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Randomised controlled trial of flexible sigmoidoscopy as an adjunct to population screening based on faecal occult blood testing.

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Short title: Flexible sigmoidoscopy and FOBT

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Abbreviations

ADR: adenoma detection rate, BCSP: NHS England Bowel Cancer Screening Programme, BoSS: bowel screening IT system, CDR: cancer detection rate, CHI: Community Health Index, CI: confidence interval, CL: confidence limit, COSPY: colonoscopy, CRC: colorectal cancer, DR: detection rate, FIT: faecal immunochemical test for haemoglobin, FOBT: faecal occult blood test, FS: flexible sigmoidoscopy, gFOBT: guaiac faecal occult blood test, HIS: Health Information Scotland, ISD: Information Services Division, NSS: National Services Scotland, OR: odds ratio, RCT: randomised controlled trial, SBoSP: Scottish Bowel Screening Programme, SIMD: Scottish Index of Multiple Deprivation, SOP: standard operating procedure, TNDR: total neoplasia detection rate, UK: United Kingdom, US: United States of America

Abstract

Objectives

Flexible sigmoidoscopy (FS) screening at around age 60 can reduce the incidence of colorectal cancer (CRC). Insufficient evidence exists on FS at 60 years in a population being offered biennial faecal occult blood test (FOBT) screening from 50 years. A randomised controlled trial (RCT) assessed if FS would be an effective adjunct to FOBT.

Setting

Scottish Bowel Screening Programme

Methods

Between June 2014 and December 2015, 51,769 individuals were randomised to be offered FS instead of FOBT at 60 years, or to continue FOBT. Those not accepting FS were offered FOBT, as were those with normal FS. All with neoplasia detected by FS and with a positive FOBT result were offered colonoscopy.

Results

Overall uptake of FS was 17.8%, higher in men than in women, and decreased with increasing deprivation from 25.7% in the least to 9.2% in the most deprived quintile. In those who underwent FS, CRC detection rate (DR) was 0.13%, adenoma DR 7.27% and total neoplasia DR 7.40%. In those who underwent colonoscopy after a positive FS, CRC DR was 0.28%, adenoma DR 8.66% and total neoplasia DR 8.83%. On an intention to screen basis, the CRC DR was no different between the study and control

groups. Adenoma and total neoplasia DR were significantly higher in the study group with odds ratios of 5.95 (95%CI: 4.69-7.56) and 5.10 (95%CI: 4.09-6.35) respectively.

Conclusions

In a single screening round at 60 years, there was low uptake and neoplasia detection rate; FS detected significantly more neoplasia than FOBT alone.

Introduction

Three randomised controlled trials (RCTs) have demonstrated that a single flexible sigmoidoscopy (FS), between 55 and 64 years, results in statistically significant and clinically substantial reductions in both mortality and incidence of colorectal cancer (CRC).¹⁻³ While some of the mortality reduction may be due to early detection of invasive cancer, the main effect, certainly on incidence, results from the identification and removal of precursor lesions, i.e., adenomatous polyps.⁴ The United Kingdom (UK) National Screening Committee recommended the addition of FS at 55 years to the NHS Bowel Cancer Screening Programme (BCSP) in England in 2011⁵ which was based on biennial guaiac faecal occult blood testing (gFOBT) offered between 60 and 74 years.

The Scottish Bowel Screening Programme (SBoSP), which followed on from three pilot screening rounds carried out from 2000 - 2007, became fully rolled out across every NHS Board in Scotland by the end of 2009. It used biennial gFOBT offered between 50 and 74 years, with a qualitative faecal immunochemical test for haemoglobin (FIT) for those with a weak positive gFOBT result. This two-tier reflex algorithm is described elsewhere⁶ and is referred to here as FOBT. In November 2017, FOBT was replaced by quantitative FIT.⁷ When FS was introduced into the BCSP in England, it was decided not to do the same in Scotland, since FOBT was being offered from 50 years rather than 60 years as in the other UK nations and because no evidence existed regarding the effectiveness of FS in a population that was already being offered biennial FOBT.

However, given the clear effectiveness of FS in a screening naïve population, a randomised evaluation of a single FS at 60 years (the mean age of participants in the previous RCTs) as an adjunct to the existing FOBT programme was performed. One rationale for this was the absence of an effect of FOBT on the incidence of CRC.⁸

Methods

The study tested the primary hypothesis that offering a FS at 60 years in addition to FOBT would result in a significant additional yield of colorectal neoplasia. Other end-points were uptake of FS and the effect of offering FS on the overall uptake of screening.

Between 19 June 2014 and 15 December 2015, 51,769 individuals in four NHS Boards (Fife, Grampian, Greater Glasgow and Clyde, and Tayside) and aged 59, 60, or 61 years, identified by their unique community health index (CHI)⁹ as eligible for FOBT screening, were randomly assigned to study and control groups. Those in the study group (n = 25,851) were offered FS at their scheduled screening invitation. Those in the control group (n = 25,918) continued being invited using the usual screening algorithm. Random allocation to the study group was carried out with a modification to the existing Bowel Screening Scotland IT System (BoSS).

Individuals who had been allocated to the study group were sent a pre-notification letter, followed two weeks later with a letter inviting them to attend for FS at the scheduled invitation to participate in the SBoSP closest to their 60th birthday. They were also sent a Participant Information Leaflet, which described the study procedure and included local contact details. This information was developed by Health Information Scotland (HIS) using focus groups and extensive user testing. Participants could contact the study team if they had any questions regarding participation and were asked to return a reply slip, using an included stamped addressed return envelope, to indicate that they wished to take part. If no response was received, a reminder letter was sent after 14 days.

Attendance for FS was in the local endoscopy unit within a target of four weeks of the invitation. Potential participants were first given an opportunity to discuss the study and FS with a specialist nurse, who also carried out pre-assessment regarding suitability for FS. Informed consent was then obtained using a FS consent form accompanied by written information about the study and FS. The patient was given an appointment date along with an enema to be used at home four hours before FS. FS was carried out by an NHS endoscopist (medical, surgical or nursing). Standard operating procedures (SOPs) were used to ensure that the FS was performed across the endoscopy units involved in as uniform a manner as possible; FS was defined as large bowel endoscopy carried out without sedation until solid faeces, pathology, or subject intolerance of the procedure required termination. Although reaching the splenic flexure was regarded as

optimal, this was not mandated to avoid causing discomfort from over-zealous endoscopy.

Those who did not accept the invitation for FS were immediately invited to FOBT screening. Those who did not respond to the invitation for FS were invited to FOBT screening within three months. Those who had a normal FS were immediately issued a FOBT to offer screening for the right colon.

Colonoscopy was offered to all with a positive FOBT result. In addition, it was offered to those in whom any adenoma (or serrated epithelial polyp of 10 mm diameter or more) was found on FS, even if it was removed, since this was the usual standard of care to ensure inspection of the entire large bowel. Those who had had polyps removed were offered a FOBT immediately and, if the polyps were found to be non-neoplastic, colonoscopy was only offered if the FOBT result was positive, since non-neoplastic polyps were not considered as an indication for colonoscopy. Individuals found to have invasive CRC at FS were referred immediately for complete colonoscopy, surgical assessment and staging.

FS was carried out using a standard therapeutic Olympus® colonoscope with a magnetic endoscope guide to allow visualisation of the position of the colonoscope within the abdomen. If possible, any small polyps (up to 7 mm) were removed using cold snare. Larger polyps were removed at subsequent colonoscopy; lesions thought to

be CRC were biopsied and the participant referred for surgical assessment and work up, including colonoscopy. Standard data from each FS was recorded on a study database in addition to that in use at the endoscopy unit. This included duration of procedure, adequacy of bowel preparation, level of patient discomfort, details of abnormality encountered, any procedures performed, extent of insertion of endoscope as estimated by the guide and any complications. These data were recorded as hard copy and transferred to a secure electronic database held by the Information Services Division (ISD) of National Services Scotland (NSS).

All polyps were sent for histological examination locally and the findings recorded on the database using the standard SBoSP proforma. The designated study pathologists (one per centre) were experienced in screening pathology and participated in the UK Bowel Screening Pathology External Quality Assurance Programme. Quality of data entry was checked by one of us (FAC) who reviewed the pathology of all FS-detected cancers across the study. In addition, the pathology of all FS positives in Tayside was reviewed since access to the relevant findings was feasible only in that NHS Board.

The population-weighted deprivation quintile of the participants in the study was assessed using the Scottish Index of Multiple Deprivation (SIMD) based on post-code.¹⁰

Results

A flow chart describing numbers invited and uptake in both arms of the trial is given in Figure 1. Overall uptake, defined as the percentage of those invited ($n = 25,851$) who underwent FS, was 17.8% ($n=4597$); the uptake of FS among those who had accepted the invitation ($n = 9,345$, 36.2%) was 49.2%. As shown in Table 1, these varied by NHS Board. Of those with a positive FS (adenoma, serrated lesion greater than or equal to 10 mm, or CRC), ($n = 440$), 96.4% went on to have a colonoscopy performed (Table 1). As shown in Table 2 and Figure 2, uptake of FS was higher in men (20.4%) than women (15.2%) and varied with deprivation index, being 9.2% in the most deprived quintile (SIMD 1) and 25.7% in the least (SIMD 5). The uptake of FOBT in the control group in SIMD 1 was 46.4% and 69.1% in SIMD 5 (Table 3 and Figure 3). The deprivation gradient for uptake of FS was significantly different from that for uptake of FOBT ($p = 0.02$) with uptake of FOBT having a steeper gradient (5.66 for FOBT compared to 4.09 for FS).

The uptake of FS was examined by screening history and, overall, 8.8% of those undergoing FS had declined participation in any previous round of FOBT screening and 14.1% had not participated in the round immediately prior to that in which FS was offered (Table 4). To determine the effect of offering FS on the overall uptake of screening, the study and control groups were compared with respect to either form of screening (FS *or* FOBT in the study group and FOBT *only* in the control group). The

uptakes were 58.6% and 59.3% in study and control groups; these were not different ($p = 0.121$) (Table 5).

The quality standard of four weeks maximum wait between invitation and FS was achieved overall for only 9.5%. Waiting times were between four to eight weeks in 46.9% and over eight weeks in 43.6%. This varied considerably between the four NHS Boards (Table 6) and indeed, one Board (B) withdrew from recruitment to the study in May 2015 owing to workload issues. No complications attributable to FS were reported, and there was only one complication of colonoscopy that resulted in hospitalisation; this was a post-polypectomy bleed that did not require intervention.

In those who underwent FS, the cancer detection rate (CDR) was 0.13%, the adenoma detection rate (ADR) was 7.27% and the total neoplasia detection rate (TNDR) was 7.40% (Table 7). In those who underwent FS and colonoscopy in response to a positive FS finding, the CDR was 0.28%, the ADR was 8.66% and the TNDR was 8.83% (Table 8). These percentages were different since not all lesions were biopsied at the time of FS, and in such cases, a definitive diagnosis was made only after colonoscopy. Of those who had a negative FS result and therefore did not go on to colonoscopy, uptake of the subsequently offered FOBT was 80.7% and the positivity was 0.82%. This group comprised 27 individuals; two were diagnosed with CRC and four with adenoma on subsequent colonoscopy. The time between the FS result and issuing the FOBT invitation was no more than two weeks.

On an intention to screen basis, the CDR was not statistically different in study and control groups. However, both the ADR and TNDR were significantly higher in the study group, with odds ratios of 5.95 (95%CI: 4.69-7.56) and 5.10 (95% CI: 4.09-6.35) respectively (Table 9).

Further information on the study and additional data may be available through discussion with the corresponding author, Professor RJC Steele.

Discussion

A single FS at around 60 years has the potential to be a highly effective population CRC screening modality. Randomised trials carried out in England (UKFSST),¹ Italy (SCORE)² and Norway (NORCAPP)³ have all shown that offering a one-off FS between 55 and 64 years results in significant and substantial reductions in both mortality from, and incidence of, CRC. In addition, a US trial showed that, in those aged 55-75 years, FS offered twice had a similar effect.¹¹

However, for FS to impact on national CRC mortality and incidence, uptake and yield of neoplasia that approach those of the RCTs must both be achieved. A comparison between the data here and those of the previous RCTs¹²⁻¹⁵ is given in Table 10; in Scotland, the uptake was well below that of the RCTs and the ADR was also less. The

reasons for the low uptake in this study are unclear, but there are several possible explanations. Randomisation in the UKFSST and the SCORE trial was only offered to those who had already expressed an interest in participation and, if those who had expressed an interest did accept an invitation to FS, the uptakes in the RCTs translate to population uptakes considerably lower than those observed. In keeping with this, uptake in the rolled-out FS programme in England has been reported to be about 43%.¹⁶ The very high uptake of 83.5% in the US trial can be explained by the fact that randomisation took place after recruitment and consent had been obtained. This makes the population uptake of 63% in the Norwegian trial (NORCAPP) remarkable, and perhaps unachievable elsewhere.

However, the fact that randomisation was carried out at a population level is unlikely to totally explain the low uptake, especially since an uptake of around 40% has been achieved in the NHS BSCP in England. One possibility is that long waiting times between invitation and performance of the FS may have led to undue attrition, leading to poor eventual uptake. However, although only half of those initially accepting the invitation actually underwent FS, there did not seem to be a link between the uptake in the four NHS Boards (Table 1) and the waiting times (Table 6). This also suggests that many participants did not appreciate the nature of the FS, despite the carefully developed and tested information leaflets provided with the invitations. Perhaps there may be cultural issues or other factors that make FS less acceptable in Scotland than elsewhere. However, in the UKFSST, Glasgow was one of the recruitment centres, then screening naïve, and uptake here amongst those invited was 62% and, when

extrapolated to the whole eligible population, would have been around 24%,¹⁷ well above our observed uptake. Another more likely explanation may be that the established and less onerous FOBT approach may have dissuaded individuals from engaging in what may appeared to be an alternative and more demanding approach.

The reduced yield of neoplastic pathology in this study as compared to the RCTs may reflect either the quality of the FS, or the fact that the population undergoing FS had been exposed to FOBT screening for up to four rounds. However, the fact that the ADR varied substantially between NHS Boards (Table 7) suggests that quality of FS may have been a factor, and, indeed, variation in ADR between endoscopists is well established.¹⁸ Unfortunately, it was impossible to assess this objectively since individual endoscopist data were unavailable. However, despite the limitations of both uptake and yield of neoplasia, the intention to screen analysis showed a very significant increase in the ADR in the group offered FS as compared to the control group who underwent FOBT screening.

Thus, if uptake and ADR could be improved, it is speculated that FS at 60 years superimposed on a FOBT programme (or a programme based on FIT with a faecal haemoglobin concentration cut-off selected to give a similar positivity rate) from age 50 could significantly enhance the effect of screening on CRC mortality and incidence. However, were FIT to be employed at a lower cut-off, giving a substantially higher positivity rate than FOBT, this might detract from the added value of FS. This

hypothesis would have to be tested by prospective studies. In addition, since FOBT screening is known to be associated with a lower CDR in the proximal colon when compared to the distal colon,¹⁹ this also has the potential to dilute the effect of FS.

An important aim of the study was to assess the feasibility of delivering a FS screening programme and, from both the waiting times and the inability of one of the NHS Boards to complete the study, introduction of FS into the SBoSP would be a significant challenge. Thus, the overall conclusion is that addition of FS to the SBoSP would be unlikely to have a beneficial effect at a population level given the observed uptake and current service constraints.

Despite these conclusions, there are some further interesting messages to take from this study. Offering FS to a population that is already being offered FOBT screening not only increases the yield of adenomas, it also appears to increase choice, since an appreciable proportion (around 9%) who took up the offer of FS had never engaged in FOBT screening. In a study from Italy, offering FIT to non-responders in a FS screening programme increased overall screening uptake.²⁰ The reverse (offering FS to FOBT non-responders) has not been recorded before, but, although this approach appeared favourable, it did not translate into an overall increase in uptake, since the uptake of any form of screening in the control and study groups was very similar, perhaps due to the very small numbers of people taking up the invitation to FS.

Another germane question would be the effect of FS on the performance of subsequent FOBT screening, which might be considerably diminished by the endoscopic procedure. Interestingly, it was recently shown, in a study done in England, that uptake, positivity and PPV of gFOBT screening were reduced following prior offer of FS screening: a quarter of FS screened participants receiving a diagnostic examination after positive gFOBT were diagnosed with advanced colorectal neoplasia.²¹ Since Scotland has now moved to a FIT based programme, it would be difficult to extrapolate from the former to the current algorithm.

As with all studies of CRC screening, variations in uptake were seen by gender and deprivation. It has been widely reported that the uptake of FOBT or FIT screening is consistently higher in women than in men.^{22,23} In FS screening, however, this gender difference is consistently reversed^{1-3,10} and the findings here are in keeping with other studies. It is not entirely clear why this should be, but a recent qualitative study from Canada suggests that women find bowel screening-associated stress to be a more important barrier than men,²⁴ and it can be argued that FS is a more stressful procedure than FOBT or FIT. However, it has been demonstrated, through a pooled analysis of RCTs, that FS is less effective in older women than in men in terms of CRC mortality and incidence reductions.²⁵ By inference, the data generated in this study support this observation given the lower uptake and the lower yield of neoplasia in 60-year-old women when compared with men.

Again, entirely consistent with previous studies, there was a significant deprivation gradient associated with the uptake of FS. Moreover, when this was compared with the gradient for uptake of FOBT screening in the control group, there was a statistically significant difference, suggesting that the effect of deprivation on the uptake of FOBT screening is greater than for FS screening. This is perhaps surprising, given the more burdensome nature of FS, but it does indicate that FS screening does not appear to increase inequalities, at least at low levels of uptake.

The strengths of this study include the ability to deliver FS to a population that was already engaged in a FOBT screening programme and the study design, which was pragmatic and mirrored what would have happened had FS been rolled out in the SBoSP. The weaknesses include the fact that the FOBT algorithm used in this study has been replaced by quantitative FIT, which could be used at a lower faecal haemoglobin concentration cut-off. Indeed, it has been shown recently that multiple rounds of FIT at a low cut-off detect significantly more advanced neoplasia, on a population level, compared with once only FS or colonoscopy screening and that significantly fewer colonoscopies are required by individuals screened by multiple FIT.²⁶ In addition, in this study, the effect of adding FS on the yield of pathology was only examined within a single round of FOBT screening and FOBT is employed as part of a biennial iterative process.

Finally, this study underlines the importance of piloting population-based screening programmes. Before national roll-out, FOBT screening was carefully piloted and learning informed the rolled-out programmes across the UK.²⁷ This did not occur to the same extent in FS screening, and both the uptake and the ability to provide FS fell short of that expected from the results of the RCTs when it was introduced in England. Of course, it is possible that the uptake of FS in the BCSP in England is an underestimate of what might be achieved in a fully rolled-out national screening programme. Because FS has not yet been offered to the whole of the eligible population, there has been little promotional material to encourage uptake. It might be that, with a fully rolled-out programme, enhanced communication with possible participants and good promotional materials, uptake would significantly increase over time. Because of these uncertainties in both countries, the UK National Screening Committee has recommended a re-appraisal of the role of FS in the UK.²⁸

Contributors

RJCS conceived the study, obtained funding and wrote the first draft of the manuscript, FAC quality assured the pathology reporting, GS and JL analysed data, manuscript, JB provided Scottish Government oversight for the project, LB provided Scottish Bowel Screening Centre support for the project, EMC chaired the Project Board, JWW was project endoscopy lead, NHS Greater Glasgow and Clyde, PSP was project endoscopy lead, NHS Grampian, CM was project endoscopy lead, NHS Tayside, JAS provided support from the Scottish Bowel Centre Screening Laboratory, A-MD collected much of

the data, CGF provided screening expertise during the study and critically evaluated all drafts of the manuscript throughout its development. All authors contributed to production of drafts of the manuscript. RJCS had full access to the data in the study and takes full responsibility for its veracity and statistical analyses. The study sponsors made no contributions to the study design, analysis, data interpretation, or publication.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: NHS Tayside, through CGF, had a paid consultancy contract with Immunostics Inc., Ocean, NJ, USA, the suppliers of gFOBT and qualitative FIT. All other authors declare no conflicts of interest.

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Ethical approval

The study was approved by the East of Scotland Ethics Service (REC Reference: 14/ES/0021, Protocol No: 2013ON22, IRAS project ID: 146024).

Trial registration

The study was registered as a trial at ClinicalTrials.gov (ID: NCT02560194).

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Legends for Figures

Figure 1.

Flow chart documenting numbers invited and uptake in both arms of the randomised controlled trial.

Figure 2.

Uptake (%) of flexible sigmoidoscopy in males and females by Scottish Index of Multiple Deprivation (SIMD – SIMD5: least deprived, SIMD 1: most deprived).

Figure 3.

Overall (males and females) uptake (%) of faecal occult blood test (FOBT - control group) and flexible sigmoidoscopy (FS - study group) by Scottish Index of Multiple Deprivation (SIMD). This illustrates an absolute difference between the most and least deprived of 22.7% for FOBT and 16.5% for FS and the differences between the deprivation gradients for FS and FOBT is statistically significant ($p = 0.02$ using analysis of covariance to compare two regression lines).

Supplementary material

Study pathway