening modality, whereby test-positive individuals are referred for follow-up investigations, usually colonoscopy. A major innovation in the last ten years or so has been the development of other more analytically sensitive and specific screening techniques for blood in faeces. The faecal immunochemical test for haemoglobin (FIT) confers substantial benefits over gFOBt in terms of analytical sensitivity, specificity and practicality and FIT are now recommended for CRC screening by the *European guidelines for quality assurance in colorectal cancer screening and diagnosis*. The challenge internationally is to develop high quality CRC screening programmes for which uptake is high. This is especially important for developing countries witnessing an increase in the incidence of CRC as populations adopt more westernised lifestyles.

This review describes the tests available for CRC screening and how they are being used worldwide. The reader will gain an understanding of developments in CRC screening and issues that arise in choosing the most appropriate screening test (or tests) for organised population-based screening internationally and optimising the performance of the chosen test (or tests). Whilst a wide range of literature has been cited, this is not a systematic review. The authors provide FOBT CRC screening for a population of 14.6 million in the south of England and the senior author (SPH) was the lead author of the *European guidelines for quality assurance in colorectal cancer screening and diagnosis* and leads the World Endoscopy Organization Colorectal Cancer Committee's Expert Working Group on 'FIT for Screening'.

Introduction

Colorectal cancer (CRC) is a major health problem worldwide. It is the third most common form of cancer, after lung and breast cancer and the fourth most common cause of cancer death [1,2]. CRC mortality rates vary by country and are affected by the local incidence rate, stage at diagnosis and the resource and effectiveness of treatment regimes, both of which are higher in developed countries where CRC ranks as the second most common cause of cancer death [3]. CRC incidence is higher in men than in women [4] and other risk factors include increasing age [5], a sedentary lifestyle, physical inactivity and excess body weight [6,7], smoking [8,9], a diet low in fibre [10], high in red meat and processed foods [11] and a personal history of the metabolic syndrome [12], diabetes [13] or inflammatory bowel disease (*e.g.* ulcerative colitis, Crohn's disease) [14]. Whilst the majority of CRC is sporadic, the risk of CRC is increased for individuals with a close family history of CRC [15]. Inherited syndromes have been associated with a very high risk of CRC and these include familial adenomatous polyposis (FAP), which accounts for <1% CRC cases and Lynch syndrome (also known as hereditary non-polyposis colon cancer), which accounts for 2–4% of CRC cases [16]. The genetics of both of these conditions has been well described and their pathogenesis is very different; FAP presents with thousands of polyps some of which progress to cancer whilst in Lynch syndrome most of the individual polyps progress to cancer. Compared with an average 5–6% lifetime risk in Western populations, the lifetime risk of CRC in Ashkenazi Jews has been reported to be 9–15%, one of the highest lifetime CRC risks of any ethnic group [17,18]. Hyperplastic polyposis syndrome

* Corresponding author at: 20 Priestley Road, Surrey Research Park, Guildford, Surrey GU2 7YS, UK.
E-mail addresses: magdalencarroll@nhs.net (M.R.R. Carroll), helenseaman@nhs.net (H.E. Seaman), s.halloran@nhs.net (S.P. Halloran).

http://dx.doi.org/10.1016/j.clinbiochem.2014.04.019
0009-9120/

(HPS) is a rare condition characterized by multiple hyperplastic polyps in the bowel and is associated with an increased CRC risk [19].

Almost 60% of CRC cases occur in the developed regions of the world; the disease is most prevalent in Australia, New Zealand, Europe and the United States and is much less common in Africa and Asia [1,2]. In countries where the incidence of CRC has been comparatively low, however, the adoption of a more westernised diet has been associated with an increasing incidence of CRC, for example in Japan, Singapore and Israel [2,6,20].

Improved survival from CRC (where 'survival' is defined as the proportion of individuals diagnosed with CRC who are alive after a defined period of time) is apparent for many countries worldwide; recent figures for the 34 OECD (Organisation for Economic Co-operation and Development) countries (including countries in North America, Asia and Europe, as well as Australia and New Zealand) demonstrate that between 2001–6 and 2006–11, five-year CRC survival improved from 58.0% to 61.3% [2]. Improved CRC survival can be attributed to advances in the diagnosis and treatment of CRC, but also to the introduction of screening for CRC [21].

In 1968, Wilson and Jungner published a seminal paper that described the principles and practice of screening for disease [22]. The Wilson and Jungner criteria have since been modified to create criteria specific to population screening [23] (Table 1). The following paragraphs address those criteria in the context of screening for CRC.

Convincing evidence for a reduction in CRC mortality with population-based screening using a guaiac-based faecal occult blood test (gFOBt) has come from four randomised-controlled trials (RCTs) conducted in the UK [24], Denmark [25], Sweden [26] and the USA [27]. In a Cochrane Library systematic review of those RCTs [28], CRC mortality was found to be reduced by 16% amongst individuals invited to participate (Relative Risk [RR] 0.84, 95% confidence interval [95% CI] 0.78,0.90) and by 25% (RR 0.75, 95% CI 0.66,0.84) in those who accepted the invitation. A follow-up study from the USA trial, the Minnesota Colon Cancer Control study, recently reported a sustained reduction in CRC mortality over thirty years for individuals screened using a gFOBt annually (RR 0.68, 95% CI 0.56,0.82) or biennially (RR 0.78 95% CI 0.65,0.93) with colonoscopy and polypectomy as indicated [29]. A similar CRC mortality benefit of biennial gFOBt after 11 years of follow-up has been confirmed by French researchers [30] and a study in the UK concluded that biennial gFOBt screening for ten years confers a mortality benefit for at least twenty years [31].

The evidence for CRC screening demonstrates that if bowel polyps are identified and removed in the early stages of development, progression to cancerous lesions can be halted. Five-year survival from CRC is greater than 90% if caught in early stages of disease before the tumours infiltrate the bowel wall, but five-year survival falls to approximately 60% if lymph nodes are involved and below 10% when metastases are present [32]. If CRC is detected once symptoms become apparent, the disease is usually well-developed. Late-stage disease is associated with high mortality; 40–50% of individuals die with metastatic disease [1]. The US National Polyp Study showed that after adenoma removal and with adequate colonoscopy surveillance, the incidence of CRC could be reduced and the ten-year mortality from CRC was half that expected in the general population (standardised incidence-based mortality ratio 0.47 95% CI 0.26,0.80) [33].

Table 1
Summary of criteria for population-based screening (according to the UK National Screening Committee [23].

Criteria for population-based screening
The condition should be an important health problem, for which the epidemiology and natural history are adequately understood. There should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
The treatment (or intervention) should be effective, and there should be evidence that earlier treatment leads to better outcomes than later treatments.
The test should be a simple, safe and validated screening test, with a suitable cut-off level defined and agreed. The test should be acceptable to the population with an agreed policy on further diagnostic investigation of individuals with positive test results.
The Screening Programme should be effective at reducing mortality and morbidity (as shown in high quality randomised controlled trials); benefits from being screened should outweigh the harms (both physical and psychological) to the patient; the programme should be affordable.

CRC has a well-established carcinogenesis pathway. The disease usually develops slowly and the latent period of approximately 10 years between pre-cancerous colonic polyps and advanced adenomas or CRC provides the opportunity for detection of early-stage, treatable disease [34]. As faeces move through the bowel, epithelial cells lining the colon are sloughed off. The cells are readily regenerated and replaced under normal conditions but sometimes epithelial cells may continue to divide after the normal cells have been replaced. The development of small polyps lining the bowel wall is common and usually those polyps are innocuous with no malignant potential. A small proportion of polyps may continue to grow and divide and form pre-cancerous adenomatous lesions. By 50 years of age, about 25% of the general population will have developed potentially pre-cancerous polyps, although only a very small proportion of these will actually progress to malignant tumours [35,36]. Brenner et al. reported that 2.6% of advanced adenomas develop into invasive colorectal cancers in people aged 50–55 years, increasing to 5.6% in those aged over 80 years [37].

The malignant potential of polyps and adenomas varies with size, histology and grade of epithelial atypia [38]. The two most common histological types of colonic polyp are hyperplastic and adenomatous. Hyperplastic polyps contain an increased number of glandular cells with decreased cytoplasmic mucus, but lack nuclear hyperchromatism, stratification, or atypia [39]. Adenomatous nuclei are usually hyperchromatic, enlarged, cigar-shaped, and crowded together in a palisade pattern. Adenomas are classified as tubular or villous. Histologically, tubular adenomas are composed of branched tubules, whereas villous adenomas contain minute finger-like processes (digitiform villi) arranged in a frond. Tubulovillous adenomas contain both elements. Tumours with villous histology are associated with a greater risk for CRC. Unlike adenomatous lesions, hyperplastic lesions generally have no malignant potential (multiple hyperplastic polyps in HPS being an exception). Other CRC prognostic polyp characteristics include polypoid morphology (sessile or pedunculated) or non-polypoid morphology (flat, ulcerated). Non-polypoid morphology is associated with the Lynch syndrome and a greater CRC risk [40].

There are several ways in which CRC screening may be implemented and different types of test can be employed. Country-specific circumstances will often dictate the way in which screening can be provided. For example, countries with a centrally organised healthcare system may incorporate population-based CRC screening programmes into routine healthcare provision. Such organised screening programmes have to be of a high standard and monitored closely. Large numbers of people may be invited to take part in organised screening and each individual is offered the same services, information and support as others of the same age. Other countries may restrict routine screening to individuals identified as 'at risk' because of a family history or co-morbidity, or there may be provision for opportunistic screening whereby, through contact with a health professional, an individual asks for, or is offered, screening. These methods of screening are very different and uptake, clinical outcomes and costs differ.

Vascularised colonic polyps, adenomas and cancers shed cells and sometimes bleed into the lumen of the colon and these markers (cell debris and blood) may be picked up by passing faeces. Most screening tests for CRC are designed to detect tiny traces of blood in faeces. Other screening methods use direct visualisation endoscopic techniques, such as colonoscopy and flexible sigmoidoscopy (FS), a few use imaging techniques such as computed tomographic (CT) colonography (or virtual colonoscopy) and, in very small numbers capsule endoscopy, or double-contrast barium enema and x-ray examination of the bowel.