Contents lists available at ScienceDirect

Public Health

Original Research

Route to diagnosis of colorectal cancer and association with survival within the context of a bowel screening programme

A.M. Golder[*], A. Mshihadani, D.C. McMillan, P.G. Horgan, C.S. Roxburgh, D. Mansouri

Academic Unit of Surgery — Glasgow Royal Infirmary, United Kingdom

ARTICLE INFO

ABSTRACT

Objectives: Bowel cancer screening has been introduced to improve colorectal cancer outcomes; however, a significant proportion of cases continue to present with TNM Stage III-IV disease and/or emergently. This study analyses the prior interaction with screening of patients diagnosed with colorectal cancer and factors associated with non-screening diagnosis.

Study design: This was a retrospective observational study.

Methods: All patients diagnosed with colorectal cancer in the West of Scotland from 2011 to 2014 were identified. Through data linkage to the Scottish Bowel Cancer Screening Programme, we analysed patient interaction with screening within 2 years before cancer diagnosis.

Results: In total, 6549 patients were diagnosed with colorectal cancer, 1217 (19%) via screening. Screening participation was associated with earlier TNM stage, reduced emergency presentations and improved 3-year survival (all $P < 0.001$). Failure to diagnose through screening was predominantly due to non-invitation (37%), non-return of screening test (29%) or negative test (13%). Three hundred fifty-one patients were below screening age, 79% of whom were aged 40—49 years and 2035 patients were above screening age. Factors associated with non-return of screening test included age, sex, SIMD (all $P < 0.001$) and raised Charlson score ($P = 0.030$). Factors associated with negative screening result included sex, anaemia, differentiation, right-sided tumours and venous invasion ($P < 0.001$).

Conclusion: Within Scotland, <20% of colorectal cancer is diagnosed through screening despite the existence of a population screening programme. Measures must be taken to improve screening participation including encouragement of those of routine screening age and those age ≥75 years in good health to participate in screening with consideration given to extending screening to under 50s. A significant false-negative rate of testing was observed in the present study and this requires further investigation within a population undergoing screening through faecal immunochemical testing.

© 2022 The Author(s). Published by Elsevier Ltd on behalf of The Royal Society for Public Health. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Colorectal cancer, the third most commonly diagnosed malignancy worldwide remains a significant cause of morbidity and mortality.[1] The majority of new cases of colorectal cancer are diagnosed electively; however, a significant proportion (10—30%) continue to present emergently, predominantly with obstructive symptoms.[2,3] TNM stage remains the main factor influencing long-term outcomes; however, significantly worse short- and long-term outcomes have been reported in the emergency compared to the elective population even after adjustment for the TNM stage.[3—5]

Bowel cancer screening programmes are now well established within the Developed World[6,7] with the aim of both identifying early-stage disease and reducing the proportion of emergency presentations. Available modalities of screening have been summarised in a recent review.[8] Currently, the most common first-line screening test is through the detection of blood in faecal samples, either through guaiac-based faecal occult blood testing (gFOBT) or, increasingly, faecal immunochemical testing (FIT). In a previous Cochrane review, screening programmes were reported to have a colorectal cancer mortality relative risk reduction of 15% overall and 25% following exclusion of non-responders.[9] The European guidelines for quality assurance in colorectal cancer screening and diagnosis recommend a minimum uptake to screening of 45% and

* Corresponding author. Academic Unit of Surgery, University of Glasgow, Level 2, New Lister Building, Glasgow Royal Infirmary, Glasgow, G31 2ER, United Kingdom.
E-mail address: allan.golder@glasgow.ac.uk (A.M. Golder).

desirable uptake of 65%[10] of the target population; however, to date participation has remained suboptimal at 50—60%. Some subsets of the population, particularly those of low socio-economic status, have been shown to have particularly poor engagement with screening.[11–14]

Within Scotland, all adults aged between 50 and 74 years are routinely invited to participate in biennial bowel screening. This programme was rolled out nationally from 2007 and aims to have a minimum uptake of 60%.[14] Before 2017, gFOBT was the first-line screening test with positive results progressing to endoscopic investigation and borderline results progressing to FIT testing. Since 2017, FIT testing has been used as the first-line investigation. Previous literature suggests that the current participation rate is approximately 57% with a further 8% of patients with a positive screening sample failing to undergo further investigation.[15] Despite this, a significant reduction in both the proportion of patients diagnosed with late-stage disease and the proportion of emergency presentations following introduction of the bowel cancer screening programme has been reported — 20% prescreening versus 13% in the postscreening cohort ($P < 0.001$).[13] However, a recent study that excluded individuals who did not participate in the bowel screening programme has suggested that the rate of emergency presentation could be reduced to as low as 5%;[16] therefore, there remains potential for significant improvement within the screening service.

Multiple studies have examined screening cohorts as a whole; however, the majority of these have failed to capture patients diagnosed with colorectal cancer out with screening. In the present study, we aim to investigate the relationship between patients diagnosed with colorectal cancer in the West of Scotland and their involvement in the most recent round of screening within 2 years before diagnosis. Furthermore, we aim to identify which clinico-pathological characteristics are associated with failure to progress through each stage of the screening programme and examine the relationship between screening diagnosis and TNM stage, mode of presentation and long-term outcomes in colorectal cancer.

Methods

The West of Scotland Colorectal Cancer Managed Clinical Network (MCN) maintains a prospectively collected data set of all patients diagnosed with colorectal cancer in the West of Scotland and contains basic clinicopathological data. This covers four health boards (Ayrshire and Arran, Forth Valley, Lanarkshire and Greater Glasgow and Clyde) and includes almost half of the population of Scotland. These patients receive treatment and follow-up in line with national guidelines.

Patients diagnosed with colorectal cancer between January 2011 and December 2014 within the West of Scotland were identified from the MCN database and additional data were obtained from electronic patient records. All patients were included within the present study regardless of disease stage, mode of presentation or subsequent treatment. Tumours were staged using the TNM classification system. Emergency presentation was defined as an unplanned admission requiring a definitive procedure within 72 h. Those patients who did not undergo a procedure did not have a recorded mode of presentation. Socio-economic deprivation has been stratified using the Scottish Index of Multiple Deprivation (SIMD).[17] Comorbidity status was classified using the Charlson Index (Royal College of Surgeons Modification).[18] Preoperative anaemia was included if a preoperative haemoglobin was available, for elective patients within 1 month before surgery and for emergency patients from the date of admission. Survival was updated through data linkage to the National Records of Scotland (NRS) deaths data until the end of 2018. Overall survival (OS) was defined

as the time from the date of surgery until the date of death of any cause. Cancer-specific survival (CSS) was defined as the time from the date of surgery until the date of death due to recurrent/metastatic colorectal cancer. A death was considered the result of colorectal cancer if this was the primary cause of death recorded on the death certificate. All patients were followed up for a minimum of 4 years from the date of diagnosis.

Through data linkage to the Scottish Bowel Screening Programme (SBoSP) data set, the interaction of each patient with the most recent round of screening (within 2 years before diagnosis of colorectal cancer) was analysed. Engagement with the bowel screening programme was categorised as: invited (yes/no), return of screening sample (yes/no), return of valid screening sample (yes/no), screening stool sample result (positive/negative), further investigation (yes/no) and diagnosis of cancer (yes/no). Further data were also available including the date of investigation and screening test used (gFOBT/FIT). Being before 2017, this patient population underwent first-line screening through the gFOBT test. Patients with positive tests progressed to endoscopic investigation. Patients with a borderline gFOBT underwent FIT with positive FIT subsequently progressing to endoscopic investigation. Screening was routinely offered to patients aged between 50 and 75 years. Patients aged 75 years and older were not routinely sent screening tests but were able to request them.

Ethical approval was granted for this project from the Public Benefit and Privacy Panel (NHS Scotland) for Health and Social Care (PBPP) and Caldicott Guardian Approval.

Statistical analysis

The relationship between clinicopathological characteristics and interaction with each stage of the bowel screening programme was analysed using the Chi-squared test. Three-year survival was calculated using a life table approach and results were displayed as percentage 3-year survival and percentage standard error. Statistical significance was calculated using the log-rank test.

Statistical analysis was carried out using IBM SPSS Statistics for Windows Version 27 (IBM Corporation, Armonk, New York USA). A two-tailed P value of <0.05 was considered significant throughout.

Results

Within the study period of January 2011—December 2014, 6549 patients were diagnosed with colorectal cancer in the West of Scotland, 4113 of whom were invited to participate in the bowel screening programme. Most patients presented electively (83%) with TNM Stage II (29%) or TNM Stage III (30%) disease. Seventy-seven percent of patients underwent either a curative or palliative procedure. During the follow-up period, there were 3519 deaths, 69% of which were cancer related.

As shown in Fig. 1, 6549 patients were diagnosed with colorectal cancer in the West of Scotland from January 2011 to December 2014. Nineteen percent of these patients ($n = 1217$) were diagnosed through screening. Reasons for failure to diagnose through screening included: no invitation to screening (37%, $n = 2436$), patient invited to screening but no valid sample returned (29%, $n = 1884$), valid sample returned however negative result (13%, $n = 844$), positive sample returned but no further investigation (2%, $n = 137$) or further investigation but no malignancy found (0.5%, $n = 31$).

The association between screening diagnosis and clinicopathological factors including mode of presentation, treatment type and survival is shown in Table 1. Of host factors, screening diagnosis was associated with age <75 years, male sex, lower socio-economic deprivation, less comorbid status (as measured by both ASA and
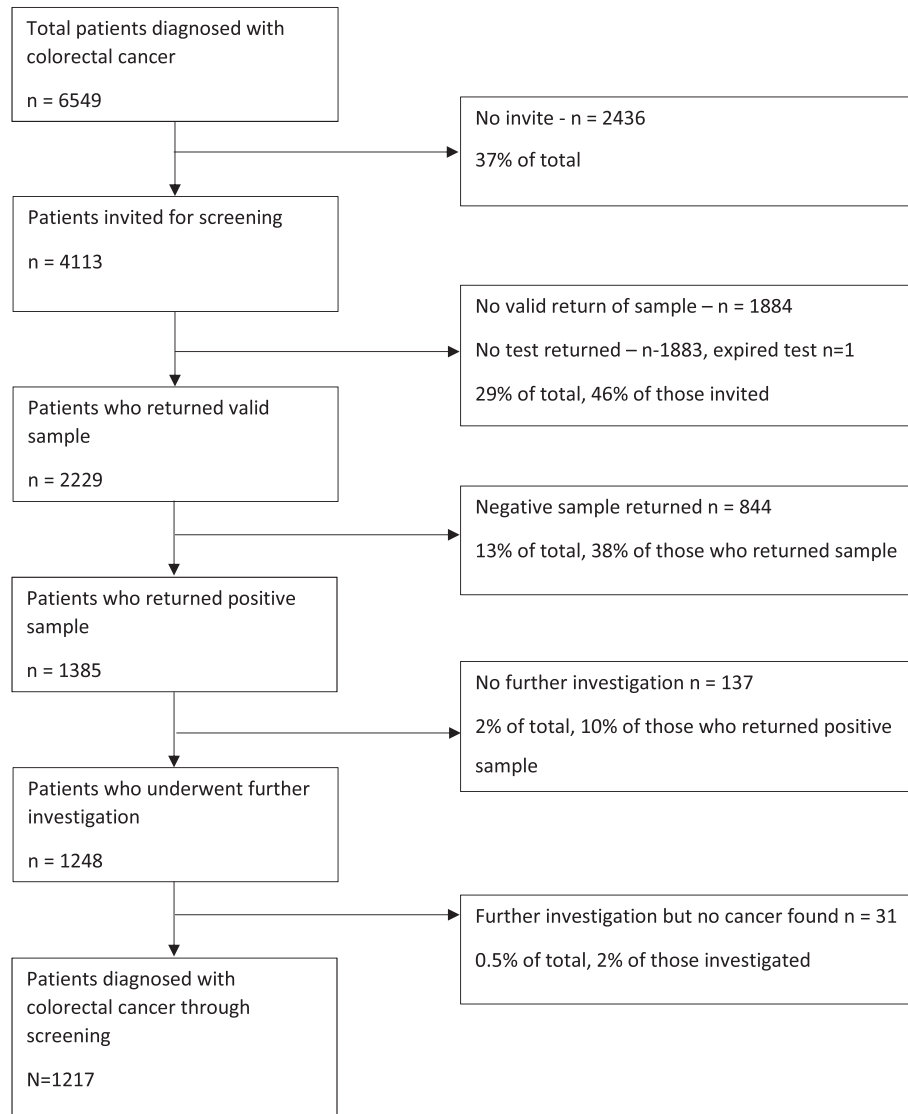
Fig. 1. Patient involvement with Bowel Cancer Screening Programme within the screening round immediately before colorectal cancer diagnosis.

Charlson score) and non-smokers (all $P \leq 0.001$). Of tumour factors, patients diagnosed through screening had less advanced, well-moderately differentiated tumours without extramural venous invasion (all $P < 0.001$). Right-sided tumours were less likely to be diagnosed through screening ($P < 0.001$). Those patients diagnosed through screening were more likely to undergo elective procedures with resectional surgery (both $P < 0.001$). Diagnosis through screening was associated with a significantly improved 3-year overall (86% vs 51%, $P < 0.001$) and CSS (90% vs 58%, $P < 0.001$) (Fig. 2).

Of the 6549 patients diagnosed with colorectal cancer during the study period, 37% ($n = 2436$) had not been invited to participate in screening. As shown in Table 2, of those patients not invited, 14% ($n = 350$) were below the age threshold for screening of whom 79% were aged between 40 and 49 years ($n = 277$). Eighty-four percent of patients ($n = 2035$) were above the upper limit of routine invitation to screening. When patient age was categorised by decade, 27%, 64% and 9% were aged 75−79, 80−89 and 90+ years, respectively. The reason for non-invitation to screening of the remaining 51 patients (2%) was uncertain.

Of 4113 patients invited to participate in the bowel cancer screening programme, 46% ($n = 1884$) of patients failed to return a valid stool sample. One patient returned a screening test; however, the sample container had expired and the remaining 1883 patients failed to return a test. The association between clinicopathological factors and return versus non-return of the screening test is shown in Table 3. Patients aged between 65 and 74 years ($P < 0.001$), female patients ($P < 0.001$), patients of a higher socio-economic status ($P < 0.001$), patients with a less comorbid status as measured by both ASA and Charlson score ($P < 0.001/0.030$, respectively), non-smokers ($P < 0.001$) and patients with an increased BMI ($P = 0.007$) were more likely to return a screening test. No significant association was seen between ethnicity and non-return of screening test ($P = 0.574$).

Of the 2229 patients who returned a valid stool sample, 38% ($n = 844$) returned a negative sample. The association between clinicopathological factors and screening test result is shown in Table 4. Female sex ($P < 0.001$), BMI <30 kg/m^2 ($P = 0.002$), increased comorbidity as measured by Charlson Score ($P = 0.002$), preoperative anaemia ($P < 0.001$), poorly differentiated tumours, extramural venous invasion ($P = 0.001$), right-sided cancers

Table 1

Association between screening diagnosis and tumour stage, mode of presentation, treatment type and survival.

| Variable	All patients	Non-screening diagnosis	Screening diagnosis	P-value
Total	**6549**	**5332 (81%)**	**1217 (19%)**	
Age (years)	**6549**	**5332 (81%)**	**1217 (19%)**	**<0.001**
<50	350 (5%)	350 (7%)	0 (0%)	
50−74	3943 (60%)	2727 (51%)	1216 (>99%)	
75+	2256 (34%)	2255 (42%)	1 (<1%)	
Sex	**6549**	**5332 (81%)**	**1217 (19%)**	**<0.001**
Male	3643 (56%)	2887 (54%)	756 (62%)	
Female	2906 (44%)	2445 (46%)	461 (38%)	
SIMD	**6549**	**5332 (81%)**	**1217 (19%)**	**<0.001**
1	1871 (29%)	1570 (29%)	301 (25%)	
2	1509 (23%)	1251 (24%)	258 (21%)	
3	1129 (17%)	923 (17%)	206 (17%)	
4	1004 (15%)	782 (15%)	222 (18%)	
5	1036 (16%)	806 (15%)	230 (19%)	
ASA	**4440**	**3425 (77%)**	**1015 (23%)**	**<0.001**
1	474 (11%)	330 (10%)	144 (14%)	
2	2342 (53%)	1706 (50%)	636 (63%)	
3	1395 (31%)	1171 (34%)	224 (22%)	
4	223 (5%)	213 (6%)	10 (1%)	
5	6 (<1%)	5 (<1%)	1 (<1%)	
Smoking	**3523**	**2724 (77%)**	**799 (23%)**	**0.001**
Non-smoker	1638 (47%)	1256 (46%)	382 (48%)	
Ex-smoker	1353 (38%)	1025 (38%)	328 (41%)	
Smoker	532 (15%)	443 (16%)	89 (11%)	
BMI (kg/m^2)	**2498**	**1874 (75%)**	**624 (25%)**	**<0.001**
<18.5	58 (2%)	51 (3%)	7 (1%)	
18.5−24.9	795 (32%)	644 (34%)	151 (24%)	
25−29.9	897 (36%)	679 (36%)	218 (35%)	
30−34.9	492 (20%)	337 (18%)	155 (25%)	
35+	256 (10%)	163 (9%)	93 (15%)	
Charlson score	**2657**	**1990 (75%)**	**667 (25%)**	**<0.001**
0	1561 (59%)	1104 (56%)	457 (69%)	
1	737 (28%)	572 (29%)	165 (25%)	
2	289 (11%)	255 (13%)	34 (5%)	
3+	70 (3%)	59 (3%)	11 (2%)	
Ethnicity	**3341**	**2688 (81%)**	**653 (20%)**	**0.655**
White British	3283 (98%)	2640 (98%)	643 (99%)	
Other	58 (2%)	48 (2%)	10 (2%)	
Preoperative anaemia	**3051**	**2377 (78%)**	**674 (22%)**	**<0.001**
None	1701 (56%)	1168 (49%)	533 (79%)	
Mild	761 (25%)	654 (28%)	107 (16%)	
Severe	589 (19%)	555 (23%)	34 (5%)	
Differentiation	**5740**	**4564 (80%)**	**1176 (21%)**	**<0.001**
Well-mod	4688 (82%)	3664 (80%)	1024 (87%)	
Poor	1052 (18%)	900 (20%)	152 (13%)	
EMVI	**4350**	**3325 (76%)**	**1025 (24%)**	**<0.001**
Negative	2579 (59%)	1856 (56%)	723 (71%)	
Positive	1771 (41%)	1469 (44%)	302 (30%)	
Tumour site	**6549**	**5332 (81%)**	**1217 (19%)**	**0.450**
Colon	4611 (70%)	3765 (71%)	846 (70%)	
Rectal	1938 (30%)	1567 (29%)	371 (31%)	
Colon tumour side	**4524**	**3684 (81%)**	**840 (19%)**	**<0.001**
Right	2363 (52%)	2038 (55%)	325 (39%)	
Left	2161 (48%)	1646 (45%)	515 (61%)	
Screening test type	**2229**	**1012 (45%)**	**1217 (55%)**	**<0.001**
gFOBT	1188 (53%)	822 (81%)	366 (30%)	
FIT	1041 (47%)	190 (19%)	851 (70%)	
TNM	**5402**	**4268 (79%)**	**1134 (21%)**	**<0.001**
I	1195 (22%)	732 (17%)	463 (41%)	
II	1575 (29%)	1281 (30%)	294 (26%)	
III	1598 (30%)	1284 (30%)	314 (28%)	
IV	1034 (19%)	971 (23%)	63 (6%)	
Unknown				
Metastatic at presentation	**6382**	**5175 (81%)**	**1207 (19%)**	**<0.001**
No	5002 (78%)	3877 (75%)	1125 (93%)	
Yes	1380 (22%)	1298 (25%)	82 (7%)	
Mode of presentation	**5193**	**4033 (78%)**	**1160 (22%)**	**<0.001**
Elective	4307 (83%)	3161 (78%)	1146 (99%)	
Emergency	886 (17%)	872 (22%)	14 (1%)	
Type of procedure	**6542**	**5325 (81%)**	**1217 (19%)**	**<0.001**
No procedure	1516 (23%)	1452 (27%)	64 (5%)	
Bypass/stent/defunctioning surgery	358 (6%)	345 (7%)	13 (1%)	
Local resection	337 (5%)	199 (4%)	138 (11%)	
Formal resection	4331 (66%)	3329 (63%)	1002 (82%)	
3-year survival (all patients)	**6549**	**5332**	**1217**	
OS	58% (SE 1%)	51% (SE 1%)	86% (SE 1%)	<0.001
CSS	64% (SE 1%)	58% (SE 1%)	90% (SE 1%)	<0.001
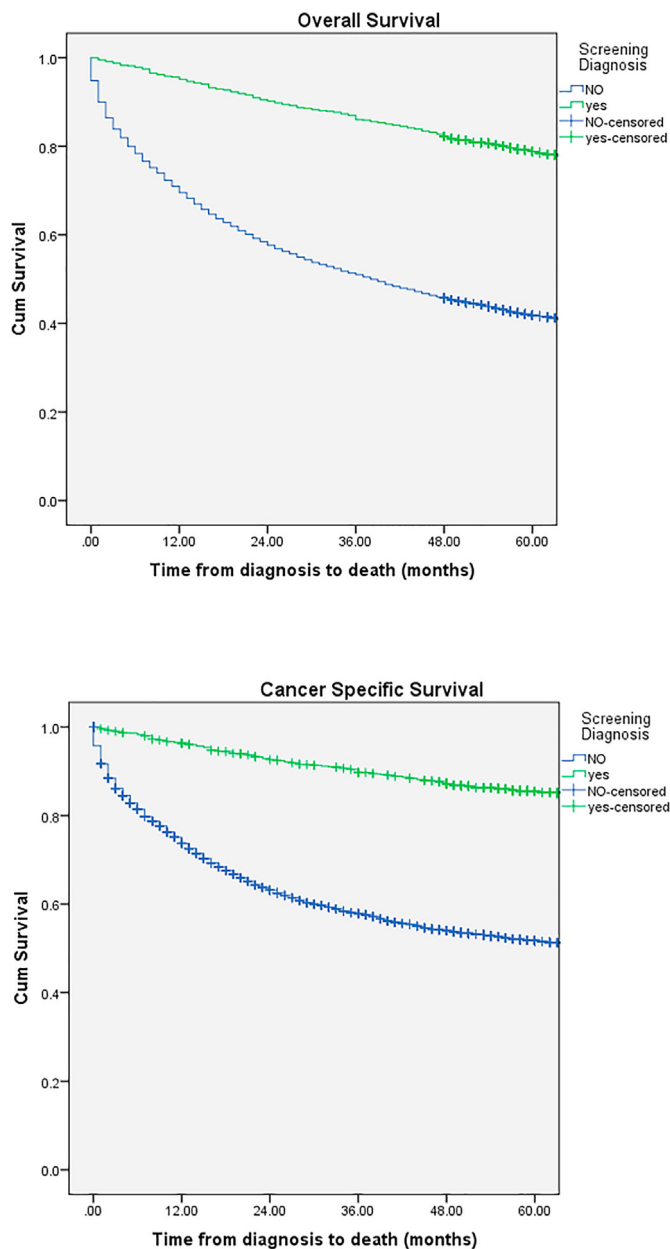
Fig. 2. Kaplan-Meier chart for survival stratified by type of diagnosis (screening vs non-screening) — (a) overall survival and (b) cancer-specific survival.

($P < 0.001$) and patients screened using gFOBT ($P < 0.001$) were associated with negative screening results.

Of the 1385 patients who had a positive screening test, 90% underwent further investigation. Of the 10% of patients ($n = 137$)

Table 2
Characteristics of patients not invited to participate in screening ($n = 2436$).

Total number of patients	**2436**
Below screening age (<50 years)	**351**
18–29	24 (7%)
30–39	49 (14%)
40–49	277 (79%)
Above screening age (75+ years)	**2035**
75–79	543 (27%)
80–89	1311 (64%)
90+	181 (9%)
Unknown	**51**

who did not undergo further investigation, the reason for this could not be established in 51 patients. As shown in Table 4, for the remaining 86 patients, this was either a patient decision (44%, $n = 38$), patient did not attend (21%, $n = 18$), patient already under endoscopic surveillance (19%, $n = 16$), clinician decision (15%, $n = 13$) or the patient died while waiting for further investigation (1%, $n = 1$).

Thirty-one patients (2%) had a negative colonoscopy after a positive screening test. Colonoscopies were complete in 20 patients, incomplete in three patients and results not available for the remaining eight patients.

Discussion

The results of the present study show that during the study period, only 19% of colorectal cancer in the West of Scotland was diagnosed through screening, and 50% of patients invited to screening fully participated in the screening process. Patients diagnosed through the bowel cancer screening programme were more likely to present electively with early-stage (TNM Stage I-II) disease and undergo curative resectional surgery with significantly better oncological outcomes than patients diagnosed outwith screening.

The present results show that despite the current stool-based bowel cancer screening programme being simple, safe and non-invasive, engagement with screening within the West of Scotland remains poor. Uptake to screening within Scotland is similar to that in England and Wales as reported in the National Bowel Cancer Audit 2020 — 60% and 57%, respectively.[19] However, within the present study, a higher proportion of patients were diagnosed through the Bowel Screening Programme than reported within the National Bowel Cancer Audit 2020 within England and Wales (19% vs 10%) likely due to the wider age range eligible for screening within Scotland compared to England and Wales (50–74 vs 60–74 years). Nonetheless, the proportion of patients diagnosed with colorectal cancer at TNM Stage I-II remains far short of the 75% target set within the NHS Long Term Plan;[20] therefore, optimisation of services are required to meet this target. Within the present study, one in five patients had metastatic disease at the time of diagnosis and of those with full TNM staging, 50% of patients had TNM Stage III-IV disease. The incidence of colorectal cancer (currently 1.9 million cases each year globally) has been predicted double over the next 10–20 years.[21] A significant survival advantage was seen in patients diagnosed through screening (3-year CSS — 90% vs 58%, $P < 0.001$). Optimisation of the screening service remains perhaps the most promising way of improving outcomes in patients with colorectal cancer.

Although traditionally considered a disease of high HDI (Human Development Index) nations, likely due to dietary and lifestyle factors, the incidence of colorectal cancer in low HDI countries has more recently been reported to be increasing, likely due to Western lifestyle changes. Meanwhile, within some high HDI countries, the incidence has been reported to be decreasing, in part due to the introduction of screening programmes aimed not just at diagnosing colorectal cancer at an early malignant stage but also within the premalignant polyp phase.[22] Outcomes have been reported to be significantly worse in low compared to high HDI nations. This is, amongst other factors the result of limited access to healthcare and late stage at diagnosis (in part due to the absence of screening programmes).[23] As summarized in a recent review, the implementation of screening programmes within low HDI nations undoubtedly carries additional challenges;[24] however, remains an opportunity to increase the proportion of patients diagnosed at early stage with improved oncological outcomes, particularly where access to adjuvant/palliative chemotherapy may be limited.

Table 3
Association between clinicopathological characteristics and return vs non-return of screening sample in patients invited to screening ($n = 4113$).

Clinicopathological factor	Missing	Total n (%)	Returned screening test n (%)	Non-return of screening test n (%)	P-value
Total	**0**	**4113**	**2230 (54%)**	**1883 (46%)**	
Age (years)	**0**	**4113**	**2230 (54%)**	**1883 (46%)**	**<0.001**
<65		1604 (39%)	859 (39%)	745 (40%)	
65–74		2026 (49%)	1155 (52%)	871 (46%)	
75+		483 (10%)	216 (10%)	267 (14%)	
Sex	**0**	**4113**	**2230 (54%)**	**1883 (46%)**	**<0.001**
Male		2422 (59%)	1252 (56%)	1170 (62%)	
Female		1691 (41%)	978 (44%)	713 (38%)	
SIMD	**0**	**4113**	**2230 (54%)**	**1883 (46%)**	**<0.001**
1		1207 (29%)	559 (25%)	648 (34%)	
2		948 (23%)	474 (21%)	474 (25%)	
3		685 (17%)	371 (17%)	314 (17%)	
4		630 (15%)	390 (18%)	240 (13%)	
5		643 (16%)	436 (20%)	207 (11%)	
ASA	**1024**	**3089**	**1784 (58%)**	**1305 (42%)**	**<0.001**
1		348 (11%)	234 (13%)	114 (9%)	
2		1752 (57%)	1090 (61%)	662 (51%)	
3		884 (29%)	434 (24%)	450 (35%)	
4		101 (3%)	25 (1%)	76 (6%)	
5		4 (<1%)	1 (<1%)	3 (<1%)	
Smoking	**1696**	**2417**	**1413 (59%)**	**1004 (42%)**	**<0.001**
Non-smoker		1085 (45%)	670 (47%)	415 (41%)	
Ex-smoker		913 (38%)	568 (40%)	345 (34%)	
Smoker		419 (17%)	175 (12%)	244 (24%)	
BMI (kg/m^2)	**2304**	**1809**	**1093 (60%)**	**716 (40%)**	**0.007**
<18.5		33 (2%)	13 (1%)	20 (3%)	
18.5–24.9		521 (29%)	293 (27%)	228 (32%)	
25–29.9		655 (36%)	401 (37%)	254 (36%)	
30–34.9		378 (21%)	242 (22%)	136 (19%)	
35+		222 (12%)	144 (13%)	78 (11%)	
Charlson score	**2292**	**1821**	**1108 (61%)**	**713 (39%)**	**0.030**
0		1157 (64%)	729 (66%)	428 (60%)	
1		459 (25%)	271 (25%)	188 (26%)	
2		166 (9%)	86 (8%)	80 (11%)	
3+		39 (2%)	22 (2%)	17 (2%)	
Ethnicity	**1990**	**2123**	**1196 (56%)**	**927 (44%)**	**0.574**
White British		2090 (98%)	1179 (99%)	911 (98%)	
Other		33 (2%)	17 (1%)	16 (2%)	

Furthermore, although the establishment of such programmes will increase the burden on endoscopy services, increased detection and management of premalignant polyps may reduce the number of people requiring resectional surgery ± adjuvant therapy. The present findings are therefore applicable to both high and low HDI nations.

In 1966, Wilson and Jungner described multiple factors that must be considered when establishing a screening service, both in terms of the health condition screened for and the population in whom to screen.[25] Many of these factors lie outwith the scope of this study. Nonetheless, within the present study, 351 patients (5%) were diagnosed with colorectal cancer below screening age of whom 79% were aged 40–49 years. It has been reported that an increasing number of younger people (age <50 years) are developing colorectal cancer,[26,27] often with poorer outcomes and it would therefore seem reasonable to consider lowering the minimum age for screening within Scotland. Indeed, several sources including the American Cancer Society[28] and the US Preventative Services Task Force[29] advocate the inclusion of patients aged between either 45–50 or 40–50 years into bowel cancer screening. Furthermore, a large proportion of patients diagnosed with bowel cancer were above the upper age limit for the routine invitation to screening although these patients were still eligible to request screening tests. As described by Nee and colleagues,[30] the inclusion of older people within screening is more complex and the benefits of screening depend on several factors including comorbid and functional status. Within the present study, fewer than 10% of patients over 75 years returned a screening sample. Despite this, a

large proportion of these patients subsequently underwent curative resectional surgery and it therefore seems reasonable that older individuals in good health should be encouraged to continue to participate in screening.

Within the present study, non-return of screening sample was a major factor precluding screening diagnosis — fewer than 55% of patients invited for screening returned a screening sample and this remains below international guidelines.[10] The reason for non-engagement in screening is likely to be multifactorial. Although the precise reason for non-engagement requires more detailed qualitative investigation, the present study described several factors associated with non-return of screening test in particular: older age, male sex, less affluent socio-economic status, current smokers, patients with a low-normal BMI and patients with an increased comorbid status. Prior research has investigated factors influencing return versus non-return of bowel screening samples and factors including: lower educational achievement, lower socio-economic status, fear of cancer diagnosis, reluctance to handle faecal samples and a lack of knowledge regarding the benefits of early asymptomatic detection were reasons for non-engagement with screening.[31–35] It is of interest that this association with socio-economic status remains within the free at point of care National Health Service. The effect of sex on screening participation remains unclear. Although the present results show that females are more likely to engage with screening, a previous review by Mosquera and colleagues[36] reported significant variation between studies and offered several hypotheses for the discrepancies observed. Despite screening aiming to identify colorectal cancer

Table 4
Association between clinicopathological factors and screening test result in those who returned valid screening test ($n = 2229$).

Clinicopathological factor	Missing	Total	Negative screening test n (%)	Positive screening test n (%)	*P*-value
Total		**2229**	**844 (38%)**	**1385 (62%)**	
Age (years)	**0**	**2229**	**844 (38%)**	**1385 (62%)**	**0.147**
<65		859 (39%)	304 (36%)	555 (40%)	
65–74		1154 (52%)	452 (54%)	702 (51%)	
75+		216 (10%)	88 (10%)	128 (9%)	
Sex	**0**	**2229**	**844 (38%)**	**1385 (62%)**	**<0.001**
Male		1251 (56%)	402 (48%)	849 (61%)	
Female		978 (44%)	442 (52%)	536 (39%)	
SIMD	**0**	**2229**	**844 (38%)**	**1385 (62%)**	**0.764**
1		558 (25%)	208 (25%)	350 (25%)	
2		474 (21%)	175 (21%)	299 (22%)	
3		371 (17%)	147 (17%)	224 (16%)	
4		390 (18%)	141 (17%)	249 (18%)	
5		436 (20%)	173 (21%)	263 (19%)	
ASA	**445**	**1784**	**644 (36%)**	**1140 (64%)**	**0.336**
1		234 (13%)	80 (12%)	80 (12%)	
2		1090 (61%)	381 (59%)	381 (59%)	
3		434 (24%)	174 (27%)	174 (27%)	
4		25 (1%)	9 (1%)	9 (1%)	
5		1 (<1%)	0	0	
Smoking	**817**	**1412**	**520 (37%)**	**892 (63%)**	**0.408**
Non-smoker		669 (47%)	246 (47%)	423 (47%)	
Ex-smoker		568 (40%)	202 (39%)	366 (41%)	
Smoker		175 (12%)	72 (14%)	103 (12%)	
BMI (kg/m^2)	**1137**	**1092**	**390 (36%)**	**702 (64%)**	**0.002**
<18.5		13 (1%)	6 (2%)	7 (1%)	
18.5–24.9		293 (27%)	118 (30%)	175 (25%)	
25–29.9		400 (37%)	159 (41%)	241 (34%)	
30–34.9		242 (22%)	69 (18%)	173 (25%)	
35+		144 (13%)	38 (10%)	106 (15%)	
Charlson score	**1121**	**1108**	**372 (34%)**	**736 (66%)**	**0.002**
0		729 (66%)	228 (61%)	501 (68%)	
1		271 (25%)	91 (25%)	180 (25%)	
2		86 (8%)	45 (12%)	41 (6%)	
3+		22 (2%)	8 (2%)	14 (2%)	
Preoperative anaemia	**1038**	**1198**	**442 (37%)**	**756 (63%)**	**<0.001**
None		858 (72%)	276 (62%)	582 (77%)	
Mild		230 (19%)	104 (24%)	126 (17%)	
Severe		110 (9%)	62 (14%)	48 (6%)	
Differentiation	**19**	**2110**	**778 (37%)**	**1332 (63%)**	**<0.001**
Mod/well		1764 (84%)	604 (78%)	1160 (87%)	
Poor		346 (16%)	174 (22%)	172 (13%)	
EMVI	**441**	**1788**	**633 (35%)**	**1155 (65%)**	**0.001**
Negative		1189 (67%)	388 (61%)	801 (69%)	
Positive		599 (34%)	245 (39%)	354 (31%)	
Tumour site (for colon cancer)	**701**	**1528**	**580 (38%)**	**948 (62%)**	**<0.001**
Right		733 (48%)	359 (62%)	374 (40%)	
Left		795 (52%)	221 (38%)	574 (61%)	
Screening test type	**0**	**2229**	**844 (38%)**	**1385 (62%)**	**<0.001**
gFOBT		1188 (53%)	748 (89%)	440 (32%)	
FIT		1041 (47%)	96 (11%)	945 (68%)	

within the asymptomatic population, there have been reports of a public perception that screening is only required if symptoms are experienced.[37] It seems likely that improved education may increase the participation rate with screening and prior research is supportive of this hypothesis.[38] The Scottish Bowel Screening Programme has recently transitioned from using gFOBT (requiring two stool samples on three separate occasions) to FIT (requiring a single stool sample). This may result in an increased uptake to screening although this effect is likely to be modest.[39] Further measures are required to encourage patient participation, and these should be targeted at particular groups including those of increased socio-economic deprivation. However, there is potential to significantly improve screening uptake across the entire population and measures should not be restricted to such individuals. A recent study summarised barriers and facilitators to screening[40] and addressing these factors with measures including reminder letters and improved education is likely to improve screening participation.

The present results show that a significant proportion of screening tests returned within 2 years before colorectal cancer diagnosis were negative. Although some of these may represent true-negative tests (and therefore true interval cancers), it seems likely that the majority of these are false-negative results. It is recognised that gFOBT (used as the first-line investigation in the era of the present study) is less sensitive than FIT (first-line investigation since 2017), particularly in right-sided disease.[41,42] Therefore, it would be of interest to repeat the present study in the screening via FIT era. One would expect the false-negative rate to be significantly lower in such a study. Unlike Scotland, countries including Germany and the USA use periodic endoscopic evaluation in addition to stool sampling within their screening programmes. Should false-negative rates remain high within a population who had previously underwent screening via FIT such periodic endoscopic evaluation may be worth considering or a reduction in the abnormal threshold level of FIT used for screening. Within the present results, poorly differentiated tumours and extramural

venous invasion were associated with cancers diagnosed outwith of bowel screening. This is likely to be due to the increased proportion of right-sided cancers and more advanced diseases within these patients.

Data, predominantly from the USA, have described an association between ethnic minority status and reduced likelihood of participation within screening. Owing to the healthcare system in the USA, socio-economic deprivation may be a confounding factor in these studies; therefore, the routine to diagnosis of colorectal cancer across ethnicities was of interest in the free at point of care health service in Scotland. However, because of the small proportion of patients who were non-white British, it was not possible to accurately analyse this. Ninety-two percent of the Scottish population in the 2011 census identified as white British. It has been shown that colorectal cancer is less common within several ethnic minority groups;[43] however, it is unclear whether this is sufficient to explain the lower proportion of patients diagnosed with colorectal cancer within this study. Notably, there was a significant quantity of missing ethnicity data raising the possibility of reporting bias particularly as a recent study within Scotland did find lower screening uptake within ethnic minority populations.[44] Nonetheless, because of the small proportion of patients of ethnic minority status, the present study is likely underpowered to reliably make the comparison between ethnic minority status and screening involvement before cancer diagnosis.

The present study has several limitations. The cohort of patients included within the present study were from an era where gFOBT was used as the first-line screening test. Scotland has now transitioned from gFOBT to FIT although many countries worldwide still use gFOBT for screening. Although it would be of interest to repeat such a study in patients screened using FIT, the results of the present study remain applicable to current practice. However, there is likely to be a smaller proportion of 'false-negative' screening tests and potentially an improved uptake of screening as a result of this transition. Within the present study, we have analysed the results of the screening round within 2 years before diagnosis of colorectal cancer. In our comparison of factors associated with negative screening test results, negative results have been assumed to be 'false-negatives'. Bowel screening aims to detect not just carcinomas but additionally advanced polyps. Given the duration of the adenoma-carcinoma sequence, this assumption is likely to be predominantly correct; however, it is impossible to know which of these tests were false-negative results and which were true interval cancers. Given the association seen between screening test result and the type of test used (gFOBT/FIT), this would be in keeping with this assumption as FIT has been widely reported to have a higher sensitivity than gFOBT. However, given that the majority of patients who received a FIT test had a prior borderline gFOBT as opposed to being randomly allocated either FOBT or FIT, this assumption may be biased.

In conclusion, the present study shows that colorectal cancer diagnosed through screening is associated with improved oncological outcomes; however, less than one in five cases of colorectal cancer within the West of Scotland were diagnosed through screening. Thirty-seven percent of patients were not invited for screening, predominantly those above the age for routine invitation (75+ years) or within the 40—49 years age group. Twenty-nine percent of patients had not returned a screening sample, in particular: males, patients with increased socio-economic deprivation or more comorbid patients. Thirteen percent of patients had returned a negative screening sample (likely false negative) within 2 years before diagnosis, in particular: females, patients with a BMI < 30 kg/m^2, patients with anaemia, right-sided tumours, patients who had a gFOBT test and patients with poorly differentiated

tumours or tumours with extramural venous invasion. Further measures are required to educate the population about the benefits of screening to increase engagement with the screening process and to encourage patients aged 75+ years who are in otherwise good health to continue to participate in screening. Consideration should be given to extending screening to individuals aged between 40 and 50 years. Finally, further analysis should be carried out within a FIT (as opposed to gFOBT) screening cohort to determine whether the false-negative rate remains high.

Author statements

Competing interests

No conflicts of interest to declare.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**(6):394—424.
2. Bakker IS, Grossmann I, Henneman D, Havenga K, Wiggers T. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. *Br J Surg* 2014;**101**(4):424—32. discussion 32.
3. Kodeda K, Nathanaelsson L, Jung B, Olsson H, Jestin P, Sjovall A, et al. Population-based data from the Swedish Colon Cancer Registry. *Br J Surg* 2013;**100**(8):1100—7.
4. McArdle CS, Hole DJ. Emergency presentation of colorectal cancer is associated with poor 5-year survival. *Br J Surg* 2004;**91**(5):605—9.
5. Askari A, Nachiappan S, Currie A, Bottle A, Abercrombie J, Athanasiou T, et al. Who requires emergency surgery for colorectal cancer and can national screening programmes reduce this need? *Int J Surg* 2017;**42**:60—8.
6. Navarro M, Nicolas A, Ferrandez A, Lanas A. Colorectal cancer population screening programs worldwide in 2016: an update. *World J Gastroenterol* 2017;**23**(20):3632—42.
7. Ferlizza E, Solmi R, Sgarzi M, Ricciardiello L, Lauriola M. The roadmap of colorectal cancer screening. *Cancers (Basel)* 2021;**13**(5).
8. Issa IA, Noureddine M. Colorectal cancer screening: an updated review of the available options. *World J Gastroenterol* 2017;**23**(28):5086—96.
9. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol* 2008;**103**(6):1541—9.
10. von Karsa L, Patnick J, Segnan N. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition–Executive summary. *Endoscopy* 2012;**44**(Suppl 3):SE1—8.
11. Lo SH, Halloran S, Snowball J, Seaman H, Wardle J, von Wagner C. Colorectal cancer screening uptake over three biennial invitation rounds in the English bowel cancer screening programme. *Gut* 2015;**64**(2):282—91.
12. Wardle J, von Wagner C, Kralj-Hans I, Halloran SP, Smith SG, McGregor LM, et al. Effects of evidence-based strategies to reduce the socioeconomic gradient of uptake in the English NHS Bowel Cancer Screening Programme (ASCEND): four cluster-randomised controlled trials. *Lancet* 2016;**387**(10020):751—9.
13. Mansouri D, McMillan DC, Crearie C, Morrison DS, Crighton EM, Horgan PG. Temporal trends in mode, site and stage of presentation with the introduction of colorectal cancer screening: a decade of experience from the West of Scotland. *Br J Cancer* 2015;**113**(3):556—61.
14. Division) IIS. *Scottish bowel screening programme key performance indicators report: invitations between 1 November 2015 and 31 October 2017*. 2018. Available from: http://www.isdscotland.org.
15. Roxburgh CS, McTaggart F, Balsitis M, Diament RH. Impact of the bowel-screening programme on the diagnosis of colorectal cancer in Ayrshire and Arran. *Colorectal Dis* 2013;**15**(1):34—41.
16. Scholefield JH, Robinson MH, Mangham CM, Hardcastle JD. Screening for colorectal cancer reduces emergency admissions. *Eur J Surg Oncol* 1998;**24**(1):47—50.

17. Government S. *Scottih index of multiple deprivation 2020*. 2020. Available from: https://www.gov.scot/collections/scottish-index-of-multiple-deprivation-2020/.
18. Armitage JN, van der Meulen JH, Royal College of Surgeons Co-morbidity Consensus G. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. *Br J Surg* 2010;**97**(5):772–81.
19. Partnership HQI. *National bowel cancer audit annual report 2020*. 2020. Available from: https://www.nboca.org.uk/content/uploads/2020/12/NBOCA-2020-Annual-Report.pdf.
20. Service NH. *The NHS long term plan*. 2019. Available from: https://www.longtermplan.nhs.uk/.
21. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**(3): 209–49.
22. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;**66**(4):683–91.
23. Gullickson C, Goodman M, Joko-Fru YW, Gnangnon FHR, N'Da G, Woldegeorgis MA, et al. Colorectal cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: a population-based registry study. *Int J Cancer* 2021;**149**(8):1553–63.
24. Schliemann D, Ramanathan K, Matovu N, O'Neill C, Kee F, Su TT, et al. The implementation of colorectal cancer screening interventions in low-and middle-income countries: a scoping review. *BMC Cancer* 2021;**21**(1):1125.
25. Organisation WH. *The principles and practice of screening for disease*. 1966.
26. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal cancer incidence patterns in the United States, 1974–2013. *J Natl Cancer Inst* 2017;**109**(8).
27. Araghi M, Soerjomataram I, Bardot A, Ferlay J, Cabasag CJ, Morrison DS, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. *Lancet Gastroenterol Hepatol* 2019;**4**(7):511–8.
28. Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin* 2018;**68**(4):250–81.
29. Stewart DB. Updated USPSTF guidelines for colorectal cancer screening: the earlier the better. *JAMA Surg* 2021;**156**(8):708–9.
30. Nee J, Chippendale RZ, Feuerstein JD. Screening for colon cancer in older adults: risks, benefits, and when to stop. *Mayo Clin Proc* 2020;**95**(1):184–96.
31. Soleimani-Nouri P, Ashburner N, Ali L. Education provision in community setting increases engagement with bowel cancer screening. *Educ Prim Care* 2021;**32**(6):366–9.

32. Smith SG, McGregor LM, Raine R, Wardle J, von Wagner C, Robb KA. Inequalities in cancer screening participation: examining differences in perceived benefits and barriers. *Psychooncology* 2016;**25**(10):1168–74.
33. Kobayashi LC, Wardle J, von Wagner C. Limited health literacy is a barrier to colorectal cancer screening in England: evidence from the English Longitudinal Study of Ageing. *Prev Med* 2014;**61**:100–5.
34. Palmer CK, Thomas MC, von Wagner C, Raine R. Reasons for non-uptake and subsequent participation in the NHS Bowel Cancer Screening Programme: a qualitative study. *Br J Cancer* 2014;**110**(7):1705–11.
35. de Klerk CM, Gupta S, Dekker E, Essink-Bot ML. Expert Working Group 'Coalition to reduce inequities in colorectal cancer screening' of the World Endoscopy O. Socioeconomic and ethnic inequities within organised colorectal cancer screening programmes worldwide. *Gut* 2018;**67**(4):679–87.
36. Mosquera I, Mendizabal N, Martin U, Bacigalupe A, Aldasoro E, Portillo I, et al. Inequalities in participation in colorectal cancer screening programmes: a systematic review. *Eur J Public Health* 2020;**30**(3):416–25.
37. Varlow M, Stacey I, Dunlop S, Young J, Kite J, Dessaix A, et al. Self-reported participation and beliefs about bowel cancer screening in New South Wales, Australia. *Health Promot J Austr* 2014;**25**(2):97–103.
38. Durkin S, Broun K, Guerin N, Morley B, Wakefield M. Impact of a mass media campaign on participation in the Australian bowel cancer screening program. *J Med Screen* 2020;**27**(1):18–24.
39. Moss S, Mathews C, Day TJ, Smith S, Seaman HE, Snowball J, et al. Increased uptake and improved outcomes of bowel cancer screening with a faecal immunochemical test: results from a pilot study within the national screening programme in England. *Gut* 2017;**66**(9):1631–44.
40. Dressler J, Johnsen AT, Madsen LJ, Rasmussen M, Jorgensen LN. Factors affecting patient adherence to publicly funded colorectal cancer screening programmes: a systematic review. *Public Health* 2021;**190**:67–74.
41. Logan RF, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C, et al. Outcomes of the bowel cancer screening programme (BCSP) in England after the first 1 million tests. *Gut* 2012;**61**(10):1439–46.
42. Gill MD, Bramble MG, Rees CJ, Lee TJ, Bradburn DM, Mills SJ. Comparison of screen-detected and interval colorectal cancers in the bowel cancer screening programme. *Br J Cancer* 2012;**107**(3):417–21.
43. Sawicki T, Ruszkowska M, Danielewicz A, Niedzwiedzka E, Arlukowicz T, Przybylowicz KE. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. *Cancers (Basel)* 2021;**13**(9).
44. Campbell C, Douglas A, Williams L, Cezard G, Brewster DH, Buchanan D, et al. Are there ethnic and religious variations in uptake of bowel cancer screening? A retrospective cohort study among 1.7 million people in Scotland. *BMJ Open* 2020;**10**(10):e037011.