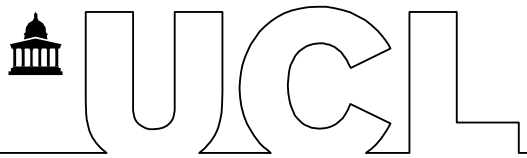

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ARTICLE

Colorectal Cancer Screening

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Introduction

Colorectal cancer (CRC) is well-suited to screening. It is a common disease, affecting approximately 1 in 20 adults in the USA and Europe, ultimately proving fatal in almost 50% of cases. Symptoms are frequently non-specific, and are often common (e.g. change in bowel habit, 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 tumours (confined to the bowel wall) having nearly 95% 5-year survival compared to 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 pre-malignant, precursor lesions – adenomatous polyps. Although the natural history of colonic adenomas is not fully understood, a proportion undergo malignant transformation to carcinoma (the "adenoma-carcinoma sequence", figure 1). In the majority of 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 (≥10mm maximal diameter) or shows significant dysplastic or villous components histologically, since these have the highest risk of malignant transformation. Accordingly, effective CRC screening programmes can reduce both disease incidence and mortality, which may prove cost-saving as well as clinically beneficial. Depending on the particular test employed, screening programmes combine the two approaches to varying degrees – prevention of cancer by removal of its precursor, or improved cure rates for established cancer via early detection.

Large-scale national screening programmes are expensive, particularly so for CRC since (unlike breast, cervical or prostate cancer) both sexes need to be screened. Furthermore, the majority of CRC 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 screenees aged over 50

years will have at least one adenoma), and any of these might potentially develop into CRC. Since the only practical method to distinguish which adenomas will ultimately become CRC is via maximal diameter, all require either removal (especially if ≥10mm) 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 randomised 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 amongst both clinicians and policy-makers about which strategy to implement. Since the development of adenomas (particularly in the distal colon) rises sharply above the age of 50 years, if the goal is to reduce cancer incidence by prophylactic polypectomy, intuitively we must employ 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, since (on average), they will have fewer co-morbidities and are likely to live longer if their CRC is prevented by polypectomy. They are also less at risk from adverse events, with the result that more aggressive interventions can be employed safely.

Conversely, since 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, since the hazards of invasive testing increase with age. Such screenees are less likely to benefit from polypectomy, since (on average) they have a greater chance of dying sooner from other pathologies. Detection of asymptomatic established cancer remains important due 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 impact more on prevalence 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 catalyses the oxidation of colorless alpha-guaiaconic acid to a blue quinone and so a positive test can be identified by this colour change. Unfortunately, various foods also catalyse 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. Even when used correctly and three 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 test positive, 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 visualise polyps or cancers directly, but instead detects them via a secondary phenomenon, i.e. 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, since half of these subsequent tests will be normal. Positive tests also cause anxiety anxiety and subject screenees to risks from endoscopy that may not be necessary. This additional step also introduces the potential for attrition from the screening pathway if screenees 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 screenee, 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 randomised trials, each of thousands of screenees, have shown a reduction in disease-specific mortality (Table 1). Meta-analysis of data from 327,043 screenes from 4 countries (Denmark, Sweden, the USA and the UK) showed mortality reduction of approximately 16% overall (23% for those who actually adhered to screening)[3].

Because of these data, and the comparative simplicity of a stool testing-based screening programme, any test that might combine the administrative benefits of gFOBt with greater sensitivity for CRC and adenomas is an attractive proposition. Fecal immunochemical testing (FIT) is one possibility. Instead of a chemical reaction catalyzed by heme, FIT relies on detecting globin via immunochemical methods. Although both qualitative and quantitative methods are available, most interest has surrounded the latter, since it allows the interpreter to vary the threshold at which a screenee becomes positive. As a result, test sensitivity and specificity can be tailored to disease prevalence in the target population; for example, if even very low levels of fecal hemoglobin are defined as a positive result, sensitivity will increase, albeit at the cost of reduced specificity. Notwithstanding this, in general most immunochemical tests are more sensitive than guaiac-based alternatives, at approximately 80% overall for one-off testing[7]. Although to date there is no direct RCT evidence supporting use of FIT, benefits are presumed by extension from the gFOBt literature. Both FIT and gFOBt are endorsed as viable screening options by many expert bodies, both in the USA and Europe. Multiple large-scale screening programmes based on fecal testing have been implemented successfully, including many European countries, parts of the Americas and Australasia.

More recently, interest has focused on detecting the underlying genetic aberrations that lead to the development of CRC, e.g. by harvesting DNA from exfoliated colonocytes in the stool (sDNA testing). Early results were limited by suboptimal sensitivity, although a recent report of a “multitarget” test, which combines assessment of several DNA markers with immunochemical testing for human hemoglobin showed a good sensitivity for CRC of 92% (versus only 74% for FIT)[8], although sensitivity for advanced premalignant lesions was only 42%.

Endoscopy

Unlike fecal testing, endoscopy inspects the colonic mucosa directly, allowing even tiny adenomas to be detected and achieving extremely high sensitivities for larger adenomas and colorectal cancer. Indeed, sensitivity for established cancer likely exceeds 95%[9], and the sensitivity for large (>10mm) adenomas, as determined by tandem colonoscopy (i.e. initial colonoscopy followed by an immediate repeat examination) is estimated at approximately 98%[10]. Furthermore, polypectomy may be performed at the same sitting, preventing future cancer development. The two options for endoscopic screening are either flexible sigmoidoscopy or colonoscopy.

Intuitively, colonoscopy seems the logical best choice since the entire colon (rather then just the distal portion) is examined. However, colonoscopy requires complete bowel cleansing rather than simply a rectal enema, sedation is frequently required, the perforation risk is higher, and the procedure is technically more challenging and takes longer than flexible sigmoidoscopy, limiting throughput. It is also usually performed by clinicians rather than nurses, which increases expense further. Approximately two-thirds of cancers are left-sided and hence within reach of a flexible sigmoidoscope. Additionally, the presence of left-sided CRC or adenoma may be used as a marker of patients at high risk of colorectal neoplasia, and hence provoke investigation of the right colon in any case. Moreover, even with

colonoscopy, right-sided adenomas may be difficult to detect, since the bowel is more difficult to cleanse, intubation of the proximal colon is technically challenging and the adenomas themselves are less conspicuous. Furthermore, a different (and more rapid) pathway of colorectal carcinogenesis occurs more commonly in the right colon (the “serrated pathway”), rendering such tumors relatively less suitable for screening because they are more likely to arise in the interval between screening tests. As a result, observational data suggest that colonoscopy affords more protection against left-sided CRC than right-sided[11]. Since much of this benefit can be provided by sigmoidoscopy at lower cost and with greater patient acceptance, the choice between the two alternatives is not clear-cut.

In recent years, the evidence in favor of flexible sigmoidoscopy (versus no screening) has become overwhelming. Three large randomised controlled trials have demonstrated that flexible sigmoidoscopy reduces disease-specific mortality by approximately 25% overall (Table 2) [12-14], confirmed by meta-analysis[4]. Moreover, subsequent incidence of CRC is also reduced by approximately 30%, confirming the hypothesis that removing adenomas prevents cancer. A further randomised study showed a non-significant reduction in CRC incidence and mortality[15], although this may be due to the relatively shorter follow-up period masking the effect of adenoma removal (which may take many years to exert effect). Studies reporting a benefit found that this primarily arose from a reduction in distal CRC incidence and mortality. However, there was some impact on proximal CRC, likely due to subsequent total colonoscopy contingent on distal abnormalities found at initial sigmoidoscopy. In the light of these studies, the English Bowel Cancer Screening Programme has introduced phased roll-out of a national flexible sigmoidoscopy screening programme, to be offered as a single screen at age 55 years.

What of colonoscopy? Unlike gFOBt and flexible sigmoidoscopy, there is no direct randomised controlled trial evidence to confirm that it reduces either CRC incidence or mortality. Nonetheless, just as arguments in favor of FIT extrapolate from the gFOBt literature, proponents of colonoscopy cite the powerful evidence from the sigmoidoscopy trials to support their position. Furthermore, observational data strongly imply that screening colonoscopy is protective against subsequent CRC[4]. Follow-up of both high-risk and asymptomatic cohorts who underwent colonoscopy found lower than expected rates of subsequent CRC when compared to expected rates for the general population, with the reduction in both incidence and mortality estimated at between 50 and 66%[16]. Case-control series have shown that patients presenting with colorectal cancer are less likely to have had previous colonoscopy than controls (without CRC), implying that undergoing colonoscopy is protective [17]. Thus, the indirect evidence that colonoscopy prevents CRC is compelling. Nonetheless, this does not necessarily mean that population screening with colonoscopy is guaranteed to be effective: Observational studies are inherently biased. Furthermore, low adherence to screening (particularly for an invasive test such as colonoscopy) may negate any beneficial effect. Fortunately, large randomised trials are in progress to address this. The NordICC trial (Nordic-European Initiative on Colorectal Cancer) will test colonoscopy versus no screening, and two trials will test colonoscopy against FIT (the COLONPREV trial from Spain[18], using biennial FIT; and the CONFIRM trial from the USA, using annual FIT). Baseline results from COLONPREV show equivalent diagnostic yield of CRC for colonoscopy and FIT (despite a 10% lower uptake of colonoscopy) but higher adenoma detection rates[18]. Whether this will translate to a greater reduction in incidence for those screened by colonoscopy (or, conversely, subsequent FIT screening rounds will narrow the gap) is unclear. Results from all three trials are expected in the early to mid 2020s.

Radiological tests

The preceding paragraphs show that the bar has been set high for any radiological alternative: Large randomised trials, some exceeding a hundred thousand participants, have demonstrated the benefits of both fecal tests and endoscopy. What role, then, for the

radiologist? The traditional test for radiological investigation of the colon, the double-contrast barium enema, falls well short of the mark. Not only is it poorly tolerated[19], radiologists have lost the skills necessary to perform and interpret it. Randomised data show that it misses more cancers and large polyps than alternatives[20], albeit in older symptomatic patients rather than screenees. When employed as a surveillance test following screen-detection of adenomas, barium enema detected only 35% of polyps subsequently proven at blinded colonoscopy[21]. The test cannot be recommended, and should be abandoned.

However, there is a viable alternative. Computed tomographic colonography (CTC) combines rapid, thin-collimation CT scanning of the gas-distended, prepared colon with (at least) dual patient positioning, usually accompanied by spasmolytics to enhance luminal distension. Reductions in the cost and increased availability of powerful computers allow the internal surface of the colon to be rendered and displayed for interpretation on demand. Thus, the radiologist may choose to "fly-through" the colonic lumen, as if following the course of a virtual colonoscope, detecting pathology *en route* (figure 2). Such images, now acquired within a few seconds and at sub-millimetre resolution, allow polyps to be depicted with high sensitivity. The remainder of this article will focus on the attributes of CTC that suggest it is a viable option for CRC screening.

Accuracy

A large number of studies have convincingly shown CTC to be sensitive for CRC, at least when interpreted by a trained reader. A recent meta-analysis suggested the sensitivity for colorectal cancer is 96%[9], similar to the estimate for colonoscopy (95%). The sensitivity for large (≥10mm) polyps is also likely to be approximately 90%, estimated at 93% in one meta-analysis[22] and 83% in another[23] (which dealt solely with studies describing screening populations). Importantly, these results seem to be generalizable, since 90% sensitivity for ≥10mm neoplasms was achieved in the multicenter ACRIN-2 study of average-risk screenees[24]. Consistent with these meta-analyses and cohort studies, the recent randomised SIGGAR trial (of symptomatic patients rather than a screening population) found that detection rates for colorectal cancers and large polyps was not significantly different between CTC and colonoscopy, across 21 separate centres [25]. CTC is clearly well able to demonstrate these clinically relevant lesions with high sensitivity. Specificity is also high in the right hands, allowing positive predictive values to exceed 90% in routine screening practice[26].

Small (6-9mm) polyps are less well depicted, but even so the test is approximately 68% sensitive for such lesions and 79% sensitive for adenomas within this size bracket[23], which is arguably the more relevant target. At this point, it is instructive to reiterate the fact that back-to-back colonoscopies suggest that initial colonoscopy may miss approximately 10-15% of 5-10mm adenomas and over 20% of <5mm adenomas[10]. Although such tandem colonoscopy studies suggest the miss rate for adenomas 10mm is around 2%[10], if CTC is used as an independent reference standard (reducing incorporation bias), as many as 10% of large adenomas may be missed at colonoscopy[27]. Therefore the commonest criticism of CTC, a relatively diminished sensitivity for small adenomas, also applies to colonoscopy, albeit to a lesser degree. Debate regarding the utility of CTC as a screening option has often been clouded by a focus on sensitivity for smaller polyps, ignoring that this is only a single facet of CRC screening, and arguably a relatively unimportant one. A small increase in screening uptake, for example predicated by improved acceptability, would almost certainly outweigh a minor reduction in sensitivity for small adenomas, the majority of which will remain stable or regress over time in any case[28]. Conversely, failure to achieve polypectomy after CTC (e.g. due to non-compliance with colonoscopy) could render the test useless as a screening option, even if sensitivity were perfect. Clearly, a more sophisticated approach is needed.

Acceptability, uptake and diagnostic yield

Whether or not screenees find the screening test acceptable is crucial to the success (or otherwise) of any programme; if the target population will not complete the test, there can be no impact on outcomes. Direct colonic tests are less well tolerated and accepted than indirect tests, simply because they are more invasive and inconvenient. As a result, screening uptake is generally greater for faecal testing than endoscopy. However, as described already, indirect tests have limited ability to detect smaller adenomas and hence affect CRC incidence. A well-tolerated direct colonic test is therefore desirable.

Amongst the screening population, CTC seems to be perceived as relatively less burdensome than colonoscopy. For example, a randomised trial comparing colonoscopy and reduced-laxative CTC found that a substantially greater proportion of those randomised to colonoscopy expected it to be painful than did those undergoing CTC (only 5% expected no pain with colonoscopy versus 35% for CTC). Similarly, expected levels of embarrassment and overall burden were greater in those randomised to colonoscopy than CTC [29]. Perhaps because of these expectations, participation rates were 22% for colonoscopy compared with 34% for CTC [30]. However, this increase in participation for CTC was almost exactly counterbalanced by a lower per-patient detection rate of advanced neoplasia, which was conducted without laxative bowel preparation in an attempt to maximize acceptability but perhaps reducing sensitivity for smaller lesions. Additionally, only screenees with polyps ≥10mm at CTC were referred for polypectomy, a situation arising in 9% of participants. This approach sacrifices short-term diagnostic yield for lower polypectomy rates (and thus costs). Ultimately, the overall yield of advanced neoplasia per screenee invited was not significantly different between CTC and colonoscopy [30]. Conversely, an Australian randomised trial of (full-laxative) CTC versus colonoscopy[31] found no significant difference in either test uptake (18% for CTC and 16% for colonoscopy) or advanced neoplasia detection (9.0% and 8.4% respectively). However, a 6mm threshold for colonoscopy after CTC was used in this study, resulting in a relatively high 30% referral rate – a costly and inconvenient addition to the screening pathway. A large non-randomised US screening series using full-laxative bowel preparation found that CTC and colonoscopy had equivalent detection rates of advanced neoplasia despite considerably lower polypectomy and complication rates in those who underwent CTC[32], and at an acceptably low referral rate for colonoscopy of 8%. The precise impact of reduced-laxative or full-laxative bowel preparation on the balance between diagnostic yield and screening participation rates is unclear. The forthcoming Italian SAVE randomised trial of CTC, FIT and colonoscopy[33] will include a nested randomization between full- and reduced-laxative CTC to help clarify this. Irrespective, currently available data from randomised trials support the hypothesis from non-randomized series that screening CTC detects similar levels of advanced neoplasia to colonoscopy. There are no randomised data comparing CTC with flexible sigmoidoscopy, although this will be addressed by an ongoing Italian RCT that will invite 20,000 screenees and compare participation rates, diagnostic yield and acceptability between CTC and flexible sigmoidoscopy[34].

These data pertain only to the first (prevalent) screening round: some CRC screening tests must be repeated in order to achieve maximum effectiveness. The optimal screening interval following negative CTC (and indeed colonoscopy) is not known precisely, but figures of 5 years for CTC and 10 for colonoscopy are suggested[35]. To date, there are limited data regarding adherence to subsequent screening rounds following CTC. When participants are deciding whether or not to undergo repeat screening, it is likely that they will be influenced by how tolerable they found the original procedure. In the Dutch trial, those randomised to CTC *expected* relatively little burden in comparison to colonoscopy, but the reality was somewhat different. After the test had been completed, average levels of pain, embarrassment and burden were lower in the colonoscopy arm than the CTC arm, perhaps because of preconceptions about each test. Nonetheless, both groups reported they were equally likely to undergo repeat screening when required. Unlike the Dutch data, a large

randomised trial of symptomatic patients from the UK found that those randomised to CTC were more satisfied and suffered less physical discomfort than those randomised to colonoscopy [36].

Overall, these data suggest that CTC is tolerated at least as well as colonoscopy and possibly better, and because the expected burden is lower, CTC may increase screening participation rates in the prevalent round without sacrificing future participation.

Extracolonic findings

Unlike other screening tests for CRC (but similar to some other radiological screening tests), CTC may detect pathology outside the colon, because the entire abdomen and pelvis is imaged unavoidably. Although low radiation dose (applied for screening examinations) limits sensitivity, in both a large clinical series[37] and a randomised trial[30], the detection rate of extracolonic cancer was similar to that for CRC itself. Other non-neoplastic but potentially life-threatening pathology such as abdominal aortic aneurysms (AAA) may also be diagnosed. As a result, the benefits of screening CTC may extend beyond any impact on CRC mortality. Although presumed to be advantageous, there are potential disadvantages to such extracolonic findings, since they may provoke further testing, resulting in patient anxiety, inconvenience and higher costs, all for no ultimate gain. Such tests may cause patient morbidity or even death if they are invasive, reducing or even outweighing the benefit of extracolonic detection in the first place. For these reasons, extracolonic imaging is considered both a strength and weakness of CTC. On average, however, the balance is likely beneficial: Additional testing occurs in only 7-11% of patients and average costs are relatively small[38]. Patients and their doctors view extracolonic detection positively, even when made aware of the theoretical risks of further testing[39]. Further, health economic modelling suggests that such extracolonic detection saves lives, with additional costs being sufficiently low that cost-effectiveness is greater for a CTC-based screening strategy than one based on colonoscopy, even if colonoscopy is complemented by ultrasound screening for AAA[40].

Safety

Safety is of crucial importance to any screening programme, since the target population is (ostensibly) healthy and the goal of the programme is largely preventative. The vast majority of those being screened will derive no ultimate benefit, since most people will never develop the disease. It is therefore paramount that adverse events are minimized, otherwise the risks of screening may outweigh any benefits.

Estimates of CTC perforation rates are largely derived from 3 large surveys, from Israel[41], the UK[42] and the USA[43]. When pooled, these described 18 perforations from 50,860 CTC examinations (approximately 1 in 2800), although many perforations were asymptomatic and only 6 required surgery (1 in 8500). It is important to note that CTC is extremely sensitive for extraluminal gas, detecting perforations that would otherwise go unmissed at endoscopy. We do not know the true extent of “subclinical” perforation at colonoscopy but, inevitably, it will be higher than symptomatic perforation rates, which occur at a frequency of approximately 1 in 1000 with death in perhaps 1 in 20,000[44]. At first glance therefore, it appears that CTC is considerably safer than colonoscopy, although absolute risks are low with both procedures. However, this naïvely considers CTC in isolation; in reality, polyps detected by CTC must be removed subsequently by colonoscopy if CTC screening is to reduce cancer incidence. Hence, screenees with CTC-detected adenomas require both procedures, considerably narrowing the difference in complication rates [30]. Nonetheless, a CTC-based screening strategy is, at worst, no more risky than a colonoscopy-based alternative, and is likely to be safer [32].

The radiation dose from CTC should also be considered when evaluating its safety. The inherently high tissue contrast between the gas-filled colonic lumen and protruding cancers

and adenomas means that imaging may be performed at low dose with no loss of sensitivity. Expert consensus guidelines now recommend a tube current of <50mAs for screenees of normal weight[45], very roughly corresponding to an effective dose of 2mSv. Even assuming considerably higher radiation doses of approximately 8mSv (derived from older studies), modeling suggests that the number of radiation-induced cancers will be greatly outnumbered by the number of colorectal cancers prevented by screening[46]. As newer dose-reduction techniques disseminate (such as iterative reconstruction), this balance will continue to move even further in favor of CTC.

Impact on mortality

From the description above, it seems that CTC is an excellent candidate for CRC screening – it detects polyps and cancers safely with high sensitivity and good patient acceptability, with modeling suggesting that it is cost-effective (Table 3). Large multicenter studies in both asymptomatic screenees[24] and symptomatic patients[25] have helped assuage earlier concerns that acceptable diagnostic performance could only be achieved in expert hands. Yet does it actually lead to improved outcomes for patients, either by a reduction in CRC mortality or incidence? Despite an observational study showing an extremely low rate of interval cancer in the 5 years following screening CTC[47], to date there are no randomized data to confirm this. Further, to our knowledge, there are no trials currently in progress designed to measure the impact of CTC on disease-specific mortality rather than the proxy endpoint of detection rates of (advanced) colonic neoplasia. Although the same is true of colonoscopy currently, large trials of that technology are in progress; analogous studies for CTC are unlikely in the forseeable future due to the huge numbers and costs required. While this need not be an insurmountable barrier to either large-scale implementation or recommendation of the technique as a screening option, policy-makers may require such evidence before implementation. The United Kingdom National Screening Committee, for example, explicitly requires RCT data showing a reduction in mortality or morbidity, thereby excluding CTC. The influential US Preventative Services Task Force (USPTF) judged there was insufficient evidence to issue a recommendation one way or another regarding CTC screening in 2008, although this decision is under review. The USPTF does not stipulate a need for RCT evidence before recommending a technique (since colonoscopy, for example, is recommended despite no RCT), meaning that once more recent data are incorporated, a positive recommendation for CTC screening is possible. Such a decision would bring the USPTF in line with other expert bodies including the American Cancer Society, the American College of Radiology and the US Multi-Society Task Force on Colorectal Cancer[35], and would likely carry wider implications for funding of CTC screening throughout the USA and beyond.

Conclusions

Colorectal cancer is an excellent candidate for screening, and there is incontrovertible evidence that both fecal testing and sigmoidoscopy reduce disease-specific mortality. Removal of precursor adenomas is now proven to prevent subsequent cancer development, meaning that CTC-based screening programmes hold considerable potential as population health interventions. If the public perception of CTC as a less invasive screening option translates to superior participation rates, diagnostic yield may match or even exceed that of colonoscopy, while simultaneously reducing costs. Concerns regarding generalizability are receding, and although there is no direct randomised trial evidence that CTC screening reduces mortality or incidence, the technique is unquestionably a viable screening option where the appropriate expertise exists.

Figure legends

Figure 1: The “adenoma-carcinoma sequence”. Over time, progressive accumulation of genetic damage in colonic epithelium leads to development of carcinoma from pre-malignant precursors. This process is believed to take many years, meaning disease can be prevented by timely polypectomy.

Figure 2: 2D (A) and 3D (B) images from a CT colonography examination depicting a mass in the caecum in a patient with intermittent melena. This was confirmed at colonoscopy to be a moderately-differentiated adenocarcinoma, and was resected by laparascopic right hemicolectomy.

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