Colorectal Cancer: Advances in Prevention and Early Detection
Colorectal Cancer: Advances in Prevention and Early Detection

Guest Editors: Anne Miles, Fränzel van Duijnhoven, Amy McQueen, and Raymond Oliphant
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Colorectal cancer (CRC) is currently the fourth leading cause of cancer death worldwide. While mortality rates are in decline in most westernised countries, global estimates predict that CRC incidence rates and the overall number of CRC-related deaths are set to rise by 77% and 80%, respectively, by 2030. The development of CRC is multifactorial, and risk factors include various lifestyle, genetic, and environmental factors. It has been estimated that at least half of CRC cases could be prevented by a reduction in known modifiable lifestyle-related risk factors. Further reductions in CRC incidence and mortality can be achieved through screening, but the uptake of screening varies across different sectors of the population. This special issue comprises articles highlighting issues in the prevention, early diagnosis, and treatment of CRC.

J. Sovich et al. provide a comprehensive review of the effectiveness and adoption of existing technologies for CRC screening. They review stool-based, endoscopic, radiological, and serum-based methods for screening, discussing both commonly used methods, such as gFOBT and colonoscopy, and newly emerging ones, such as faecal DNA testing, capsule endoscopy, and serum-based tests. Colonoscopy remains the gold standard, but the authors highlight improvements in the sensitivity of the newer stool-based tests (FIT and faecal DNA tests) and raise the important point that "the best test is often the one that patients will do."

J. Krok-Schoen et al. report the results of a randomised trial aimed at increasing CRC screening among adults living in Ohio Appalachia, an area with higher than average rates of both CRC incidence and mortality. The intervention comprised both a media campaign (billboards, posters, and newspaper articles) and a clinic intervention (brochures and posters). Randomisation was performed at the county level, with counties stratified by the proportion of people with late-stage diagnosis. The communication-focused intervention was not effective in promoting the uptake of screening, and the authors suggest that while such strategies may increase knowledge and awareness of screening, additional interventions or resources may be needed to change behaviour.

B. White et al. not only compared multiple interventions to increase stool blood test uptake in a national screening program but also examined multiple moderators of intervention effects to assess what is needed by whom. Only the combined intervention group (endorsement flyer plus kit enhancement plus community advertisements) significantly increased screening rates compared with controls for all participants, whereas all other significant intervention effects were conditional on other factors. More resources may be needed to increase screening uptake among people not previously screened, aged 70 and older, and living in economically deprived areas. Future research could examine the mediators of intervention effects in these population subgroups to reveal the mechanisms by which the interventions work and how they might be further enhanced. For example, all the interventions tested involved health communication approaches; however, individuals living in more deprived areas may need increasingly personal and novel interventions to compete with the cognitive demands of scarcity (see [1]).
S. H. Lo et al. explored potential pathways of influence on CRC screening uptake in a national screening program to better understand the processes that may influence behavior. Specifically, they explored factors that may explain sociodemographic differences in screening behavior. Their cross-sectional results support future research to confirm cognitive determinants such as knowledge, perceived barriers to screening, and social norms as mediators of the effects of sociodemographic predictors on screening uptake. Elucidating the mechanisms and interrelations between known determinants of screening behavior will enable improved message development and intervention design to increase screening rates and decrease disparities across sociodemographic subgroups.

A. Anderson et al. investigated the awareness of lifestyle risk factors associated with CRC in patients who had been diagnosed with a colorectal adenoma through a colorectal screening program in Scotland, UK. Their study shows that the knowledge of relevant CRC risk factors was low in people at increased risk of the disease. The authors suggest exploring opportunities within routine CRC screening settings to raise awareness about lifestyle and prevention and to provide further guidance and personalised support to enhance the translation of improved knowledge into effective behavioural changes to reduce CRC risk.

C. Mojica et al. present the results of a large population-based study examining the relationship between population characteristics, English proficiency, and the diagnosis of advanced CRC in California, USA. This cancer registry based study found that late-stage CRC diagnosis was higher in areas with a greater proportion of recent immigrants and those of limited financial means. However, it suggests that amongst Hispanic groups a lower proportion of English proficiency was associated with lower odds of advanced disease. This interesting original paper highlights the complexity of the relationship between the patient, socioeconomic and neighborhood characteristics, and CRC risk.

L. A. Siminoff et al. examine the patient and medical correlates of a missed diagnostic opportunity (MDO) among patients diagnosed with CRC in Virginia and Ohio, USA. Patients had experienced symptoms prior to diagnosis and were not diagnosed through routine screening. This study involved the review of patient medical records and found that a third of patients with symptoms presumptive of CRC experienced a delay in the diagnostic process for CRC. An MDO was more likely to occur among patients under 50 years of age, women, and patients who had seen a greater number of physicians. In addition to reminders and educational interventions for patients and providers about CRC and screening options, future applications of electronic medical records may reduce MDOs through systematic symptom recording and analysis.

M. Hav et al. present a comprehensive review of the prognostic implications in the pathological assessment of rectal cancer after treatment with chemoradiotherapy. The review highlights many of the challenges encountered in the interpretation and prediction of outcome after surgical resection in patients who have already undergone neoadjuvant therapy. The authors emphasize the importance of careful specimen handling in addition to accurate microscopic pathological assessment to achieve optimal prognostication in this group of patients and highlight several key areas of note.

In conclusion, CRC remains a significant health problem across the world. This special issue highlights the contribution different disciplines can make towards tackling CRC, through developments in screening technologies and treatment and understanding and encouraging lifestyle changes and participation in screening, as well as determining those at risk from late-stage at diagnosis. Innovations in methods of diagnosis and treatment can make vital contributions to CRC incidence and mortality; however, more research is needed to reduce disparities in access to and uptake of the best screening, diagnostic, and treatment methods that are available.

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Amy McQueen
Raymond Oliphant

References

Research Article

Piloting the Impact of Three Interventions on Guaiac Faecal Occult Blood Test Uptake within the NHS Bowel Cancer Screening Programme

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This study evaluated the impact of three interventions on uptake of the guaiac faecal occult blood test (gFOBT) in Greater London. The interventions were designed to improve awareness and understanding of the NHS Bowel Cancer Screening Programme (BCSP) and assist stool sampling. Logistic regression analysis of BCSP London data (N = 205,541 invitees aged 60–74) compared uptake at 12 weeks between intervention groups and a control group, sent kits as usual between January-April 2013 and January-April 2014. An endorsement flyer, included with gFOBT kits, had no impact on uptake (P = 0.68). In 60–69-year-olds, there was a small but significant increase in modelled uptake amongst invitees sent both the flyer and a kit enhancement pack compared with controls (45.1% versus 43.4%, OR = 1.07, P = 0.047). In North East London, the flyer together with outdoor advertising was associated with a small but significant increase (45.6% versus 43.4%, OR = 1.09, P = 0.027). The largest increases were seen when all three interventions (flyer, pack, and advertising) were combined (49.5% versus 43.4%, OR = 1.28, P < 0.001). The increased uptake in the intervention groups was largest in "first-timers" and smaller amongst previous nonresponders and previously screened invitees.

1. Introduction

The NHS Bowel Cancer Screening Programme (BCSP) invites eligible adults aged 60–74 in England to complete a guaiac-based faecal occult blood test (gFOBT) every two years. The English programme was launched in 2006 for 60–69-year-olds and has since been extended to 70–74-year-olds. Initial randomised controlled trials found a reduction in mortality risk from bowel cancer using gFOBT screening [1–4], with a systematic review of these trials finding a 15% relative risk reduction in bowel cancer mortality in studies using biennial screening [5]. It has been predicted that the biennial gFOBT bowel cancer screening programme could save 1,800 to 2,400 lives each year by 2025 in England [6].

Overall, gFOBT screening uptake in the NHS BCSP is around 54% [7], which is lower than the English NHS cervical screening and breast cancer screening programmes [8, 9]. Uptake is lower amongst more socially deprived invitees, unmarried invitees, and males and in more ethnically diverse areas [7, 10–12]. Uptake is much higher amongst invitees who have been adequately screened before [13]. Overall, research suggests that uptake increases with age, although there are discrepancies, with some studies reporting no association [10] and others reporting lower uptake amongst younger invitees [12], higher uptake with age in males [7], or a peak in uptake at 64–66 years [13].

Relatively few interventions designed to improve uptake of gFOBT screening have been conducted in the UK [14], although there has been some success using endorsement letters and additional information leaflets [15–17]. Hewitson et al. found that a GP endorsement letter and an enhanced screening information leaflet (providing further detail about how to complete the kit) each increased uptake of gFOBT
by approximately 6 percentage points and had an additive impact on uptake when trialled together [15].

Commonly reported barriers centre on the procedure required to complete the test, for example, distaste and embarrassment around sampling and storing faecal samples, concerns about completing the test at home rather than in a formal health setting, and misunderstanding the instructions [14, 18–21]. Published research into the effectiveness of providing practical aids in the stool sampling process is limited. A faeces collection paper aiming to address discomfort with the sampling process has been tested in the Netherlands [22]. It was not associated with significantly increased participation in Faecal Immunochemical Test (FIT) bowel cancer screening, although the authors provided little information about the collection paper tested and did not collect any data on reported use.

Public awareness and understanding of the test are likely to be an issue for some, given the programme’s relative infancy compared to those for breast and cervical cancer and given that it is the first national screening programme for men in the UK. To our knowledge, no published studies have yet assessed the impact of a bowel screening advertising campaign on uptake in the UK. Nevertheless, the positive effects that mass media campaigns can have on health behaviours have been reported previously, including short term increases in breast and cervical cancer screening uptake in countries with organised screening services [23]. A previous study found that media coverage of the UK Flexible Sigmoidoscopy Trial was associated with a small but positive increase in early uptake of gFOBT screening, particularly among previous nonresponders [24].

This study reports the findings from a bowel cancer screening service improvement pilot that ran from January to April 2014. The project aimed to increase uptake of the NHS gFOBT in Greater London, by raising awareness of the programme and reducing key barriers to completion. The project trialled different combinations of three interventions, which attempted to increase awareness and understanding about screening, build on the previous success of GP endorsement, and address practical issues people may have with the test.

2. Materials and Methods

2.1. Setting. The pilot was delivered by Cancer Research UK (CRUK), who worked with NHS England (London region), Public Health England, the Department of Health, and the English NHS Bowel Cancer Screening Programme (BCSP). It targeted men and women aged 60–74 years in Greater London, who were due to receive their kit from the BCSP during the study period.

The BCSP sends all eligible men and women an invitation to participate in bowel screening, which also includes an information leaflet about bowel cancer and the screening process. It then sends a second letter one to two weeks later, containing the cardboard gFOBT kit, cardboard sticks, instructions for completing the kits, and a prepaid return envelope. Invites are instructed to collect two small faecal samples each from three separate bowel motions, to spread onto six different windows on the kit.

Ethical approval was not required for this study, as it was an evaluation of a service improvement pilot.

2.2. Design. Different combinations of the following three interventions were trialled: a CRUK endorsement flyer, “kit enhancement packs,” and an outdoor advertising campaign. These interventions are described in more detail below.

Table 1 illustrates how different combinations of the interventions were piloted in different intervention groups. Intervention groups A and B were trialled across all of Greater London (including North East London), whilst groups C and D were trialled in North East London only, alongside the advertising campaign that was simultaneously conducted in North East London. Differences in uptake between intervention groups A and B and C and D could partly be due to particular characteristics of the North East London population that are known to affect bowel screening uptake. These characteristics include ethnicity and/or marital status [10, 11], which we were unable to account for in the logistic regression analysis, and therefore any comparisons of uptake between different intervention groups must be made cautiously.

2.3. Interventions

2.3.1. CRUK Endorsement Flyer. An A5 flyer (Supplementary Figure 1 in Supplementary Material available online at http://dx.doi.org/10.1155/2015/928251) was included with the routine gFOBT kit mailings from the London BCSP Hub, which administers the bowel cancer screening programme regionally. The flyer was designed to increase understanding and encourage people to consider completing the test by emphasising its effectiveness, privacy, and ease of use and providing information about how many other people complete screening in London. The flyer also provided an endorsement of screening by CRUK and a reminder that participation in the programme was the recipient’s own choice. Printing costs for this intervention were minimal, and there was no extra postage cost as they were included in the routine gFOBT kit mailings.

2.3.2. “Kit Enhancement Packs”. Packs (Supplementary Figure 2) included latex-free gloves and “poo catchers,” which slip over the toilet seat and are designed to make sample collection easier. Three sets of each were included in each pack, one for each stool sample required for the gFOBT screening kit, and “poo catchers” came with simple, visual instructions. The packs were distributed through the London BCSP Hub two days after the gFOBT kits had been mailed. Feedback about the packs from focus group testing commissioned by CRUK indicated that people would value both the gloves and “poo catchers.” Plus, participants who tested the “poo catcher” said it was easy to use, with one saying it was “much better than hunting around for some sort of vessel.” The production costs were £1.53 per pack (including gloves and “poo catcher”).

2.3.3. Outdoor Advertising Campaign. Advertisements (Supplementary Figure 3) were placed at bus stops, on pharmacy bags, on digital screens (“Amscreens”) in GP practices, and in
Table 1: Total sample of invitees in each intervention group and number included in the final multivariate logistic regression models.

<table>
<thead>
<tr>
<th>Intervention group</th>
<th>Dates invited (control group)/dates kits sent (interventions)</th>
<th>Total sample of invitees aged 60–74 years (before exclusions)</th>
<th>Number of invitees aged 60–69 years (after exclusions)</th>
<th>Number of invitees aged 70–74 years (after exclusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>4th January–5th April 2013, 4th January–5th April 2014 (excluding trialled interventions)</td>
<td>187,554</td>
<td>145,427</td>
<td>31,959</td>
</tr>
<tr>
<td>Greater London interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A) CRUK endorsement flyer only</td>
<td>27th January–4th February 2014</td>
<td>10,286</td>
<td>8,093</td>
<td>1,609</td>
</tr>
<tr>
<td>(B) CRUK endorsement flyer, plus kit enhancement pack</td>
<td>5th February–11th February 2014</td>
<td>9,096</td>
<td>7,148</td>
<td>1,475</td>
</tr>
<tr>
<td>North East London interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C) CRUK endorsement flyer, plus advertising campaign</td>
<td>24th February–13th March 2014</td>
<td>5,121</td>
<td>4,332</td>
<td>466</td>
</tr>
<tr>
<td>(D) CRUK endorsement flyer, plus kit enhancement pack and advertising campaign</td>
<td>24th March–14th April 2014</td>
<td>5,297</td>
<td>3,980</td>
<td>1,052</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>217,354</td>
<td>168,980</td>
<td>36,561</td>
</tr>
</tbody>
</table>

Local press. The advertisements were developed using insights from a range of sources, including the Department of Health’s Healthy Foundations Segmentation Model [25], previous campaigns, and input from the target audience. The creative design featured people chosen to reflect local demographic characteristics and emphasised the effectiveness of screening with the headline “this little kit saves lives from bowel cancer” and byline “the test can detect invisible early signs of bowel cancer” plus an additional banner highlighting ease of use “it’s easier than you think.” The cost of placing the advertisements was £150,000 in total, although costs vary depending on various factors, such as the time of year and location.

2.4. Measures. Anonymised data were provided by the BCSP for all men and women invited for bowel cancer screening in Greater London from 4th January 2013 to 5th April 2013 and 4th January 2014 to 5th April 2014. Data included the date that each recipient was invited, the date they were subsequently sent a gFOBT kit, the date that participants initially returned their first kit, the date they returned subsequent kits if required (e.g., if the original kit was spoilt or yielded a weak positive result), and the date that they were adequately screened (if at all). A recipient was defined as adequately screened if they reached a definitive gFOBT outcome of either “normal” or “abnormal” within 12 weeks from the date they were sent an invitation.

An area-level measure of socioeconomic deprivation of the invitee (Index of Multiple Deprivation (IMD) score [26]) was included as a continuous variable, where a low IMD score (e.g., 10) denoted a lower level of deprivation and a high score (e.g., 60) denoted a higher level of deprivation. Previous screening status split all invitees into one of three categories: those who had not been invited to bowel screening before (“first-timers”), those who had been invited before and been adequately screened at least once (previously screened), and those who had been invited before and never been adequately screened (previous nonresponders). Gender and age at invitation were also included. Each invitee’s designated intervention group was included (A: endorsement flyer, B: endorsement flyer and enhancement pack, C: endorsement flyer and advertising, and D: endorsement flyer, enhancement pack, and advertising).

2.5. Data Analysis. Analysis aimed to determine whether the interventions were associated with a significant increase in gFOBT uptake at 12 weeks after the invitation date, compared to controls, whilst controlling for other factors known to affect uptake. A secondary aim was to examine how the impact of the interventions varied across different demographic groups and to identify groups where the interventions appeared to have the greatest impact.

Multivariate logistic regression models were then used to model the probability of screening uptake in each intervention group compared to a predefined “control group,” whilst keeping all other variables at their mean values in the models. The control group included all those eligible for bowel cancer screening across London who were invited to complete a gFOBT from 4th January to 5th April 2013 or from 4th January to 5th April 2014 and who did not receive an intervention (and also were not excluded under any of the criteria below). Models controlled for other variables that were available and known to affect uptake, including gender, age, previous screening status, and deprivation. In order to control for any underlying trend in daily uptake across both
four-month periods studied and over the two years, the date that each invitee was sent their gFOBT kit was also included as a discrete noncategorical variable.

The logistic regression models were then used to explore differences in the size of each intervention’s impact on uptake in different invitee groups (i.e., in different previous screening status groups, at various deprivation levels, and in males and females). We compared the difference in predicted uptake probabilities between each intervention group and controls in one invitee group (e.g., first-timers) to the difference in predicted uptake probabilities between each intervention group and controls in another group (e.g., previous nonresponders).

2.6. Data Validation and Exclusions. Eighteen invitees were excluded because their screening records contained inconsistent data. An additional 11,795 invitees were excluded from analysis because the invitee’s age at invitation was under 60 or over 74 years, they were missing an IMD score, or they were sent an invitation but not later sent a kit (i.e., the date the kit was sent was missing). The reasons for not being sent a kit include the invitee opting out of that screening episode out of choice or by notifying the London BCSP Hub of a significant medical condition (including cancer), the invitation being recorded as returned mail, the invitee’s relocation outside the catchment area of the Hub, or their death. Therefore, uptake was calculated as the percentage of those sent kits that were adequately screened within 12 weeks, in order to better isolate the impact of the interventions. Uptake figures are therefore not directly comparable with figures published by BCSP.

2.7. Model Development and Sensitivity Analysis. Initial inspection of the data showed that different relationships between previous screening status, age, and uptake were apparent for 60–69-year-olds and 70–74-year-olds. Uptake amongst invitees included in the final analysis increases with age until 70 years (including a slight levelling off between 66 and 69 years), after which uptake decreases. The percentage of invitees at each age that have been previously screened follows a similar pattern, increasing with age until 70 years and subsequently decreasing. This was most likely because the 70–74 age extension was not yet well established in all areas of London. Therefore, subsequent analyses were carried out separately for these two age groups, and the majority of the analysis focused on 60–69-year-olds, as we predicted that the relationships in the older age group would be likely to change as the age extension becomes better established in London.

Invitees from North East London sent their kits in 2014 could have been exposed to the advertising campaign, despite being in the control group or being in intervention group A or B. For example, an invitee in intervention group A in North East London who was sent their kit on 3rd February 2014 could have delayed returning their kit until after the advertising campaign began in North East London on 24th February, and then seen the advertising, and returned their kit in time to be adequately screened within 12 weeks of their invitation.

A sensitivity analysis was conducted to examine the effect of accounting for this contamination using different methods. A contamination variable was subsequently included in the final analysis, to adjust for the possible impact of “contaminated” records on uptake in the control group, intervention A, and intervention B. This method used the full sample available for each intervention group, whilst allowing the effect of contamination to vary between contaminated records from the control group, intervention group A, and intervention group B.

The final model included an interaction term between previous screening status and age, as these factors, and their effect on uptake, were already known to be closely related [13]. Previous models identified other interactions between predictor variables. The overall impact of the interventions on uptake was similar in these models, although in some versions of the model for 60–69-year-olds uptake amongst intervention group C was not significantly different from controls.

One model, which was not chosen as the final model, included an interaction between intervention group and previous screening status. This model showed that the impact of intervention B was smaller in first-timers (interaction term; OR = 0.82, \( P = 0.011 \)) and previous nonresponders (interaction term; OR = 0.76, \( P = 0.001 \)) than in previously screened invitees, whilst the impact of D was also smaller in first-timers (interaction term; OR = 0.80, \( P = 0.016 \)) than in previously screened invitees (data not shown). These results are not consistent with the final model, and therefore results in this paper suggesting that the impact was greater in first-timers should be viewed with some caution.

3. Results

3.1. Impact of Interventions

3.1.1. Greater London. Screening uptake amongst intervention group A (the CRUK endorsement flyer alone) was not associated with an increase in gFOBT uptake at 12 weeks compared to controls, in either age group (60–69 years: 43.0% versus 43.4%, OR = 0.99, \( P = 0.68 \); 70–74 years: 45.1% versus 46.7%, OR = 0.94, \( P = 0.381 \)) (Tables 2, 3, and 4). Modelled uptake amongst intervention group B (the CRUK endorsement flyer plus kit enhancement pack) was significantly higher (45.1%) than controls (43.4%) (OR = 1.07, \( P = 0.047 \)), amongst 60–69-year-olds, but there was no difference observed in 70–74-year-olds (OR = 1.03, \( P = 0.739 \)).

3.1.2. North East London. Modelled uptake amongst intervention group C (the CRUK endorsement flyer plus advertising) was significantly higher (45.6%) than controls (43.4%) in 60–69-year-olds (OR = 1.09, \( P = 0.027 \)), but not in 70–74-year-olds (OR = 0.88, \( P = 0.318 \)).

Intervention group D (the CRUK endorsement flyer plus the kit enhancement pack and advertising) was associated with the largest increases in modelled uptake compared to controls, in both age groups (60–69 years: 49.5% versus 43.4%, OR = 1.28, \( P < 0.001 \); 70–74 years: 53.9% versus 46.7%, OR = 1.34, \( P = 0.001 \)). Intervention group D was the only intervention in 70–74-year-olds with significantly higher uptake compared to controls.

3.2. Covariates. Multivariate analysis accounted for the effects of other variables known to be associated with uptake
Table 2: Multivariate logistic regression model for gFOBT uptake amongst 60–69-year-olds (n = 168,980).

<table>
<thead>
<tr>
<th>Adequately screened at 12 weeks</th>
<th>Odds ratio</th>
<th>P value</th>
<th>95% lower confidence limit</th>
<th>95% upper confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group (reference = control group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.99</td>
<td>0.680</td>
<td>0.92</td>
<td>1.05</td>
</tr>
<tr>
<td>B</td>
<td>1.07</td>
<td>0.047</td>
<td>1.00</td>
<td>1.15</td>
</tr>
<tr>
<td>C</td>
<td>1.09</td>
<td>0.027</td>
<td>1.01</td>
<td>1.18</td>
</tr>
<tr>
<td>D</td>
<td>1.28</td>
<td>&lt;0.001</td>
<td>1.18</td>
<td>1.39</td>
</tr>
<tr>
<td>Contamination variable (reference = uncontaminated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contaminated-control</td>
<td>1.09</td>
<td>0.006</td>
<td>1.03</td>
<td>1.17</td>
</tr>
<tr>
<td>Contaminated-A</td>
<td>1.26</td>
<td>0.001</td>
<td>1.10</td>
<td>1.44</td>
</tr>
<tr>
<td>Contaminated-B</td>
<td>1.29</td>
<td>0.001</td>
<td>1.11</td>
<td>1.51</td>
</tr>
<tr>
<td>Age at invitation (reference = 60 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous screening status (reference = previously screened)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-timers</td>
<td>0.17</td>
<td>&lt;0.001</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>0.05</td>
<td>&lt;0.001</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Interaction term: previous screening status × age at invitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-timers</td>
<td>0.94</td>
<td>&lt;0.001</td>
<td>0.92</td>
<td>0.96</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>0.91</td>
<td>&lt;0.001</td>
<td>0.90</td>
<td>0.93</td>
</tr>
<tr>
<td>IMD score</td>
<td>0.98</td>
<td>&lt;0.001</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>Gender (reference 0 = female, 1 = male)</td>
<td>0.83</td>
<td>&lt;0.001</td>
<td>0.81</td>
<td>0.85</td>
</tr>
<tr>
<td>Date the kit was sent (days)</td>
<td>0.9997</td>
<td>&lt;0.001</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Constant</td>
<td>5653.54</td>
<td>&lt;0.001</td>
<td>1369.18</td>
<td>23344.31</td>
</tr>
</tbody>
</table>

In 60–69-year-olds, uptake was substantially lower amongst people who were being invited to screening for the first time (“first-timers,” OR = 0.17, P < 0.001) compared to those who had been successfully screened at least once before (“previously screened”). Odds of uptake were lower still amongst those who had been invited before but had not yet been screened successfully (“previous nonresponders,” OR = 0.05, P < 0.001), compared to previously screened invitees (Table 2). The model showed that the relationship between age at invitation and uptake was different in first-timers (OR = 0.94, P < 0.001) and previous nonresponders (OR = 0.91, P < 0.001), compared with previously screened invitees. Consistent with previous studies, there were decreasing odds of uptake with increasing deprivation (IMD score, OR = 0.98, P < 0.001). These patterns were also present in 70–74-year-olds (Table 3).

In 60–69-year-olds, odds of uptake were significantly higher amongst “contaminated” invitees in the control group (OR = 1.09, P = 0.006), intervention A (OR = 1.26, P = 0.001), and intervention B (OR = 1.29, P = 0.001) who could have been exposed to advertising, compared to uncontaminated invitees (Table 2). Although contamination was not a significant predictor of uptake in 70–74-year-olds, the variable was also included in this model to account for this design limitation in a consistent way.

The date that each invitee was sent their gFOBT kit was included in the model as a discrete noncategorical variable, to control for any underlying trend in uptake across both four-month periods studied and over the two years. This showed that there was also a decrease in the odds of uptake each day amongst both 60–69-year-olds (OR = 0.9997, P < 0.001) and 70–74-year-olds (OR = 0.9996, P < 0.001).

3.3. Variation in Impact of Interventions by Invitee Characteristics. Further analysis showed that the impact of the intervention groups on gFOBT uptake varied depending on the invitees’ previous screening status. For example, keeping other characteristics (i.e., age, deprivation, gender, and date the kit was sent) constant, in 60–69-year-old first-timers, modelled uptake was 39.4% in intervention group D and 33.7% in controls (Table 4). In 60–69-year-olds who were previously screened, uptake was 83.0% in intervention group D and 79.3% in controls, whilst in previous nonresponders it was 15.4% and 12.5%, respectively. This equates to a larger
Table 3: Multivariate logistic regression model for gFOBT uptake amongst 70–74-year-olds (n = 36,561).

<table>
<thead>
<tr>
<th>Adequately screened at 12 weeks</th>
<th>Odds ratio</th>
<th>P value</th>
<th>95% lower confidence limit</th>
<th>95% upper confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group (reference = control group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.94</td>
<td>0.381</td>
<td>0.81</td>
<td>1.08</td>
</tr>
<tr>
<td>B</td>
<td>1.03</td>
<td>0.739</td>
<td>0.89</td>
<td>1.19</td>
</tr>
<tr>
<td>C</td>
<td>0.88</td>
<td>0.318</td>
<td>0.69</td>
<td>1.13</td>
</tr>
<tr>
<td>D</td>
<td>1.34</td>
<td>0.001</td>
<td>1.13</td>
<td>1.59</td>
</tr>
<tr>
<td>Contamination variable (reference = uncontaminated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contaminated-control</td>
<td>1.03</td>
<td>0.806</td>
<td>0.84</td>
<td>1.26</td>
</tr>
<tr>
<td>Contaminated-A</td>
<td>1.08</td>
<td>0.725</td>
<td>0.72</td>
<td>1.61</td>
</tr>
<tr>
<td>Contaminated-B</td>
<td>1.03</td>
<td>0.906</td>
<td>0.64</td>
<td>1.67</td>
</tr>
<tr>
<td>Age at invitation (reference = 70 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-timers</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td>0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Interaction term: previous screening status × age at invitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-timers</td>
<td>1.12</td>
<td>0.018</td>
<td>1.02</td>
<td>1.24</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>1.24</td>
<td>&lt;0.001</td>
<td>1.19</td>
<td>1.29</td>
</tr>
<tr>
<td>IMD score</td>
<td>0.99</td>
<td>&lt;0.001</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>Date the kit was sent (days)</td>
<td>0.9996</td>
<td>&lt;0.001</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Constant</td>
<td>11733.30</td>
<td>&lt;0.001</td>
<td>484.95</td>
<td>283884.90</td>
</tr>
</tbody>
</table>

(5.7%) absolute increase in uptake between intervention group D and controls within first-timers, compared to previously screened invitees (3.8%) and previous nonresponders (3.0%). Similar patterns were identified in 70–74-year-olds (Table 4).

The impact of the interventions also varied with the deprivation level of the invitee. Table 5 shows modelled uptake for selected IMD score points, from 10 to 60 (the majority of invitees included in the model had IMD scores that fell within this range). Keeping other characteristics constant, in less deprived 60–69-year-olds (i.e., those who had an IMD score of 10), modelled uptake was 54.8% in intervention group D, compared to 48.6% in controls (Table 5). In contrast, in more deprived 60–69-year-olds (i.e., IMD score of 60), uptake was 35.7% in intervention group D, compared to 30.2% in controls. This equates to a larger (6.2%) absolute increase in uptake between intervention group D and controls amongst less deprived invitees, compared to the increase amongst more deprived invitees (5.5%). Similar patterns were identified in 70–74-year-olds (Table 5).

In 60–69-year-olds, there was little variation in the impact of the interventions between males and females. Gender was not included in the final analysis of 70–74-year-olds, as it was not a significant predictor of uptake in this age group.

4. Discussion

Results indicate that a combination of mailed interventions together (CRUK endorsement flyer and kit enhancement pack) was associated with an increase in uptake that was small but significantly higher than for controls, among adults invited for bowel cancer screening across London. In North East London, the combination of these mailed items together with advertising in the local area had a substantial impact. The size of the impact varied considerably by previous screening status and deprivation.

In Greater London, the CRUK endorsement flyer alone (intervention group A) did not significantly increase uptake. This contrasts with findings by Hewitson et al., which showed that an endorsement from a GP in the form of a separate letter sent with gFOBT kits was associated with a 6 percentage point increase in uptake compared with controls [15]. Both the CRUK flyer in this study and the materials in the study by Hewitson et al. were sent together with NHS gFOBT kits, suggesting that although Cancer Research UK is a well known charity, it could be that a letter from someone's own GP provides a stronger endorsement. Further research could investigate whether endorsement from an organisation such as Cancer Research UK has more impact if sent separately from the gFOBT kits.
Table 4: Modelled absolute and relative differences in gFOBT uptake across the intervention groups overall and within different previous screening status groups.

<table>
<thead>
<tr>
<th>Previous screening status</th>
<th>(1) Analysis of 60–69-year-olds</th>
<th>(2) Analysis of 70–74-year-olds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
<td>(A) CRUK endorsement flyer only</td>
</tr>
<tr>
<td></td>
<td>(n = 145,427)</td>
<td>(n = 8,093)</td>
</tr>
<tr>
<td>Overall</td>
<td>43.4%</td>
<td>43.0%</td>
</tr>
<tr>
<td>Previously screened</td>
<td>79.3%</td>
<td>80.4%</td>
</tr>
<tr>
<td>First-timers</td>
<td>33.7%</td>
<td>35.3%</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>12.5%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Predicted probability of uptake in each intervention group and control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>43.4%</td>
<td>45.1%</td>
</tr>
<tr>
<td>Previously screened</td>
<td>79.3%</td>
<td>80.7%</td>
</tr>
<tr>
<td>First-timers</td>
<td>33.7%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>12.5%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Absolute difference in modelled uptake in each significant intervention group, compared to control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>43.4%</td>
<td>+1.7%</td>
</tr>
<tr>
<td>Previously screened</td>
<td>79.3%</td>
<td>+1.4%</td>
</tr>
<tr>
<td>First-timers</td>
<td>33.7%</td>
<td>+2.0%</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>12.5%</td>
<td>+0.8%</td>
</tr>
<tr>
<td>Relative difference in modelled uptake in each significant intervention group, compared to control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>43.4%</td>
<td>+4.0%</td>
</tr>
<tr>
<td>Previously screened</td>
<td>79.3%</td>
<td>+1.4%</td>
</tr>
<tr>
<td>First-timers</td>
<td>33.7%</td>
<td>+5.9%</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>12.5%</td>
<td>+6.3%</td>
</tr>
</tbody>
</table>

Data shows the predicted probability of uptake using multivariate logistic regression models, after accounting for other factors known to affect uptake. Data shown for separate analyses of (1) 60–69-year-olds and (2) 70–74-year-olds.

i Absolute and relative differences may not exactly equal differences in modelled uptake due to rounding.

ii Differences are not shown for intervention groups that were not statistically significant overall.
### Table 5: Modelled absolute and relative differences in gFOBT uptake across the intervention groups, at selected IMD scores (levels of deprivation).

<table>
<thead>
<tr>
<th>IMD score (deprivation level)</th>
<th>(1) Analysis of 60–69-year-olds</th>
<th>(2) Analysis of 70–74-year-olds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
<td>(A) CRUK endorsement flyer only</td>
</tr>
<tr>
<td></td>
<td>(n = 145,427)</td>
<td>(n = 8,093)</td>
</tr>
<tr>
<td>10—lower deprivation</td>
<td>48.6%</td>
<td>50.3%</td>
</tr>
<tr>
<td>20</td>
<td>44.7%</td>
<td>46.4%</td>
</tr>
<tr>
<td>30</td>
<td>40.9%</td>
<td>42.6%</td>
</tr>
<tr>
<td>40</td>
<td>37.2%</td>
<td>38.8%</td>
</tr>
<tr>
<td>50</td>
<td>33.6%</td>
<td>35.2%</td>
</tr>
<tr>
<td>60—higher deprivation</td>
<td>30.2%</td>
<td>31.7%</td>
</tr>
<tr>
<td>Predicted probability of uptake in each intervention group and control group</td>
<td>48.6%</td>
<td>50.3%</td>
</tr>
<tr>
<td>Absolute difference in modelled uptake in each significant intervention group, compared to control group</td>
<td>44.7%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Relative difference in modelled uptake in each significant intervention group, compared to control group</td>
<td>40.9%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Data shows the predicted probability of uptake using multivariate logistic regression models, after accounting for other factors known to affect uptake.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute and relative differences may not exactly equal differences in modelled uptake due to rounding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differences are not shown for intervention groups that were not statistically significant overall.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adding the kit enhancement pack to the endorsement flyer (intervention group B) was associated with a significant, if small, increase in uptake compared to controls in 60–69-year-olds (45.1% versus 43.4%). As the flyer alone did not affect uptake, this suggests that the enhancement pack may have helped reduce barriers to completing the gFOBT kits. This contrasts with a previous study in the Netherlands that found that a faeces collection paper sent with Faecal Immunochemical Test (FIT) kits was not associated with significantly increased participation in bowel cancer screening [22]. However, the kit enhancement packs in this pilot were sent as a separate mailing (two days after the gFOBT kits were sent), so it is possible that this effect was a result of the additional communication acting as a reminder. Future research could further explore the individual impact of the enhancement pack on uptake and relative impact of the gloves or “poo catchers.”

In North East London, the CRUK endorsement flyer and advertising campaign were associated with significantly higher uptake (45.6%) compared to controls (43.4%) when trialled together (intervention group C). To our knowledge, this is the first study to assess the impact of an advertising campaign that aimed to improve uptake of gFOBT in the UK, although findings support those of a previous study that identified an association between media activity around the publication of the UK Flexible Sigmoidoscopy Trial and increased early uptake of gFOBT [24]. It would be interesting to see the impact of an advertising campaign in isolation and extend the follow-up period to assess longevity.

The addition of the kit enhancement pack to the CRUK endorsement flyer and advertising (intervention group D) was associated with the largest increases in uptake compared to controls, in both age groups (60–69 years: 49.5% versus 43.4%; 70–74 years: 53.9% versus 46.7%). This suggests that the kit enhancement packs had an additive effect, possibly by further helping to reduce barriers to completing screening and/or appealing to a different set of invitees. This is in line with evidence suggesting that multichannel interventions tend to be more effective than those using just one approach [23].

The impact of the interventions varied depending on previous screening status, with intervention group D having the largest impact in first-timers amongst both 60–69-year-olds and 70–74-year-olds. This is encouraging, because previous studies have shown that completing screening once is a strong predictor of future participation, with 86.6% of those who complete screening once, participating in the next round [13]. These results should be viewed with some caution, as an alternative model that included an interaction between intervention group and previous screening status suggested that the impact of intervention groups B and D was smaller in first-timers.

The increase in uptake in intervention group D amongst previous nonresponders, whilst smaller in absolute terms (3.0% for 60–69-year-olds), is also noteworthy given the substantially lower uptake in this group (the relative increase is 23.7%). A cohort study in the NHS BCSP Southern Hub by Lo et al. [13] confirmed that a majority (66.2%) of people invited to gFOBT screening will eventually accept the offer at least once, suggesting that repeated attempts to engage with previous nonresponders are important.

Less encouraging, however, was the finding that the interventions increased uptake by a smaller amount amongst more deprived invitees. This is disappointing, given the well-documented social gradient in uptake, and means that if rolled out, care needs to be taken to ensure that interventions do not exacerbate existing inequalities [7]. As nonresponders to screening and more deprived populations are generally less responsive to follow-up, future research could potentially use surveys and focus groups of the eligible population to further explore reasons why these interventions may appeal more or less to different demographic groups [18].

4.1. Strengths and Limitations. A strength of this study lies in the large dataset of individual level records included in the final analysis (n = 205,541), which made it possible to detect absolute differences in uptake in the magnitude of 1 to 2% and also take into account other demographic characteristics that could have confounded the effects of the intervention groups on uptake. There is considerable variation in screening uptake from week to week and year on year. The analysis included a number of covariates known to be associated with this variation (i.e., deprivation, gender, and previous screening status), as well as the date the invitee was sent their kit, in order to control for this variation.

However, it is possible that the impact of the interventions on gFOBT uptake was not statistically significant amongst 70–74-year-olds because of the smaller sample sizes in this model and a subsequent lack of power. The number of records included in the intervention groups in this model ranged from 1,609 for intervention A to 466 for intervention group C (Table 1).

Another strength comes from a relatively low proportion of cases excluded due to missing or inconsistent data (n = 11,813 or 5.4% of the original data), offering a relatively complete snapshot of uptake for the eligible population. Furthermore, interventions were trialled within the BCSP, enhancing external validity of the study.

However, some limitations of this study should be noted. As previously mentioned, it was not possible to compare the impact of interventions run across London with those run only in North East London, due to population differences that we could not account for in analysis. Some factors known to affect uptake could not be controlled for (e.g., ethnicity and marital status), because they are not routinely collected by the Bowel Cancer Screening Programme. Therefore, comparisons between interventions carried out within London (interventions A and B) and within North East London (interventions C and D) should be interpreted with caution.

As previously mentioned, some invitees from North East London in the control group and intervention groups A and B could potentially have been exposed to the advertising campaign before completing their kits. However, models included a contamination variable to account for this.

It is also not known what proportion of first-timers and previous nonresponders could have moved into the catchment area of the BCSP London Hub from another country of the UK or abroad and previously been invited
(or potentially successfully screened) at their previous residence.

To our knowledge, this was the only pilot running in the BCSP London Hub area at the time, but it is possible that there were other activities, taking place outside the Hub, which also aimed to improve uptake and could have had an impact on screening uptake and our results.

5. Conclusions

The greatest increase in gFOBT uptake at 12 weeks was seen in North East London, where all three interventions (CRUK endorsement flyer, kit enhancement pack, and advertising campaign) were combined. The CRUK endorsement letter together with the advertising campaign was also associated with a small but significant increase in uptake compared to controls in North East London. In Greater London, the CRUK endorsement letter, together with the kit enhancement pack, also had a small positive impact on uptake. However, the CRUK endorsement letter alone did not affect uptake across London.

These findings suggest that a combination of interventions designed to improve awareness and understanding of the English NHS Bowel Cancer Screening Programme, along with packs that ease the stool sampling process, are associated with increased gFOBT uptake. Future research should investigate the effectiveness of each intervention component, such as which part of the kit enhancement packs (gloves or “poo catchers”) is most effective in increasing gFOBT uptake, and attempt to identify the mechanisms through which they have an effect. However, adoption of the Faecal Immunochemical Test (FIT) by the BCSP may also address some of the practical barriers to gFOBT screening.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The authors would like to thank the staff at the NHS Bowel Cancer Screening Programme London Hub for their help with delivering the interventions and for providing individual level data and background information. They would like to acknowledge Julia Snowball from the Southern Hub for undertaking data extraction of BCSP data, as well as providing advice. They would also like to thank Public Health England, who part funded this pilot.

References


Research Article

A Media and Clinic Intervention to Increase Colorectal Cancer Screening in Ohio Appalachia

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Objective. To test the effectiveness of a colorectal cancer (CRC) screening intervention among adults living in Ohio Appalachia.

Methods. We conducted a group-randomized trial of a county-level intervention among adults living in 12 Ohio Appalachian counties who received a media campaign and clinic intervention focused on either CRC screening or fruits and vegetables. Participants’ percentage within CRC screening guidelines was assessed with cross-sectional surveys conducted annually for four years, and validated with medical record review of screening.

Results. On average, screening data were obtained on 564 intervention and 559 comparison participants per year. There was no difference in the Wave 4 CRC screening rates of intervention and comparison counties (35.2% versus 31.4%). Multivariate analyses found that high perceived risk of CRC, willingness to have a CRC test if recommended by a doctor, doctor recommendation of a CRC screening test, and patient-physician communication about changes in bowel habits, family history of CRC, and eating fruits and vegetables were significant ($p < 0.05$) predictors of being within CRC screening guidelines.

Conclusions. The intervention was not effective in increasing CRC rates among Ohio Appalachian adults. Future research should determine how media and clinic-based interventions can be modified to improve CRC screening rates among this underserved population.

1. Introduction

Colorectal cancer (CRC) is the third leading type of cancer and the second leading cause of cancer death among men and women in the United States [1]. Significant disparities in incidence, mortality, and survival rates exist among underserved populations for this disease [1–6]. Moreover, CRC screening modalities are less likely to be used regularly among underserved populations [4–6]. One underserved population that bears an excess burden of CRC is residents of Ohio Appalachia, a 32-county region in southern and eastern Ohio [6]. Rates of CRC incidence and mortality are
approximately 17% and 18% higher, respectively, among Ohio Appalachian residents compared to the average age-adjusted US population in 2005 [7, 8]. Many factors common among residents living in Ohio Appalachia may contribute to CRC disparities, particularly limited access to cancer screening, low socioeconomic status (SES), and behavioral factors (poor diet, increased tobacco use) [2, 7, 9]. Screening and early detection have the potential to significantly reduce CRC incidence and mortality [10]. Previous media campaigns about CRC screening have resulted in greater reported exposure to messages about CRC screening [11, 12], increased intention to speak to doctors about CRC screening [12], and increased CRC screening [13, 14] at a relatively low cost per person screened [14]. The goal of this study was to implement and evaluate a county-level intervention consisting of media and clinic-level components to increase CRC screening in Ohio Appalachian residents.

2. Materials and Methods

This study used a group-randomized trial design. A CONSORT diagram (Figure 1) outlines the study design. Twelve Ohio Appalachian counties were stratified into three groups (high, medium, and low) based on the average percent of late stage CRC diagnoses (obtained from the Ohio Cancer Information Surveillance System). Within each of the groups, the four counties were randomized to either the intervention or comparison condition. Details regarding the development and design of the CRC screening intervention have been previously reported [15, 16]; however, we briefly describe the intervention components below.

2.1. Study Design. The effect of the intervention program, “Get Behind Your Health! Talk to Your Doctor About Colon Cancer Screening,” on CRC screening rates was evaluated, using telephone surveys of randomly selected residents in each of the 12 counties. Surveys were conducted annually for four years over a four-month period each year (preintervention (Wave 1), postmedia only (Wave 2), postclinic intervention only (Wave 3), and postcombination media and clinic intervention (Wave 4)), with medical record review (MRR) for those who reported completing a CRC screening test to validate self-reports of CRC screening behavior (fecal occult blood test (FOBT), flexible sigmoidoscopy, or colonoscopy).

The study was powered for a mixed model ANCOVA analysis [17] based on a comparison of Wave 4 screening rates. It was estimated that a sample size of 90 participants per county was needed to achieve 80% power to detect a difference of 10% in screening rates assuming a screening rate of 32% in the comparison arm (based on Ohio BRFSS data) and an Intraclass Correlation Coefficient (ICC) of 0.0046. Based on this calculation, 6 counties were randomized to each condition (intervention and comparison) and 90 residents from each county were recruited for each survey.

2.2. Eligibility and Recruitment. The following methodology was used for each wave of data collection. Names of residents in each of the 12 Ohio Appalachian counties were randomly selected from InfoUSA County Directories. Names were sampled with replacement at each wave. Potentially eligible participants were mailed a study packet that included a recruitment letter and a study information handout outlining key elements of standard informed consent and HIPAA authorization documents. Five days after the letters were sent, trained interviewers called potential participants and described the study, addressed concerns, answered questions, and assessed eligibility. Verbal informed consent and HIPAA authorization were obtained, and then the cross-sectional survey was administered.

Participants were eligible if they (1) were men and women aged 51–75 years; (2) had a working phone number; (3) were English-speaking and able to give informed consent; (4) were a resident of one of the 12 Ohio Appalachian counties at the time of the interview; (5) had no prior history of invasive cancer (including CRC), polyps, inflammatory bowel disease, Crohn’s disease, or colitis; and (6) had no strong family history of polyps, CRC, or hereditary CRC syndromes. Participants received a $10 gift card after completing each survey as an expression of appreciation for their time. A medical record release form was also sent to each participant with a postage-paid envelope to return the completed form to the study office. Informed consent procedures and the study protocol were approved by the Institutional Review Board of The Ohio State University.

2.3. Intervention. The “Get Behind Your Health! Talk to Your Doctor About Colon Cancer Screening” intervention utilized a community-based participatory research approach to develop and pilot the CRC screening intervention. Based on results from a community assessment and in partnership with community members from Ohio Appalachia, a culturally sensitive media campaign that focused on increasing CRC screening was developed for use in the current study [15].

The intervention consisted of two main components: (1) a media campaign and (2) a clinic intervention [15, 16]. The intervention was based on health behavior theories, including the Health Belief Model (HBM) [18], the Theory of Reasoned Action (TRA) [19], Social Cognitive Theory (SCT) [20, 21], and Attitude Accessibility Theory (AAT) [22]. The theoretical constructs included in the campaign were as follows: HBM, which helped identify perceived benefits and barriers associated with CRC screening; TRA, which helped identify specific beliefs that must be reinforced or countered (e.g., community members talk about media campaigns, influencing social norms); SCT, which provided a structure for creating messages that model desirable behaviors and teach skills necessary to enact the behaviors (e.g., “Talk to your doctor about CRC screening”); and AAT, which suggested that messages should be proximal to opportunities to enact behavior for maximum impact (e.g., clinic-based reminders).

2.4. Media Campaign Intervention. The media campaign was conducted in the six intervention counties in Waves 2 and 4 of the study. The campaign in each county featured county-specific CRC survivors, individuals who had completed CRC
screening, local physicians/nurses, and community members who were selected by the local community cancer coalition. The campaign images and messages were used in all campaign materials including billboard, posters, and articles sent to local newspapers. Although the billboard information was limited (slogan and photos of community members), the posters and newspaper articles included information about CRC, CRC risk factors and symptoms, CRC screening, and the message that CRC screening saves lives [15]. The billboard and posters were placed in high volume areas near the geographic center of each county, as determined by the local community cancer coalitions.

2.5. Clinic Intervention. Clinics within the six counties randomized to receive the intervention also received an intervention that included American Cancer Society (ACS) CRC educational posters and brochures in Wave 3 through the end of Wave 4 of the study. Clinic posters and brochures provided information about the mortality rates for CRC and motivational messages such as “If you’re over 50, you need to get tested for colon cancer” and “Talk to your doctor about getting tested for colon cancer.” Local clinic managers were asked to display the ACS CRC materials in high visibility areas in waiting areas and exam rooms.

2.6. Comparison Group. The six comparison counties received a media campaign and patient education material in clinics related to healthy eating, “PEACHES” (Promoting Education in Appalachia on Cancer and Healthy Eating Styles), at the same time points the CRC screening intervention occurred in the intervention counties in Waves 2 through 4 of the study. The PEACHES campaign in each county featured local community members and farmers who were selected by the local community cancer coalition.

2.7. Study Timeline. The baseline participant recruitment began in September 2009 and was completed in April 2010. The media component of the intervention began in August 2010 and finished in July 2011. The clinic-based component of the intervention began in August 2011 and finished in July 2012. The combined intervention (i.e., media and clinic components) began in August 2012 and finished in July 2013. The final cross-sectional surveys (Wave 4) and final MRR were completed by December 2013.

2.8. Measures. The primary outcome was whether the participants were within the current U.S. Preventive Services Task Force (USPSTF) CRC screening guidelines for adults ages 50–75 (e.g., completed either an annual FOBT, a flexible sigmoidoscopy in the past five years combined with FOBT
within the past three years, or a colonoscopy in the past 10 years) [10] as determined by MRR. The main independent variable was whether each participant lived in an intervention or comparison county.

2.9. Independent Variables

2.9.1. Participant Demographic Characteristics. Participants provided information about their age, gender, race, ethnicity, marital status, education, household income, employment status, and health insurance.

2.9.2. Participant Healthcare. Participants were asked about their comorbidities, CRC screening history, regular sources of medical care, and most recent CRC test (where the test and results were obtained).

2.9.3. Perceived CRC Risk. To assess CRC risk, participants were asked “Compared to other men/women your age, what do you think your risk of getting colon cancer is in your lifetime?” Response was on a 5-point Likert scale (much lower, somewhat lower, about the same, somewhat higher, and much higher) [20]. Responses were dichotomized into high perceived risk (i.e., somewhat higher and much higher) and low perceived risk (i.e., much lower, somewhat lower, and about the same).

2.9.4. Intention to Screen. Participants were asked (yes/no) if they were willing to have a CRC screening test if recommended by their doctor, have thought about talking to their doctor about completing a CRC screening test in the next year, intended to complete a CRC screening test in the next 6 months, and asked their doctor to order a CRC screening test.

2.9.5. Participant-Reported Physician Actions regarding CRC and CRC Screening. Participants were asked (yes/no) if their doctor ever asked them about eating more fruits and vegetables, their family history of CRC, changes in bowel habits, rectal bleeding, and having a CRC screening test.

2.10. Process Evaluation. Process evaluation in Wave 2 involved a subset of participants (80 adults per county) responding to the mail-in survey asking if they had seen the campaign messages (billboards/posters used in the media campaign) during the past year. In order to ensure correct identification of campaign messages, pictures of fictitious CRC screening campaigns and similar questions addressing the sham campaign were included in the survey to serve as a control [15, 23]. Process evaluation in Wave 4 involved a subset of participants (80 adults per county) responding to a phone survey asking if they had seen the clinic-based educational materials (posters, brochures) during the past year.

2.11. Statistical Analyses. The primary outcome was being within guidelines for CRC screening at the end of each intervention period (as determined by MRR) and the time point of interest was Wave 4. Because 18% of the participants could not have their CRC screening status confirmed through a medical record, their screening status was imputed using a linear mixed model containing random county effects and fixed effects of predictors whose association with baseline screening status was significant at the 0.25 level or better as reported in Paskett et al. [16]. For each of the 50 imputed data sets, the proportion screened at Wave 1 and 4 was computed for each county. An ANCOVA model weighted by the inverse of the theoretical variance of the Wave 4 cluster means [24] was then used to compare Wave 4 screening rates between the intervention and comparison groups adjusting for Wave 1 screening rates and the results were combined across imputed data sets. As a sensitivity analysis, ANCOVA modeling was repeated for subjects whose medical record confirmed CRC screening status was observed (i.e., complete case analysis) and using self-reported CRC screening status. The same methods were used to compare intervention and comparison at Waves 2 and 3.

Linear models weighted by the number of participants in each arm at Wave 4 were used to explore the effect of the intervention on whether they talked with their doctor about family history of CRC, changes in bowel habits, rectal bleeding, and having a CRC screening test. The association between several patient/doctor interaction variables assessed at Wave 4 and CRC screening were assessed using multivariable logistic regression. Each behavior was included in a model that adjusted for county, marital status, insurance status, gender, smoking status, education, and employment. All analyses were performed using SAS v9.2 and v9.3 (SAS Institute, Cary, NC). Imputations were performed using the MMLIMPUTE SAS macro [25].

3. Results

The demographic characteristics of participants (n = 4,491) by study wave in the intervention and comparison counties are presented in Table 1.

3.1. CRC Screening Rates. The estimated screening rates by wave are presented in Figure 2. The rates presented are averages across 50 imputed data sets. Participants from intervention counties were slightly more likely to have been within guidelines at Waves 1 and 4. However, after adjusting for baseline CRC screening rate, there was no difference in the Wave 4 screening rates between the intervention and comparison counties (p = 0.50). Wave 2 screening rates did not differ by treatment arm (p = 0.74), while participants in the intervention counties were less likely to be screened at Wave 3 than participants in the comparison counties (p = 0.02) controlling for the county-level rates in Wave 1.

3.2. Participant-Reported Physician Actions regarding CRC and CRC Screening. Of the 1,091 participants who completed the survey at Wave 4, 39 (6.9%) participants from the intervention counties and 40 (7.6%) participants from the comparison counties reported that their doctor asked them
Table 1: Participant characteristics by wave and study arm.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Comparison</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td>(n = 562)</td>
<td>(n = 544)</td>
<td>(n = 601)</td>
<td>(n = 584)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>61.7(6.9)</td>
<td>61.2(6.8)</td>
<td>61.7(6.5)</td>
<td>61.4(6.6)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>229(40.7)</td>
<td>228(41.9)</td>
<td>258(42.9)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>333(59.3)</td>
<td>316(58.1)</td>
<td>343(57.1)</td>
</tr>
<tr>
<td>Race-White</td>
<td>No</td>
<td>20(3.6)</td>
<td>15(2.8)</td>
<td>21(3.5)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>542(96.4)</td>
<td>529(97.2)</td>
<td>578(96.5)</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>No</td>
<td>553(98.8)</td>
<td>541(99.6)</td>
<td>591(98.5)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>7(1.3)</td>
<td>2(0.4)</td>
<td>9(1.5)</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
<td>425(75.6)</td>
<td>427(78.6)</td>
<td>475(79.0)</td>
</tr>
<tr>
<td></td>
<td>Divorced/widowed</td>
<td>112(19.9)</td>
<td>92(16.9)</td>
<td>98(16.3)</td>
</tr>
<tr>
<td></td>
<td>Single</td>
<td>25(4.4)</td>
<td>24(4.4)</td>
<td>28(4.7)</td>
</tr>
<tr>
<td>Education level</td>
<td>&lt;High school</td>
<td>51(9.1)</td>
<td>38(70)</td>
<td>45(75)</td>
</tr>
<tr>
<td></td>
<td>High school</td>
<td>204(36.3)</td>
<td>191(35.2)</td>
<td>210(34.9)</td>
</tr>
<tr>
<td></td>
<td>Some college/college</td>
<td>307(54.6)</td>
<td>313(57.7)</td>
<td>346(57.6)</td>
</tr>
<tr>
<td>Annual household income in last year</td>
<td>&lt;$30K</td>
<td>163(35.1)</td>
<td>144(31.7)</td>
<td>150(28.1)</td>
</tr>
<tr>
<td></td>
<td>$30K–$60K</td>
<td>148(31.8)</td>
<td>159(35.0)</td>
<td>200(37.5)</td>
</tr>
<tr>
<td></td>
<td>$60K+</td>
<td>154(33.1)</td>
<td>151(33.3)</td>
<td>184(34.5)</td>
</tr>
<tr>
<td>Employment status</td>
<td>Full/part time</td>
<td>252(45.0)</td>
<td>239(44.0)</td>
<td>270(45.0)</td>
</tr>
<tr>
<td></td>
<td>Retired/volunteer</td>
<td>219(39.1)</td>
<td>209(38.5)</td>
<td>222(37.0)</td>
</tr>
<tr>
<td></td>
<td>Disabled/unemployed</td>
<td>89(15.9)</td>
<td>95(17.5)</td>
<td>108(18.0)</td>
</tr>
<tr>
<td>Insurance</td>
<td>Uninsured</td>
<td>49(8.8)</td>
<td>48(8.8)</td>
<td>61(10.2)</td>
</tr>
<tr>
<td></td>
<td>Public</td>
<td>217(38.8)</td>
<td>192(35.4)</td>
<td>220(36.9)</td>
</tr>
<tr>
<td></td>
<td>Private</td>
<td>294(52.5)</td>
<td>303(55.8)</td>
<td>316(52.9)</td>
</tr>
</tbody>
</table>
about their family history of CRC ($p = 0.65$). Fifty-six (9.9%) participants from intervention counties and 76 (14.5%) participants from comparison counties reported that their doctor asked about changes in their bowel habits ($p = 0.009$). A similar proportion of participants from intervention counties (8.1%) and comparison counties (9.0%) reported that they talked to their doctor about rectal bleeding ($p = 0.64$). One hundred ninety-two (33.9%) participants from intervention counties and 172 (32.8%) participants from comparison counties reported that they talked to their doctor about having a CRC screening test ($p = 0.64$). Lastly, a similar proportion of participants from intervention counties (85.1%) and comparison counties (81.9%) reported their willingness to have a CRC screening, if recommended by a doctor ($p = 0.47$, adjusting for baseline rate).

### 3.3. Predictors of CRC Screening

In separate multivariable models adjusting for county and demographic data (age, gender, race, ethnicity, marital status, education level, income, employment, and insurance), perceived CRC risk, intention to screen, and physician actions regarding CRC and CRC screening were statistically significant predictors of being within guidelines for CRC screening at Wave 4 (Table 2). Specifically, high perceived risk of CRC (OR = 1.79, 95% CI = 1.08, 2.95), willingness to have a CRC screening test if recommended by a doctor (OR = 6.23, 95% CI = 3.45, 11.27), and not thinking about talking to their doctor about a test in the next year (OR = 0.53, 95% CI = 0.35, 0.78) were associated with being within guidelines for CRC screening. Participants who asked their doctor for a CRC screening test (OR = 1.96, 95% CI = 1.13, 3.38) and talked to their doctor about eating more fruits and vegetables (OR = 1.47, 95% CI = 1.07, 2.03), family history of CRC (OR = 1.95, 95% CI = 1.11, 3.41), changes in bowel habits (OR = 1.86, 95% CI = 1.21, 2.87), and having a CRC screening test (OR = 1.82, 95% CI = 1.34, 2.46) were more likely to be within guidelines for CRC screening. Lastly, those participants whose doctors asked them to have a CRC screening test (OR = 10.02, 95% CI = 5.68, 17.69) were more likely to be within guidelines for CRC screening.

### 3.4. Process Evaluation

After the media campaign (Wave 2), 14.3% of the 502 participants from intervention counties reported seeing the correct billboard encouraging CRC screening. Of the 507 participants from intervention counties who answered questions about seeing the study posters, 12.4% reported seeing at least one of the three correct CRC screening posters. Odds of CRC screening were not greater among participants who reported having seen the correct billboard versus those who did not (OR = 0.87, 95% CI = 0.51–1.50), nor were they greater among participants who reported having seen at least one of the correct posters (OR = 1.42, 95% CI = 0.82–2.46, resp.), versus those who did not.

After the combined media and clinic campaign (Wave 4), 978 participants (503 intervention and 475 comparison) who reported having visited a doctor in the past year answered questions about seeing the clinic-based educational materials. Of the 503 participants from intervention counties who reported having visited a doctor in the past year, 57.9% reported seeing an ACS poster and 53.3% reported seeing a brochure about CRC screening at the doctor’s office. There was no effect of reporting having seen either an ACS poster (OR = 1.34, 95% CI = 0.90–2.01) or a brochure (OR = 1.03, 95% CI = 0.69–1.52) on being within CRC screening guidelines.

### 4. Discussion

This group-randomized trial assessed the impact of a county-level intervention, consisting of media and clinic components, to increase CRC screening among Ohio Appalachian adults. The findings indicate that, despite a high willingness to have CRC screening, the intervention did not have an effect on CRC screening among the adults in the intervention counties, as approximately 35% of the participants had completed a CRC screening test in both the intervention and comparison counties. This result is similar to previously reported rates among Appalachian residents [15, 26–28]. Significant predictors of CRC screening within guidelines among participants were high perceived risk of CRC, willingness to have a CRC test if recommended by a doctor, doctor recommendation of a CRC screening test, and patient-physician communication about changes in bowel habits, family history of CRC, and eating fruits and vegetables.

We considered a number of possible explanations for the null results, including low exposure to the intervention. Participants may not have visited the locations where the posters and billboards were displayed. Process evaluation indicated that participants from the intervention counties were exposed to the clinic-directed intervention (i.e., 52% reported seeing the brochures); however, CRC screening rates did not differ between the two study groups suggesting that the media campaign and the clinic educational materials about CRC screening were not effective, as designed. Results of similar studies have raised questions about the efficacy of these types of interventions to bring sustained lifestyle...
Table 2: Multivariable logistic regression results for being within CRC screening guidelines (Wave 4)*.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR for CRC screening (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High perceived risk of CRC</td>
<td>1.79 (1.08, 2.95)</td>
<td>0.0233</td>
</tr>
<tr>
<td>Willingness to have a CRC screening test if recommended by doctor</td>
<td>6.23 (3.45, 11.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thought about talking to doctor about completing a CRC screening test in the next year</td>
<td>0.53 (0.35, 0.78)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Patient asked doctor for a CRC screening test</td>
<td>1.96 (1.13, 3.38)</td>
<td>0.0160</td>
</tr>
<tr>
<td>Talked to doctor about eating more fruits and vegetables</td>
<td>1.47 (1.07, 2.03)</td>
<td>0.0184</td>
</tr>
<tr>
<td>Talked to doctor about family history of CRC</td>
<td>1.95 (1.11, 3.41)</td>
<td>0.0199</td>
</tr>
<tr>
<td>Talked to doctor about changes in bowel habits</td>
<td>1.86 (1.21, 2.87)</td>
<td>0.0048</td>
</tr>
<tr>
<td>Talked to doctor about having a CRC screening test</td>
<td>1.82 (1.34, 2.46)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Doctor asked patient to have a CRC screening test</td>
<td>10.02 (5.68, 17.69)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Each variable was considered individually after adjusting for county and demographic factors. Each line represents a separate model. Results are from 30 multiply imputed datasets.

changes and promote use of preventive health services [29–31]. When applied to a lower SES population with challenges related to health care access [9, 24, 28, 32], perhaps this media and clinic intervention only raised consciousness and intention (as demonstrated by previous media campaigns [11–13]) but could not lead to a major behavior change.

Future studies should consider utilizing media- and clinic-based interventions to increase knowledge and awareness of CRC screening coupled with personal contact from lay health advisors (LHAs) and patient navigators (PNs) to facilitate access to and completion of screening. LHA and PN interventions among underserved populations have been successful because they typically use trusted community members who understand the association between SES and cultural factors, as well as provider factors, associated with behavior change [33, 34]. With this knowledge, they serve as a bridge between the community and health care system by providing information, support, and encouragement [33, 34]. Previous studies using LHA and PN intervention programs to promote cancer screening have found significantly increased CRC screening rates [34–37]. Modeling these coordinated, targeted, and community-based programs in Ohio Appalachia could be similarly successful.

4.1. Limitations. The current study had several limitations. First, the overall rates of CRC screening in the clinics during the study were not measured. This would provide information about the potential for increasing rates of CRC screening among specific clinic patients. Also, we did not survey physicians about their recommendations for CRC screening and perceived barriers to CRC screening faced by their patients. This study utilized cross-sectional data which can limit the comparability across study waves and prohibits insight into the impact of the intervention. It is possible that people who completed the surveys after the clinic-based intervention (i.e., Wave 3) could have seen Wave 2 intervention material, causing a bias in their response. However, the main outcome was the comparison between Wave 4 and Wave 1 screening rates, and a cumulative effect of the interventions was expected. Lastly, study results may have limited generalizability because participants lived in one region of the US and were primarily non-Hispanic white.

5. Conclusion

This study tested the effectiveness of an intervention to increase rates of CRC screening among adults living in Ohio Appalachian counties. The county-level campaign consisted of media- (billboards, posters, and newspaper advertisements) and clinic-based (ACS brochures and posters) components about CRC and CRC screening. There were no differences in CRC screening rates between participants from the intervention and comparison counties at the end of the study, as measured by cross-sectional survey and MRR. Future research should examine how media- and clinic-based interventions can be modified to improve CRC screening rates among this underserved population.

Conflict of Interests

There is no actual, potential, or perceived conflict of interests by any of the authors.

Acknowledgments

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References


Review Article

Pathologic Assessment of Rectal Carcinoma after Neoadjuvant Radio(chemo)therapy: Prognostic Implications

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Neoadjuvant radio(chemo)therapy is increasingly used in rectal cancer and induces a number of morphologic changes that affect prognostication after curative surgery, thereby creating new challenges for surgical pathologists, particularly in evaluating morphologic changes and tumour response to preoperative treatment. Surgical pathologists play an important role in determining the many facets of rectal carcinoma patient care after neoadjuvant treatment. These range from proper handling of macroscopic specimens to accurate microscopic evaluation of pathological features associated with patients’ prognosis. This review presents the well-established pathological prognostic indicators and discusses challenging features, especially those with clinical impact, in order to provide both surgical pathologists and treating physicians with a checklist that is useful in a neoadjuvant setting.

1. Introduction

Preoperative radiotherapy with or without chemotherapy (RCT) followed by total mesorectal excision (TME) has become a standard treatment for locally advanced rectal cancers [1–4]. The increasing use of RCT in rectal cancer creates new challenges for surgical pathologists, particularly in evaluating morphologic changes and tumour response to preoperative treatment. Various systems have been suggested for grading tumour response to RCT [5–10]. However, the majority of these systems do not consistently correlate with prognosis [11–14], and their reproducibility is poor [11, 15–17]. Moreover, RCT alters the macroscopic and microscopic assessment and prognostic relevance of a few well-recognized pathological features (i.e., tumour and nodal stage, circumferential resection margin, and lymphovascular invasion) [18–20]. For example, difficulty exists when no remaining tumours can be identified on macroscopic examination. In this context, accurate pathological tumour stage (ypT) depends on how assiduously the pathologists search for residual tumour, as well as on the number of blocks and slide sections processed. In addition, RCT may significantly decrease the number of retrieved lymph nodes [19]. This could cause underestimation of the nodal status in the absence of rigorous lymph node search. Controversy also persists concerning the optimal distal and circumferential margins [21–28]. Thus, surgical pathologists play an important role in determining the many facets of rectal carcinoma patient care after neoadjuvant treatment. These range from proper handling of macroscopic specimens to accurate microscopic evaluation of pathological features associated with patients’ prognosis.

The aim of this review is to present the well-established pathological prognostic indicators and discuss challenging features, especially those with clinical impact, in order to provide a checklist that is useful in a neoadjuvant setting, for both surgical pathologists and treating physicians.
2. Macroscopic Assessment of TME Specimen

The TME technique is based on the sharp dissection of the avascular plane between autonomic nerve plexuses and the mesorectum. This operation results in the excision of the rectum enveloped by a mesorectal fat column of 2 to 3 cm. This part of the review presents the methods of assessment of mesorectal quality, circumferential resection margin (CRM), distal resection margin, and lymph nodes.

2.1. Evaluation of the Mesorectum. TME specimen handling begins with assessment of the quality of the mesorectum (Table 1) [29]. Inspection of the mesorectal surface gives the first indication of its quality. Full thickness slicing of the tumour and the mesorectum allows a good assessment of the adequacy of excision and the regularity of the CRM, which is the second indicator of the resection quality.

2.2. Specimen Processing. Quirke et al. [29] and Nagtegaal et al. [30] have developed an approach for the assessment and processing of the TME specimen. This assessment is performed by direct visual inspection of the fresh specimen; the anterior and posterior planes of the mesorectum are photographed to document their smoothness or irregularity. Then, the mesorectal fat is inked; care should be taken not to ink the peritonealized surfaces of the specimen, especially anteriorly, where the serosa extends lower down, as this may produce artifact and lead to difficulty in interpreting serosal involvement by upper rectal tumours that are either circumferential or anterior in their location [31]. Then, the specimen is measured and cut open along the anterior aspect from the top, leaving the bowel intact at a level just above the peritoneal reflection. After placing loose, formalin-soaked gauze wicks into the unopened segment of the rectum, the specimen should be pinned under tension on a corkboard to minimize shrinkage [32]. After an optimal fixation of at least 72 hours, the unopened segment is sliced transversely at 5 mm intervals in order to identify the area of deepest invasion, and the slices are photographed again to keep a record of the quality of the excised mesorectum, the tumour size, localization, and distance to all surgical margins. Concerning tumour sampling, the guideline of the Belgian Project on Cancer of the Rectum (PROCARE; http://www.kankerregister.org/), which was adapted from Quirke et al. [29] and Nagtegaal et al. [30], suggests that five initial blocks be taken from the site of the tumour or suspicious area. In cases with obvious macroscopic tumour remnant, in addition to taking the superficial and deepest part of the tumour, sections showing the closest relationship of tumour to CRM or to peritoneal surface as well as those containing the transition from suspicious mesorectal nodules to the CRM should be taken, as this allows proper evaluation of other pathological prognostic parameters [33]. When only mucin pools are taken, as this allows proper evaluation of other pathological prognostic parameters [33].

Recommended method for tumour sampling and examination in rectal carcinoma following radio(chemo)therapy and surgery is as follows.

**Step 1.** Take 5 blocks from the tumour or scarred area (assuming no obvious tumour was found grossly). These should include the superficial and deep part of the tumour as well as the relationship between the tumour and the CRM or peritoneal surface. If there are any mesorectal nodules, blocks containing their relation to the CRM should also be taken.

**Step 2.** If no viable microscopic tumour is identified within the initial 5 blocks, the entire scarred area should be sampled.

**Step 3.** If no residual tumour is found after examining sections from the additional blocks, three levels should be cut through each block. If no viable tumour cells are present even after rigorous examination of these sections, complete pathologic response or ypT0 can be reasonably and reliably reported.

2.3. Distal Margin. The distal margin, although less important than the CRM in terms of frequency of involvement and impact on recurrence, is still important to assess. There are two issues to keep in mind when considering the distal margin: the extent of intramural and extramural continuous tumour growth and the discontinuous distal mesorectal spread through lymphatics. In 20% of cases with positive nodes, there is lymphatic spread distal to the primary tumour. Furthermore, in many cases these positive distal nodes are located ≥2 cm away from the main tumour mass [34]. By contrast, intramural distal spread >2 cm is seen in only 3.6% of cases [35]. Zhao et al. [36] found that the rate of discontinuous tumour deposits within the distal mesorectum was 17.8% and that the extent of distal mesorectal spread was greater than the extent of intramural spread. From their data, they concluded that a 1.5 cm distal rectal wall margin and a 4 cm distal mesorectal margin are necessary to achieve adequate surgical clearance. Yet, in many cases, distal rectal wall margin of ≤1 cm also proved to be sufficient in preventing local recurrence, particularly in tumours limited to the rectal wall [37, 38].

One final issue to keep in mind, when measuring the distal margin, is shrinkage artifact. Goldstein et al. [39] have shown that a 5 cm length of colon and rectum in vivo is equivalent to 3 cm after resection and 2.2 cm after fixation. This highlights, once again, the importance of pinning the specimen on a corkboard to reduce the degree of shrinkage.

2.4. Lymph Node Retrieval. Lymph node status probably constitutes the single most important prognostic determinant in patients with rectal cancer whether treated preoperatively or not [40, 41]. International guidelines recommend that at least 12 lymph nodes are needed for adequate CRC staging [42, 43]. Nevertheless, there has been evidence suggesting that preoperative RCT for rectal cancer could reduce lymph node yield by roughly 33% [19, 44]. Despite this finding, a high motivation to retrieve as many nodes as possible must be maintained, since several studies support the concept that...
When associated with microsatellite instability (MSI) [67–69], mucinous carcinoma tends to be prognostically favorable [61–66]. On the other hand, not confirming mucinous histology to be a stage-independent adverse prognostic factor [57–60], larger studies did not confirm mucinous histology to be a stage-independent predictor of poor outcome [61–66]. On the other hand, mucinous carcinoma tends to be prognostically favorable when associated with microsatellite instability (MSI) [67–69].

In summary, based on current evidence, it can be concluded that the only histological types of CRC that are prognostically significant are signet-ring cell and small-cell carcinoma (poor prognosis) and medullary and MSI-related mucinous carcinoma (favorable prognosis).

### 3. Microscopic Assessment

#### 3.1. Tumour Histological Type

In the pathological reporting of colorectal cancer (CRC), the internationally accepted histological classification of colorectal cancers proposed by the World Health Organization [51] (WHO) is recommended by the College of American Pathologists (CAP) [52]. Based on this classification, the majority of rectal cancers are adenocarcinomas of no special type. Besides a few exceptions, histological type has no stage-independent prognostic significance [52]. The exceptions include the non-gland-forming tumours such as signet-ring cell carcinoma, small-cell carcinoma, and undifferentiated carcinoma, which are prognostically unfavorable [53–55], and medullary carcinoma, which is prognostically favorable [56]. In contrast to the findings in a few studies, mainly limited to univariate analyses, suggesting that mucinous adenocarcinoma may be an adverse prognostic factor [57–60], larger studies did not confirm mucinous histology to be a stage-independent predictor of poor outcome [61–66]. On the other hand, mucinous carcinoma tends to be prognostically favorable when associated with microsatellite instability (MSI) [67–69].

#### 3.2. Tumour Differentiation Grade

In the WHO classification [70], grading of colorectal adenocarcinoma is based on the extent of gland formation. Therefore, the non-gland-forming histological types (e.g., signet-ring, small-cell, and undifferentiated carcinoma) are always regarded as high-grade or poorly differentiated tumours. In most cases, however, the estimation of the degree of glandular formation is subjective, resulting in interobserver variation, mainly in grading well and moderately differentiated tumours. The lack of uniformity in histopathological grading is further complicated by a number of different grading systems without consensus among pathologists [52, 71–73]. At present, the available data are insufficient to support one approach over the other, and the issue remains problematic. Irrespective of the complexity of the criteria, most systems stratify adenocarcinomas into four grades:

(i) Grade 1: well differentiated (>95% glandular formation),
(ii) Grade 2: moderately differentiated (50%–95% glandular formation),
(iii) Grade 3: poorly differentiated (5%–50% glandular formation),
(iv) Grade 4: undifferentiated (<5% glandular formation).

Nevertheless, the most recent World Health Organization series on tumours of the digestive system recommends using the two-tier grading system (low versus high grade) in grading colorectal cancer [74]. Despite interobserver variation in assessment and the lack of standardization, histological grade has been repeatedly shown by multivariate analyses to be a stage-independent prognostic factor in a nonneoadjuvant setting [75–77]. After RCT, however, its impact on patient survival remains debatable [5, 11, 13, 78–80].

#### 3.3. Lymphovascular and Perineural Invasion

The prognostic significance of lymphovascular (LVI) and perineural (PNI) invasion has been suggested and largely confirmed in a nonneoadjuvant setting [76, 77, 81–84]. Venous invasion has been demonstrated by numerous multivariate analyses to be

---

### Table 1: Assessment of the quality of mesorectal excision or completeness of resection*

<table>
<thead>
<tr>
<th>CRM</th>
<th>Complete</th>
<th>Nearly complete</th>
<th>Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM Smooth, regular</td>
<td>Intact, smooth</td>
<td>Moderate bulk, irregular</td>
<td>Little bulk</td>
</tr>
<tr>
<td>CRM Defects</td>
<td>Not deeper than 5 mm</td>
<td>Unexposed muscularis propria</td>
<td>Exposed muscularis propria</td>
</tr>
<tr>
<td>CRM Coning</td>
<td>No coning</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>CRM Irregular</td>
<td>Regular</td>
<td>Irregular</td>
<td>Irregular</td>
</tr>
</tbody>
</table>

CRM, circumferential resection margin.

* Both the whole fresh specimen and formalin-fixed slices are examined to achieve optimal assessment.
an independent adverse prognostic factor in CRC [76, 77, 81, 82, 85–87]. In series of studies identifying the exact location of the involved vessels (i.e., extramural as opposed to intramural location), it was found that the extramural type was most predictive of survival [87–89]. In some studies, LVI, without distinction between venous and lymphatic vessels, has been found to be prognostically significant [81, 90]. More discordant results have been reported for lymphatic vessel invasion alone [91, 92]. It is likely that the disparities among existing studies on vascular invasion are related to inherent problems in the pathological identification of this feature. Definitive diagnosis of vascular invasion requires the identification of tumour within an endothelial-lined channel. However, this may be difficult when tumour induced vascular fibrosis or endothelial destruction is present. In addition, fixation artifact in the tumour may mimic small vessel involvement. For these reasons, interobserver variation may be substantial in the interpretation or recognition of vascular invasion. Additional limitations in the detection of vessel invasion are related to specimen sampling. For example, it has been shown that the reproducibility of detection of extramural venous invasion increases proportionally from 59% with examination of 2 blocks of tissue at the tumour periphery to 96% with examination of 5 blocks [89, 93, 94]. Other studies have suggested that taking various types of tissue blocks such as tangential ones in addition to perpendicular blocks raises the chances of detecting extramural venous invasion [94, 95].

Following preoperative RCT, the prognostic significance of LVI and PNI has been demonstrated in several studies, mostly by univariate analysis [96–98]. A study by Du et al. [97] showed that the disease progression of patients with LVI in irradiated tumours was significantly delayed as compared with that with LVI-positive tumours in nonirradiated tumours. They suggested that the aggressiveness of those tumour cells in the blood or lymphatic vessels may have been significantly weakened by radiotherapy, though they were not completely eliminated. In this respect, the stage-independent prognostic impact of LVI and PNI after RCT needs to be confirmed in larger studies with multivariate analysis.

3.4. Tumour Deposits (TDs). Tumour deposits (TDs) are discrete adenocarcinoma nodules encountered in the pericolic and perirectal fat during routine histopathological examination of advanced CRC specimens. Their prevalence in the mesorectum ranges from 6% to 64% [99–101]. TDs are histologically heterogeneous and may be associated with several types of recognizable anatomic structures such as veins, lymphatic vessels, and nerves, whereas in other cases carcinoma cells are seen scattered in small aggregates in the perirectal adipose tissue. This may account for the different classifications that TDs have undergone over time [102–104], particularly in the TNM classification series. Table 2 summarizes the major changes in the last four editions of TNM classification for colorectal cancer.

The TNM5 introduced the 3 mm rule, resulting in a classification based exclusively on size, independent of histological features. Accordingly, discontinuous mesorectal tumour cell aggregates were considered as being primary tumour extensions (pT category) if measured ≤3 mm or as lymph node metastasis (pN category) if >3 mm [105]. The TNM6 replaced the size criterion with the shape criterion. Based on this classification, discontinuous mesorectal tumour nodules were considered as venous invasion if they have an irregular contour and as regional lymph node metastasis if they have the shape and smooth contour of a lymph node [106].

These two classifications have limited value since the TD classifications are based on a single morphologic criterion (i.e., size or shape). Moreover, the 3 mm rule was based on unpublished data, which were subsequently not confirmed [102, 107], and the shape criterion is insufficient to consistently distinguish different types of tumour involvement of the perivisceral fat [108], being the source of interobserver variation [107]. In 2009, Puppa et al. [103] proposed a new categorization of TDs:

(i) vascular-invasion type (extramural venous or lymphatic invasion): pT category,

(ii) non-vascular-invasion type (smooth contour, surrounded by lymphocytes, not associated with veins or nerves): pN category,

(iii) aggressive TDs (scattering pattern, not surrounded by lymphocytes, having close association with large vessels or neural invasion): pM1a (in-transit metastasis).

The TNM7 again introduced changes regarding the definition and classification of TDs. In the last edition, discrete foci of tumour found in the perivisceral fat or in adjacent mesentery away from the leading edge of the tumour and showing no evidence of residual lymph node tissue are considered to be TDs. If TDs are observed in lesions that would otherwise be classified as T1 or T2, then the primary tumour classification is not changed, but the nodule is classified in N1c category [109].

It seems that the different editions of TNM replace one subjective definition with another. Moreover, they do not appear to have prospectively tested this new TD classification and evaluated its reproducibility, since TNM7 states that a perivisceral nodule should be recorded as a positive lymph node if the nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour) [109].

In summary, although the existing classifications of TDs need further improvement in terms of reproducibility and prognostic stratification, results from most studies on patients not receiving preoperative RCT indicated a worse prognosis for patients with TDs: increased local recurrence rates, increased development of distant metastases, and decreased survival [107]. In studies by Ratto et al. [99, 110] who looked at the incidence and prognostic impact of TDs in rectal cancer specimen after RCT, TDs occurred in up to 15.40% of cases and their presence was associated with reduced disease-free and overall survival. In contrast, Nagtegaal and Quirke [107] and Quirke et al. [111] considered the presence of TDs as a sign of good response to RCT.
Table 2: Major changes in the last 4 editions of TNM classification for colorectal cancer.

<table>
<thead>
<tr>
<th>Edition (year)</th>
<th>T category</th>
<th>N category</th>
<th>M category</th>
<th>Stage grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th (1987)</td>
<td></td>
<td>Introducing N3 category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th (1997)</td>
<td></td>
<td>Removing N3 category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6th (2002)</td>
<td>TDs: replacing the 3 mm rule with the contour rule</td>
<td>T4 split into T4a and T4b</td>
<td>ITC considered as N0</td>
<td>Subdividing stage III into IIIA, IIIB, and IIIC</td>
</tr>
<tr>
<td>7th (2009)</td>
<td></td>
<td>Subdividing N1 into N1a, N1b, and N1c and N2 into N2a and N2b</td>
<td>M1 split into M1a and M1b</td>
<td>Subdividing stage IV into IVA and IVB</td>
</tr>
</tbody>
</table>

ITC, isolated tumour cells.

Whether or not the presence of TDs after RCT is a stage-independent predictor of poor outcome remains questionable. In daily practice, the presence of TDs must be included in the pathology report, specifying their total number, size, and growth patterns, in order to create more homogeneous groups of patients for enrolment in clinical trials [112].

3.5. Pathological Stage. Pathological staging following complete resection has long been considered the most powerful prognostic indicator in CRC [113]. The same holds true in rectal carcinoma after preoperative RCT [114–116]. Although a large number of staging systems have been developed for CRC over the years, the tumour node metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) is by far the most widely recommended. Table 2 lists the major changes made in the last four editions [109, 113, 117]. TNM 7th edition received a number of criticisms primarily for the new classification of TDs which lacks both scientific evidence and reproducibility [118, 119]. In reporting CRC, some centers prefer the 5th edition of the TNM classification to the other editions, mainly because of the reproducibility in TD classification [118, 120]. For future evaluation of the prognostic relevance of the changes in TNM classification, however, the 7th edition should be used, yet the conflicting feature, that is, TDs, should be reported in detail with description of their number, size, and growth pattern.

For accurate staging of treated rectal carcinoma, it is important to keep in mind that when microscopic remnants of tumour are not found, the scarred area must be entirely sampled [73, 120]. Moreover, if viable tumour is not present even after examining sections from the whole scarred area, three levels should be cut through each block to exclude residual tumour foci, as suggested in the CORE phase II study [121].

3.6. Acellular Mucin (aMUC). In routine microscopic examination of neoadjuvantly treated rectal carcinoma specimens, mucus pools can be encountered in up to one-third of cases [122, 123]. With regard to this, a few recent studies have demonstrated that the presence of acellular mucin (aMUC) in rectal carcinoma after neoadjuvant RCT did not have significant impact on patient outcome [122, 124, 125]. de Campos-Lobato et al. looked at the prognostic value of aMUC in rectal cancer patients achieving ypT0 after preoperative RCT and concluded that aMUC did not affect local recurrence but may suggest a more aggressive tumour biology [125]. These findings are in support of the current CAP consensus statement that acellular mucin pools are not to be regarded as residual tumour and that their presence is to be recorded separately from the ypT category [122].

3.7. Local Inflammatory Response. The tumour associated inflammatory infiltrate has long been considered a type of host response and an important prognostic factor in rectal cancer [126, 127]. After preoperative RCT, rectal cancer could undergo tumour regression by eradication of carcinoma cells and replacement by fibrous or fibroinflammatory tissues [123, 128, 129]. Nagtegaal et al. [130] and Shia et al. [123] found that patients with an extensive fibroinflammatory infiltrate around the tumour had lower recurrence rates. Two recent studies by Debucquoy et al. [128, 129] showed a better disease-free survival in rectal cancer patients whose TME specimens contained fibroinflammatory changes after RCT (Figure 1). Overall, a marked inflammatory cell component is not commonly seen in posttreatment rectal tumours [123, 128, 129]. Shia et al. [123] reported that, in 60% of cases, the inflammatory infiltration was only minimal. These findings imply an impaired or inhibited immune function in patients treated with RCT. Accordingly, it can be suggested that patients who maintain a more extensive inflammatory response at the tumour bed after RCT have a better outcome, and this factor is relevant in assessing the prognosis of these patients [123, 128, 129].

3.8. Therapy Response Assessment. Response to RCT ranges from minimal treatment effects to complete eradication of the primary tumour. Some authors used cellular-response grading which is based on the amount of residual viable tumour in relation to stromal fibrosis [5–8, 16, 131], whereas others looked at stage shift in the treated specimens, including tumour and nodal downstaging, when assessing response
To date, none of the cellular-response grading systems has gained universal acceptance [11, 132, 133], not only because the majority of them could not consistently predict patient outcome [11–14] but also because their reproducibility is poor, particularly for categories defining moderate to minimal regressive changes [11, 15–17]. On the other hand, evaluation of downstaging is objective and reproducible. Moreover, downstaging has been consistently demonstrated to correlate significantly with improved survival [11, 128, 129, 135]. Nevertheless, no study has investigated the prognostic impact of both cellular-response grading and downstaging in the same study cohort. Some studies [14, 136–138] specifically examined the prognostic impact of pathological complete response (pCR), defined by the complete absence of viable tumour cells in the primary tumour site (ypT0). The precise classification of pCR or ypT0 can be an effort- and time-consuming task provided that residual viable tumour cells could be identified in many cases upon rigorous microscopic examination (i.e., multilevel sectioning of the blocks containing the scarred area) [7, 121]. In this regard, the varying proportion of pCR observed in previous studies might have been due to the difference in dissection and examination methods used in each laboratory. In spite of this variation, the pCR status has been shown, in a few randomised trials and other studies, to significantly correlate with decreased local recurrence rate and improved survival [137–143].

3.9. Circumferential Resection Margin (CRM). On microscopic examination, the distance of the tumour to the CRM may be the single most critical factor in predicting local recurrence (LR) after RCT and surgery [13, 29, 37]. The CRM involvement by tumour also has been shown to predict distant recurrence and overall survival (OS) in some studies [27, 144]. Although the definition of positive CRM varies among studies [27, 28], the majority of them involving several thousands of patients support the use of 1 mm as cut-off value for involved CRM [27]. The methods on which CRM measurement is based have been discussed in a study by Nagtegaal et al. [30] who looked at the difference in LR rates among cases with positive CRM as measured from the deepest point of invasion of the primary tumour and those with positive CRM as measured from invaded lymph nodes in the perirectal fat. They showed that patients with a positive CRM due to direct tumour extension developed local recurrence more frequently than those with a positive CRM due to positive nodes (22.1% versus 12.4%, \( p = 0.06 \)). However, in the same study, there was no difference in the rate of local recurrence between patients with a positive CRM due to positive nodes compared to those with a negative CRM. As previously described, TDs are a frequent phenomenon in the mesorectum. Nevertheless, to date, no study has examined the prognostic relevance of CRM measurement based on the distance from lateral resection margin to TDs. Therefore, to allow further investigations on the prognostic significance of these two new CRM measurement methods (i.e., based on distance from positive nodes or TDs), it is recommended that, in cases with positive lymph nodes or TDs, practicing pathologists keep a record of the distance from the lateral resection margin to these perirectal tumour nodules in addition to reporting the classic CRM.

4. Summary and Conclusion

Preoperative RCT induces changes in both gross appearance of the surgical specimen and its pathological features, which could have impact on patient management and outcome. First of all, the assessment of the mesorectum is necessary as it is an important indicator of the resection quality. Then, the resected specimen should be sampled and examined properly, as summarized in Steps 1, 2, and 3, warranting not leaving out any prognostically relevant samples, particularly those containing the relationship of the lateral margins with the primary tumour and mesorectal nodules. Standardized protocols for the grossing of TME specimens should be available in order for pathologists, pathology residents, and pathologists’ assistants to handle these specimens in a uniform and effective manner. Pathological features that have been consistently reported to significantly influence patient outcome after RCT include posttreatment pathological stage (ypTNM), microscopic status of the CRM, and local fibroinflammatory response, whereas the stage-independent prognostic value of histologic grade, LVI, PNI, and TDs requires further investigation in neoadjuvant setting. Concerning therapy response assessment, downstaging appears to be better than cellular-response grading in terms of both reproducibility and clinical outcome prediction.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


[120] K. D. Smith, D. Tan, P. Das et al., “Clinical significance of acellular mucin in rectal adenocarcinoma patients with a


Research Article

Awareness of Lifestyle and Colorectal Cancer Risk: Findings from the BeWEL Study

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It is estimated that 47% of colorectal cancers (CRC) could be prevented by appropriate lifestyles. This study aimed to identify awareness of the causes of CRC in patients who had been diagnosed with a colorectal adenoma through the Scottish Bowel Screening Programme and subsequently enrolled in an intervention trial (using diet and physical activity education and behavioural change techniques) (BeWEL). At baseline and 12-month follow-up, participants answered an open-ended question on factors influencing CRC development. Of the 329 participants at baseline, 40 (12%) reported that they did not know any risk factors and 36 (11%) failed to identify specific factors related to diet and activity. From a potential knowledge score of 1 to 6, the mean score was 1.5 (SD 1.1, range 0 to 5) with no difference between intervention and control groups. At follow-up, the intervention group had a significantly greater knowledge score and better weight loss, diet, and physical activity measures than the control group. Awareness of relevant lifestyle factors for CRC remains low in people at increased risk of the disease. Opportunities within routine NHS screening to aid the capability (including knowledge of risk factors) of individuals to make behavioural changes to reduce CRC risk deserve exploration.

1. Introduction

Despite significant advances in our understanding of prevention and early detection, colorectal cancer remains the third most common cancer and cause of cancer death in the UK [1]. Most cases (95%) occur in older adults (>50 years) who commonly have other lifestyle-related conditions including type two diabetes mellitus and cardiovascular disease [2, 3]. These diseases share common risk factors related to obesity, altered glucose-insulin pathways, and abnormal lipids [4, 5]. Meta-analysis studies have demonstrated a consistent association between obesity and CRC (notably in men) and with colorectal adenomas in men and women [6, 7].

Recent UK estimates on cancer preventability indicate that 12% of colorectal cancers could be prevented by increased physical activity, 14% by the avoidance of excess weight, 27% by changes in diet (increasing fibre intake and decreasing red and processed meat), and 7% by reducing alcohol intake [8]. Thus a number of modifiable risk factors can be identified and acted upon for potential reduction of colorectal cancer risk and proven benefit on risk reduction for type two diabetes mellitus and cardiovascular disease.

Investigations in the UK suggest that awareness of lifestyle factors for disease prevention is generally low and is lower for cancer than for heart disease [9]. A recent YouGOV poll commissioned by the World Cancer Research Fund [10] in the UK reported that 59% of people did not know about the links between cancer and body weight and 62% did not know about the association with processed meat. In a secondary data analysis of the US National Health Interview Survey, Bittner Fagan et al. [11] reported that, compared with normal weight respondents, overweight or obese participants did not perceive themselves to be at an increased risk for cancer or specifically for colorectal cancer. Previous qualitative
research by our research group [12] reported that people who had been diagnosed with adenomas gave little thought as to what might have caused the adenoma, and in those who gave possible explanations, these tended to relate to age, genetics or "chance." Similar findings have been reported from studies of cancer survivors where genetic factors, smoking and environmental factors (e.g., pollutants or occupation), and psychosocial factors are the most frequently quoted causes of cancer [13].

The NHS colorectal cancer screening programmes offer a timely opportunity to provide risk factor advice to adults at increased risk of CRC as part of a portfolio of advice (within wider scale population level actions). The current study aims to identify awareness of the causes of CRC in patients who were diagnosed with a colorectal adenoma through the NHS Scotland Bowel Screening Programme and had subsequently been enrolled in a randomised controlled trial of a lifestyle intervention [14].

2. Methods

The BeWEL trial was a multicentre randomised controlled trial of a 12-month weight loss intervention delivered by a lifestyle counsellor versus usual care (booklet only) [15]. The intervention was delivered by a lifestyle counsellor who provided a personalised energy prescription with detailed educational information on food choices and a pedometry based physical activity programme as well as body weight scales. Motivational interviewing techniques and behavioural strategies were used to promote relevant changes in diet, physical activity, and body weight [16].

Individuals (aged 50 to 74 years) who had received an adenoma diagnosis following a positive faecal occult blood test and colonoscopy, undertaken through the Scottish Bowel Screening Programme, and who had a BMI ≥ 25 kg/m² were invited to participate in the BeWEL trial. All participants received a letter from an NHS consultant with their adenoma results, endorsing the study and highlighting the importance of lifestyle in adenoma recurrence and CRC risk. A full invitation letter as well as participant information leaflet was then sent out by a research nurse to eligible respondents.

At baseline and 12-month follow-up, questionnaires were administered by the research nurse. Knowledge of lifestyle risk factors for CRC was assessed at both time-points. Participants responded to the open text question "What do you personally think are the main factors that might increase or decrease a person's chance of developing colorectal cancer?" The research nurse encouraged participants to list as many risk factors as possible under the heading of increase risk or decrease a risk factors and had a significantly greater mean knowledge score +6.

2.1. Statistical Analysis. Statistical analyses were carried out using IBM SPSS Statistics for Windows (IBM Corp.: version 21.0, released 2012, Armonk, NY). Descriptive statistics were used to characterise the cohort with regard to knowledge of risk factors for colorectal cancer. Chi-squared tests were performed for comparison of proportions and independent t-tests for differences in means. Significance was taken as \( p < 0.05 \). Between-group differences are presented as odds ratios for differences in proportions, or as mean differences with 95% confidence intervals.

3. Results

Full sociodemographic and clinical details of participants at baseline and 12-month follow-up have been presented elsewhere [14]. Participants had a mean age of 63.6 years (SD 6.8) at baseline, with the majority being male (74%) and having had at least some further, professional, or higher education beyond secondary school (60%).

Of the 329 participants, 40 (12%) reported that they did not know any risk factors and a further 36 (11%) failed to identify specific factors related to diet and activity. The mean score for knowledge was 1.5 (SD 1.1, range 0 to 5). The most frequently cited factors were physical activity and alcohol followed by foods containing dietary fibre. Body weight (in this overweight cohort) was cited by 13%. Two participants cited quantitative recommendations ("5 a day" and "2 alcohol free days per week"). It is notable that "low fluid intake" was reported by 8%, suggesting that people were more familiar with this myth than evidence based recommendations to decrease processed meat (6%). Other factors frequently reported included family history (9%) and stress (6%). A number of other risk factors were also cited including bowel function (constipation), sexual transmission, and intake of dairy foods.

No differences in awareness were found between intervention and control groups at baseline; however at 12-month follow-up the intervention group participants were significantly more aware of body fatness (OR 1.99 (95% CI 1.07–3.70)) and red meat (OR 1.99 (95% CI 1.04–3.81)) as CRC risk factors and had a significantly greater mean knowledge score (1.8 versus 1.5, mean difference 0.29 (95% CI 0.05–0.54)) (Table 1). Overall, the results from the main trial showed that the intervention group had significantly better weight loss, diet, and physical activity measures than the control group after 12 months of follow-up [14].

4. Discussion

This study aimed to examine the awareness of lifestyle risk factors associated with colorectal cancer risk amongst a cohort of overweight people who had experienced NHS bowel screening and had a diagnosis of an adenoma. Despite these health service experiences in this motivated, high risk group, the results show that the baseline knowledge about CRC risk factors was low.
<table>
<thead>
<tr>
<th></th>
<th>All Baseline</th>
<th>Intervention Baseline</th>
<th>Control Baseline</th>
<th>Between-group difference at baseline OR/mean (95% CI) p value</th>
<th>Between-group difference at 12 months follow-up OR/mean (95% CI) p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (%)</td>
<td>148 (45.0)</td>
<td>73 (44.8)</td>
<td>77 (52.0)</td>
<td>75 (45.2)</td>
<td>76 (48.7)</td>
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<tr>
<td></td>
<td>0.98 (0.64–1.52)</td>
<td>0.943</td>
<td></td>
<td>1.14 (0.73–1.79)</td>
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<td>Physical activity (%)</td>
<td>153 (46.5)</td>
<td>81 (49.7)</td>
<td>86 (58.1)</td>
<td>72 (43.4)</td>
<td>80 (51.3)</td>
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<tr>
<td></td>
<td>1.29 (0.84–1.99)</td>
<td>0.251</td>
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<td>1.32 (0.84–2.07)</td>
<td>0.232</td>
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<td>Body fatness (%)</td>
<td>44 (13.4)</td>
<td>25 (15.3)</td>
<td>32 (21.6)</td>
<td>19 (11.4)</td>
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<td></td>
<td>1.40 (0.74–2.66)</td>
<td>0.300</td>
<td></td>
<td>1.99 (1.07–3.70)</td>
<td>0.028</td>
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<tr>
<td>Foods containing fibre (%)</td>
<td>111 (33.7)</td>
<td>57 (35.0)</td>
<td>58 (39.1)</td>
<td>54 (32.6)</td>
<td>56 (35.9)</td>
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<tr>
<td></td>
<td>1.12 (0.71–1.76)</td>
<td>0.640</td>
<td></td>
<td>1.15 (0.73–1.83)</td>
<td>0.533</td>
</tr>
<tr>
<td>Red meat (%)</td>
<td>44 (13.4)</td>
<td>21 (12.9)</td>
<td>29 (19.6)</td>
<td>23 (13.9)</td>
<td>17 (10.9)</td>
</tr>
<tr>
<td></td>
<td>0.92 (0.49–1.74)</td>
<td>0.796</td>
<td></td>
<td>1.99 (1.04–3.81)</td>
<td>0.034</td>
</tr>
<tr>
<td>Processed meat (%)</td>
<td>6 (1.8)</td>
<td>2 (1.2)</td>
<td>3 (2.0)</td>
<td>4 (2.4)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td></td>
<td>0.50 (0.09–2.79)</td>
<td>0.423</td>
<td></td>
<td>0.63 (0.15–2.66)</td>
<td>0.521</td>
</tr>
<tr>
<td>Quantity mentioned (%)</td>
<td>2 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>1.02 (0.06–16.42)</td>
<td>0.990</td>
<td></td>
<td>~</td>
<td>0.304</td>
</tr>
<tr>
<td>Do not know any (%)</td>
<td>40 (12.2)</td>
<td>15 (9.2)</td>
<td>12 (8.1)</td>
<td>25 (15.1)</td>
<td>15 (9.6)</td>
</tr>
<tr>
<td></td>
<td>0.57 (0.29–1.13)</td>
<td>0.104</td>
<td></td>
<td>0.83 (0.38–1.84)</td>
<td>0.644</td>
</tr>
<tr>
<td>Total score [mean (SD)]</td>
<td>1.5 (1.12)</td>
<td>1.5 (1.07)</td>
<td>1.8 (1.06)</td>
<td>1.4 (1.17)</td>
<td>1.5 (1.11)</td>
</tr>
<tr>
<td>Range</td>
<td>0–5</td>
<td>0–5</td>
<td>0–5</td>
<td>0–5</td>
<td>0–5</td>
</tr>
<tr>
<td></td>
<td>0.12 (−0.36 to 0.13)</td>
<td>0.340</td>
<td></td>
<td>0.29 (0.05 to 0.54)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*p < 0.05, significant.
The study is limited by the use of a selected group of patients who have chosen to participate in a lifestyle trial and may not be representative of all patients with colorectal adenomas. However, the results concur with previous qualitative research [12] with patients who had had adenoma diagnosis and surgery suggesting that patients are given little information about the potential causes of adenoma during their treatment and that the “all clear” message received after adenoma removal may be interpreted by some patients as meaning that their lifestyle is not a cause of concern.

The findings are consistent with those of Dowswell et al. [17], who studied attitudes to lifestyle in patients aged 60 to 74 years, diagnosed with an intermediate- or high-risk adenoma. They reported that participants believed that their current dietary and physical activity behaviours were good and they perceived no risk between current health behaviours and their adenoma diagnosis. The authors concluded that intervention programmes should tailor interventions to individual habits as well as lack of knowledge about the aetiology of colon cancer. The BeWEL study [14] did target both of these approaches and the intervention was associated with overall change in knowledge and subsequent change in diet and body weight.

It is unlikely that increasing knowledge and awareness of lifestyle and CRC risk factors will in itself promote behaviour change [18], but both are important prerequisites and platforms from which to develop evidence based behavioural change techniques for planning health improvements. The role of knowledge on behaviour change is considered by Michie et al. [19] in the Capability, Opportunity, and Motivation- (COM-) Behaviour (B) model whereby knowledge and skills are two of the factors which can influence the capability of an individual to change health behaviours. This model demonstrates both the importance of individual level influence and how these might be linked to wider public policy.

The NHS CRC screening setting is a unique opportunity to raise awareness about lifestyle and prevention and to provide further guidance and personalised support to enhance the translation of improved knowledge into action. The current work has utilised a one-to-one lifestyle programme to achieve changes in knowledge and health behaviour which may not be routinely possible within NHS budgets but the results strongly support the need to explore the development of lifestyle counsellors in the same way that many health boards employ smoking cessation counsellors.

5. Conclusion

Despite a growing evidence base on lifestyle and CRC, awareness of relevant factors remains low in people at increased risk. Opportunities within the routine NHS screening setting to aid the capability of individuals to make effective behavioural changes to reduce CRC risk deserve further exploration.

Trial Registration

The trial was registered with Current Controlled Trials (ISRCTN53033856).

Ethical Approval

The study was conducted with the understanding and the consent of the participants. Ethics committee approval was granted by Tayside Committee on Medical Research Ethics B on 16 July 2010 (REC ref. no. 10/S1402/34).

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper with the exception of Prof. Robert J. C. Steele who declares his work as Director of the Scottish Bowel Screening Programme.

Authors’ Contribution

Annie S. Anderson (guarantor) had the original idea for the study and, with Angela M. Craigie, Stephen Caswell, Martine Stead, and Robert J. C. Steele, designed the trial parameters and formed the investigator group who obtained the funding. Annie S. Anderson, Angela M. Craigie, Robert J. C. Steele, and Stephen Caswell were responsible for overseeing study implementation and data collection. Angela M. Craigie, Martine Stead, Stephen Caswell, and Maureen Macleod carried out the analysis. Annie S. Anderson, Angela M. Craigie, Martine Stead, and Maureen Macleod drafted the paper which was revised by all authors. All researchers were independent from funders. The study sponsor and funder played no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments

The authors would like to thank the participants of this trial, the trial manager, trial administrator, research nurses, and lifestyle counsellors whose enthusiastic support made the trial possible. Financial support was provided by the National Prevention Research Initiative (http://www.npri.org.uk), Grant Award no. G0802030. National Prevention Research Initiative is a national research initiative administered by the Medical Research Council made up of the following funding partners: Alzheimer’s Research Trust; Alzheimer’s Society; Biotechnology and Biological Sciences Research Council; Cancer Research UK; Chief Scientist Office, Scottish Government Health Directorate; Department of Health; Diabetes UK; Economic and Social Research Council; Engineering and Physical Sciences Research Council; Health & Social Care Research & Development Office for Northern Ireland; Medical Research Council; Welsh Assembly Government; and WCRF. Further financial support was provided by NHS Research Scotland to carry out this work. The BeWEL Team consists of Shaun Treweek, Fergus Daly, Jill Belch, Jackie Rodger, Alison Kirk, Anne...
Ludbrook, Petra Rauchhaus, Patricia Norwood, Joyce Thompson, and Jane Wardlej.

References


Research Article

The Relationship between Neighborhood Immigrant Composition, Limited English Proficiency, and Late-Stage Colorectal Cancer Diagnosis in California

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Despite the availability of effective early detection technologies, more than half (61%) of colorectal cancers in the United States and 55% in California are identified at an advanced stage. Data on colorectal cancer patients (N = 35,030) diagnosed from 2005 to 2007 were obtained from the California Cancer Registry. Multivariate analyses found a relationship among neighborhood concentration of recent immigrants, neighborhood rates of limited English proficiency, and late-stage colorectal cancer diagnosis. Hispanics living in neighborhoods with a greater percentage of recent immigrants (compared to the lowest percentage) had greater odds (OR 1.57, 95% CI 1.22, 2.02) of late-stage diagnosis whereas Hispanics living in neighborhoods with the highest percentage of limited English proficiency (compared to the lowest percentage) had lower odds (OR .71, 95% CI .51, .99) of late-stage diagnosis. These relationships were not observed for other ethnic groups. Results highlight the complex relationship among race/ethnicity, neighborhood characteristics, and colorectal cancer stage at diagnosis.

1. Introduction

Colorectal cancer (CRC) is the second-leading cause of cancer death and the third-most common type of cancer among men and women in the United States [1]. In 2013, an estimated 142,820 new cases of colorectal cancer will occur, causing 50,830 deaths [1]. Similar to most other cancers, colorectal cancer survival and mortality are linked to stage of disease at diagnosis [2–5]. The 5-year survival rate drops from 90% for those diagnosed with early-stage colorectal cancer to 68% for regional spread (spread to adjacent organs and lymph nodes) and 10% for distant metastases [1]. Despite the availability of effective early detection technologies, more than half (61%) of colorectal cancers in the United States and 55% in California are identified at an advanced stage [1, 6]. Given the availability of effective colorectal cancer screening tests, communities across the USA are unnecessarily suffering from a disease for which early detection has proven effective. And as with many diseases, racial and ethnic minority groups share a disproportionate burden of late-stage colorectal cancer diagnoses. Numerous studies have found that African-Americans, Latinos, and various Asian subgroups are often diagnosed at later stages of diseases [1, 4, 7–11] and have lower survival and higher mortality rates compared to Whites [5, 9, 10, 12, 13].

Research exploring the reasons for diagnosis of late-stage colorectal cancer has implicated determinants at the individual and community level. Most studies to date have
focused on individual characteristics such as low socioeconomic status [14–17] and lack of health insurance [1, 18]. Fewer studies have examined the relationship between community characteristics and late-stage colorectal cancer. Community factors associated with a greater likelihood of late-stage CRC diagnosis include living in rural [19] and medically underserved areas [20], great distances to cancer centers [21], and low neighborhood socioeconomic status, generally measured by income, education, composite measures of socioeconomic status, contextual poverty, and social deprivation [22–25]. However, prior studies have not examined how the proportion of recent immigrants within a community or the level of English proficiency among community residents influences stage at diagnosis for CRC. California provides an ideal setting in which to investigate these factors, given that 27% of residents are immigrants [26] and 6.9 million residents are considered having limited English proficiency, that is, having limited ability to read, write, speak, or understand English [27]. Research indicates that limited English proficiency results in difficulty accessing primary, preventive, and public health services [28–33], and limited English proficient individuals are more likely to receive low quality of care [34] and experience delays in care [35] once they access the system. Research on the effect of immigrant enclaves on health has produced conflicting results. Some studies suggest that immigrants tend to live in poor neighborhoods and that neighborhood poverty may have a detrimental effect on health including low birth weight and physical activity level [36, 37]. Other researchers found that a high concentration of immigrants in one area may shield individuals from the detrimental effects of poverty [38]. The prevailing thought is that ethnic/immigrant enclaves are protective of Latino health as enclaves provide opportunities to foster social relationships [39, 40]. A recent study found that Latinos living in neighborhoods with high concentrations of Latinos and immigrants were more socially integrated and had large, diverse networks [41]. However, no prior research has examined the effect of neighborhood concentration of recent immigrants or neighborhood level measures of limited English proficiency on CRC stage at diagnosis.

Therefore, the purpose of this study was to examine the relationship between neighborhood concentration of recent immigrants and neighborhood level rates of limited English proficiency in relation to late-stage CRC diagnosis in California after controlling for individual and other neighborhood-level factors.

2. Methods

2.1. Data Sources. Data on colorectal cancer cases diagnosed in California between 2005 and 2007 were obtained from the California Cancer Registry (CCR), a large, population-based cancer registry with information on all newly diagnosed cancer cases in California. The CCR is a collaboration of the California Department of Public Health, the Public Health Institute, the California Association of Regional Cancer Registries, the Centers for Disease Control National Program for Cancer Registries, and National Cancer Institute’s Surveillance, Epidemiology, and End Results Program. CCR data were obtained geocoded to the census tract.

Data on neighborhoods (i.e., census tracts) were obtained from the RAND Data Core in the Center for Population Health and Health Disparities, National Institutes of Health Center for Population Health and Health Disparities, National Institutes of Health Center for Population Health and Health Disparities, National Institutes of Health Center for Population Health and Health Disparities, National Institutes of Health. The RAND Data Core is a data resource center available to researchers and community-based organizations interested in how neighborhoods affect health, and houses all measures from the 2000 U.S. decennial census geocoded to the census tract.

2.2. Study Population. Between 2005 and 2007 a total of 39,980 individuals aged 50+ were diagnosed with colorectal cancer in California (see Figure 1). From among these cases, 3,950 were excluded: 107 were not geocoded; 1,981 were diagnosed as in situ; and 1,862 were diagnosed as unknown stage. Thus, the final sample size was 36,030 cases across 6,617 census tracts (mean of 5.45 and median of five participants per census tract, range 1–67), with 93% of cases living in urban areas.

2.3. Variables. The outcome measure for this study was colorectal cancer stage at diagnosis, a derived variable created by the CCR. The derived variable is coded in accordance with guidelines from the CCR and the National Cancer Institute’s Surveillance Epidemiology and End Results Program: in situ, localized, regional by direct extension, regional by lymph nodes, regional by direct extension and lymph nodes, regional (no lymph nodes), remote, and unknown. For this analysis, stage of colorectal cancer at diagnosis was coded as a binary variable (early versus late stage). Early-stage colorectal cancer was defined as cancer at a “localized” stage, whereas late-stage colorectal cancer was defined as cancer diagnosed at a “regional or remote” stage.

Factors examined as potential predictors of stage at diagnosis included both individual and neighborhood-level...
measures. Individual-level measures obtained from the California Cancer Registry for each colorectal cancer case were age at diagnosis (50–75, 75+), sex, race/ethnicity (White, Hispanic/Latino, Black, and Asian), marital status when patient was diagnosed (married versus unmarried), and health insurance (uninsured, Medicaid, Medicare, military/veterans, unknown, and private). Neighborhood measures obtained from the 2000 U.S. Census were percentage of recent immigrants (year of entry: 1995 to March 2000); percentage of limited English proficiency (speak English “well, not well, or not at all”); median household income; and percentage neighborhood deprivation. The neighborhood deprivation summary measure (index/scale) was created by calculating the average percentages of population ≥ 25 years of age without a high school diploma, population receiving public assistance, households with children headed by females, and male population aged 16 and over who are unemployed.

2.4. Statistical Analysis. Descriptive analyses were performed to summarize the characteristics of the study population. Quartiles of the neighborhood measures were used for all the analyses. Associations between stage at diagnosis and individual and neighborhood characteristics were examined using chi-square tests. Bivariate analyses were also used to examine the effects of each variable on stage at diagnosis. Multivariate analyses were used to examine the independent effects on stage at diagnosis. Generalized estimating equation logistic regression modeling was used to account for the potential correlation between participants residing in the same neighborhood. Analysis was performed using SAS (Windows version 9.1).

3. Results

3.1. Demographic Characteristics. Table 1 presents descriptive information on the 36,030 colorectal cancer cases diagnosed in California between 2005 and 2007. The sample consisted of 66% White, 15% Hispanic, 12% Asian, and 7% African-American cases. Most cases (62%) were aged 50–75 years, which is consistent with national data regarding age at diagnosis. Slightly over half were married and most had either private insurance (46%) or Medicare (45%). Only 6% were on Medicaid and 2% reported having no insurance.

3.2. Frequency of Late versus Early Stage at Diagnosis. Overall, the sample contained 20,472 (57%) cases of late-stage and 15,558 (43%) cases of early-stage colorectal cancer. In unadjusted analyses, the proportion of late-stage cancer differed significantly by all variables, with the exception of age.

3.3. Association of Stage at Diagnosis with Individual- and Neighborhood-Level Characteristics in Multivariate Analyses. Table 2 presents the relationship between stage at diagnosis and individual/neighborhood characteristics from multivariate regression analyses. The following independently predicted stage at diagnosis in adjusted analyses.

3.3.1. Percentage Recent Immigrants. Hispanics who live in neighborhoods with a greater percentage of recent immigrants had greater odds of being diagnosed with late-stage colorectal cancer compared to Hispanics who lived in neighborhoods with the lowest percentage of recent immigrants.
<table>
<thead>
<tr>
<th></th>
<th>All races OR</th>
<th>All races CI</th>
<th>White OR</th>
<th>White CI</th>
<th>Hispanic OR</th>
<th>Hispanic CI</th>
<th>Black OR</th>
<th>Black CI</th>
<th>Asian OR</th>
<th>Asian CI</th>
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<td><strong>Age</strong> Continuous</td>
<td>1.01</td>
<td>(0.98, 1.03)</td>
<td>0.99</td>
<td>(0.97, 1.02)</td>
<td>1.00</td>
<td>(0.95, 1.06)</td>
<td>1.03</td>
<td>(0.95, 1.13)</td>
<td>1.05</td>
<td>(0.99, 1.13)</td>
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<td><strong>Sex</strong> Female</td>
<td>1.08</td>
<td>(1.03, 1.13)</td>
<td>1.08</td>
<td>(1.03, 1.14)</td>
<td>1.05</td>
<td>(0.94, 1.18)</td>
<td>1.09</td>
<td>(0.92, 1.30)</td>
<td>1.11</td>
<td>(0.98, 1.27)</td>
</tr>
<tr>
<td><strong>Marital status</strong> No</td>
<td>1.07</td>
<td>(1.02, 1.12)</td>
<td>1.09</td>
<td>(1.03, 1.15)</td>
<td>1.02</td>
<td>(0.90, 1.15)</td>
<td>1.09</td>
<td>(0.91, 1.30)</td>
<td>1.05</td>
<td>(0.91, 1.21)</td>
</tr>
<tr>
<td><strong>Insurance status</strong> Not insured</td>
<td>1.54</td>
<td>(1.28, 1.86)</td>
<td>1.42</td>
<td>(1.06, 1.90)</td>
<td>1.69</td>
<td>(1.21, 2.36)</td>
<td>1.28</td>
<td>(0.64, 2.56)</td>
<td>1.86</td>
<td>(1.21, 2.87)</td>
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<tr>
<td><strong>Marital status</strong> No</td>
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<td>1.09</td>
<td>(1.03, 1.15)</td>
<td>1.02</td>
<td>(0.90, 1.15)</td>
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<td>(1.06, 1.90)</td>
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<td>(1.21, 2.36)</td>
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<td>(0.64, 2.56)</td>
<td>1.86</td>
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<td>1.02</td>
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<td>1.09</td>
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<td>1.69</td>
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<td>(0.64, 2.56)</td>
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<td>(1.21, 2.87)</td>
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<td><strong>Marital status</strong> No</td>
<td>1.07</td>
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<td>(0.91, 1.30)</td>
<td>1.05</td>
<td>(0.91, 1.21)</td>
</tr>
</tbody>
</table>

*PP < .05.
3.3.2. Percentage Limited English Proficiency. Hispanics who live in neighborhoods with the highest percentage of limited English proficiency had lower odds of being diagnosed with late-stage colorectal cancer compared to Hispanics who live in neighborhoods with the lowest percentage of limited English proficiency.

3.3.3. Health Insurance. Non-Hispanic Whites and Asians with no insurance, Medicaid, or “unknown” insurance had higher odds of being diagnosed with late-stage colorectal cancer compared to those with private insurance. Hispanics with no insurance or Medicaid had higher odds of being diagnosed with late-stage colorectal cancer compared to those with private insurance, whereas Hispanics with military/veterans insurance had lower odds of being diagnosed with late-stage colorectal cancer. Only African-Americans with Medicaid had higher odds of being diagnosed with late-stage cancer compared to those with private insurance.

3.3.4. Median Household Income. Income seemed to be predictive of stage at diagnosis for only Asians. Asians living in neighborhoods with a higher median household income had lower odds of being diagnosed with late-stage colorectal cancer compared to Asians living in the neighborhoods with the lowest median household income.

4. Discussion

This study merged California Cancer Registry and U.S. Census data to examine individual- and neighborhood-level predictors of late-stage colorectal cancer in California. Results showed late-stage colorectal cancer diagnosis was predicted by a greater proportion of recent immigrants living in a neighborhood, lower proportion of limited English proficiency in the neighborhood (for Hispanics), and median household income of the neighborhood (for Asians). Lack of health insurance at the individual-level, for all groups except African-Americans, also remained an independent predictor of late-stage colorectal cancer.

4.1. Neighborhood Percentage of Recent Immigrants. We found no studies assessing the relationship between percent recent immigrants in a neighborhood and late-stage colorectal cancer diagnosis. However, our results are similar to those in a study focused on breast cancer stage at diagnosis: authors found that an increased concentration of immigrant populations within neighborhoods contributed to risk of late-stage diagnosis of breast cancer [42]. Part of the explanation may be related to the nature of neighborhoods with large proportions of recent immigrants. These neighborhoods are generally transitory in nature and immigrants come and go as they arrive and acculturate to this country. Individuals living in such neighborhoods (with little to no social support or networks) are less likely to seek screening, which in part may contribute to later stage at diagnosis. Thus, recent immigrants do not benefit from the protective health effects of social capital.

4.2. Neighborhood Percentage of Limited English Proficiency. We expected to find higher late-stage colorectal cancer in neighborhoods with a higher percentage of limited English proficiency, yet we found that neighborhoods with a higher percentage of limited English proficiency had lower odds of late-stage disease. The literature on access to health care may help explain this finding. Recent research among U.S. Hispanics has found that neither English or Spanish language has an effect on determining access to care [43] or that Mexican-American immigrants have better access to care when living in areas with more Spanish speakers or more Hispanic immigrants [40]. A likely explanation may be that, living in areas where a majority of individuals speak the same language or where there are large groups of people with the same background, people form strong social networks [40, 44]. These bonds may increase the probability that health information is disseminated among the groups or neighborhood. A number of studies at the individual-level among Latina women have found that the presence of social networks is related to getting preventive care and cancer screenings [45, 46]. This may be the case in California: neighborhoods with a higher percentage of limited English proficiency may not necessarily be transitory in nature but have higher social cohesion and social capital that has been shown to be protective of health. Additionally, such neighborhoods may benefit from resources and the presence of local organizations and clinics that assist minorities and immigrants, including employing physicians who can communicate in Spanish [40]. Title VI of the 1964 Civil Rights Act requires entities receiving federal funds to provide language assistance to persons with limited English proficiency [47].

4.3. Health Insurance and Median Household Income. Our result on health insurance status shows that individuals with no insurance, Medicaid, and “unknown” insurance are more likely to be diagnosed with late-stage colorectal cancer compared to individuals with private insurance, which is similar to what has been found in other studies, namely, that uninsured and Medicaid patients are more likely to present with late-stage colorectal cancer [16, 18]. Also, we expected that individuals living in neighborhoods with higher incomes would have early stage at diagnosis, and we only saw this for Asians. While there is not much in the literature to help explain this finding, one study examining neighborhood income and Asian ethnicity with respect to liver cancer reported that Asians living in low socioeconomic status neighborhoods had a greater proportion of late-stage liver cancer [48]. These findings may be a result of higher income neighborhoods having more available resources and services that confer a health advantage.

There are several limitations to this study. We were not able to include individual-level data on English language proficiency, length of residence in the USA, or socioeconomic status that might interact with neighborhood-level factors and help explain observed results. Similarly, we have no data on health beliefs, lifestyle factors, and rates of colon cancer screening. Yet disparities in colorectal cancer screening, in particular, may contribute to observed differences in cancer
stage at diagnosis, especially late-stage disease [49]. Also, we did not have data on Hispanic or Asian subgroups that might help explain results. Although these groups are often grouped together, they are not homogenous.

Despite these limitations, this paper highlights the importance of neighborhood characteristics in late-stage colorectal cancer diagnosis. Efforts are needed to reach these populations or find affordable ways to get them screened for colorectal cancer. Also, further research is needed to tease out the contribution of individual- and neighborhood-level factors on influencing uptake of colorectal cancer screening; yet collecting individual-level data through surveys can be costly and time-consuming, and cancer registry data often does not include individual-level measures of socioeconomic status, language, or acculturation. Also evidence-based interventions are needed to increase use of colorectal cancer screening and reduce late-stage diagnosis, taking into account both individual and neighborhood factors.

5. Conclusions

Implementation of the Affordable Care Act (ACA), which does not require copayment for colorectal cancer screening, will likely reduce the magnitude of the influence of health insurance coverage as a contributing factor to late-stage colorectal cancer diagnosis. However, only US citizens and legal residents will be able to obtain health coverage under the ACA [50]. California, home to an estimated 1.8 million undocumented immigrants aged 18–64 [51], is likely to have one of the largest populations of individuals left out of the ACA. On the other hand, studies have not consistently found that public insurance predicts a higher likelihood of early-stage diagnosis [18] but rather that complex combinations of factors influence likelihood of receiving screening in addition to insurance status and actual health care access.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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References


Research Article

Missed Opportunities for the Diagnosis of Colorectal Cancer

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Objective. To examine patient and medical characteristics which predict a missed diagnostic opportunity (MDO) for colorectal cancer (CRC). Methods. The sample consisted of 252 patients diagnosed with Stages 1–4 CRC who were diagnosed in the prior six months, had experienced symptoms prior to diagnosis, and were not diagnosed through routine screening. Systematic review of all medical records prior to patients’ diagnosis was conducted. An MDO was defined as a clinical encounter where, even in the presence of presumptive CRC symptoms, the CRC diagnostic process was not started. Results. 92 patients (36.5%) experienced an MDO. Almost 80% of alternate diagnoses were other GI-GU diseases, including hemorrhoids and diverticulitis. Stomach pain, anemia, and constipation were the most common symptoms experienced by the MDO group. These symptoms, and weight loss and vomiting, were more likely to be noted in the charts of the MDO patients (P < 0.04). Independent risk factors for MDO included age (<50) [OR = 2.29 (1.14–4.60), P = 0.02] and female sex [OR = 2.19 (1.16–4.16), P = 0.03]. Each additional physician seen, more than doubled the MDO risk [OR = 2.05 (1.53–2.74), P < 0.001]. Conclusions. Females, younger patients, and those consulting more physicians were all more likely to experience an MDO. Continued increased training of physicians to enhance knowledge of who is vulnerable to CRC is needed in addition to an increased focus to adherence to screening recommendations.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in the world and fourth most common cause of cancer death worldwide [1]. In the United States (US), it is also the third most common cancer in both men and women, but the second leading cause of cancer-related deaths [2]. Early stage at diagnosis, associated with screening, is linked to better prognosis and reduced mortality from CRC [3, 4]. When identified at its earliest stages, reductions in morbidity and costs have been identified [5]. However, only 40% of CRCs are diagnosed at an early stage [6]. Therefore, recognition of CRC symptoms as early as possible coupled with prompt provision of medical attention for those who are experiencing associated symptoms is critical.

Initial patient appraisal of CRC symptoms is frequently delayed by underrecognition of symptom significance and poor follow through with physician recommendations. The literature defines patient appraisal delay as patients’ failure to recognize, acknowledge, or act on symptoms [7]. A systematic review of the literature reports that appraisal delay is the main patient factor associated with lengthier patient times between experiencing a symptom and presenting it to a practitioner [8]. There is some evidence to suggest that demographic characteristics are associated with delayed medical care seeking for CRC, and these include female sex, younger age, lower education, and being a member of a minority community [9–11]. However, more research is needed to fully understand these factors.

Physicians may also delay the diagnosis by attributing CRC symptoms to other less serious causes [12]. In one study, diagnostic delay was reported to be more likely to occur when a physician did not recognize symptoms as serious [13]. This can occur with many CRC symptoms, including the cardinal symptoms of rectal bleeding, anemia, abdominal pain, weight loss, or changes in bowel habits; these symptoms...
are also indicative of many other, more common, but non-life threatening diseases [14, 15]. Other factors contributing to diagnostic delay may include poor physician-patient communication, resulting in physician or patient failure to explore symptoms or obtain follow-up tests or referrals to specialists [16]. Poor communication results when patients understate or minimize symptoms or when physicians do not thoroughly explore symptoms [13]. The results of these factors may result in missed diagnostic opportunities (MDOs) and unintentional delay in initiating treatment [17]. Although, to date, gender has not been shown to play a role in diagnostic delay [11] of CRC, research on patient gender in physician-patient communication suggests that female patients ask more questions, present more symptoms, and give more information in their medical history [18, 19].

There is some evidence to suggest longer CRC diagnostic delay for ethnic minorities [20], and considerable research to indicate differences in physician-patient communication based on race/ethnicity, including less provision of biomedical information, less psychosocial counseling, and less relationship building with non-White breast cancer patients [21], as well as less patient-centered communication and less positive affect towards African American patients [22].

This study examined the factors associated with MDOs. Using a sample of recently diagnosed CRC patients in two US states, data was reviewed and extracted from all medical records prior to patients’ diagnoses. The study was designed to specifically test whether individuals would be more likely to have an MDO based on race and gender. Specifically, we hypothesized that MDO would be more common in non-Caucasians (potentially as a result of less patient-centered visits) and in females (possibly because providing a large amount of information increases the complexity of their clinical presentation). We also examined whether patients who had more symptoms and certain types of symptoms would be less likely to have an MDO. The importance of this to CRC is suggested by the study conducted by Astin et al. (2011) suggesting certain symptoms and multiple symptoms have increased positive predictive value [23].

2. Methods

2.1. Participants. Patients with a confirmed diagnosis of Stages 1–4 CRC were identified, between 2008 and 2010, through multiple sources to obtain complete ascertainment of eligible patient cases, at the three academic and two large private community oncology practices in Virginia and Ohio. Case finding was conducted over a two-year period by reviewing billing codes, obtaining cases from tumor board or multidisciplinary conferences, and by reviewing pathology reports of patients prospectively. All patients diagnosed in the six months prior to initial case identification were contacted and phone screened. Inclusion criteria required that patients have a diagnosis of CRC in the prior six months and have experienced symptoms prior to their diagnosis. Patients whose CRC was diagnosed as a result of routine screening were excluded. The patients’ medical histories started at their diagnoses in oncology practices and were then traced back to their primary care physicians. Although case finding occurred at oncology practices, the primary care physicians who saw these patients were in private practice and fed into many healthcare systems and followed many different clinical practice guidelines for the management of CRC symptoms. This study was approved by all relevant Institutional Review Boards and all participants provided informed consent.

2.2. Measurement. A systematic review of all patient medical records, both electronic and paper, prior to CRC diagnosis was conducted. As in previous studies [24], a detailed review of progress notes, consultations, laboratory and pathology reports, and additional relevant data in the records were reviewed to evaluate the diagnostic process and assess it for MDOs. Three raters were trained to conduct the review under the auspices of one of the investigators (SHH), a board certified family physician. The reviews were guided by a 20-page coding manual. The coders extracted the information according to the coding manual that operationalized the definitions associated with each item; 20% were double coded with discrepancies resolved via consensus. Records were reviewed as far back as 8 years, when warranted.

The data extracted from the medical record included patient sociodemographic characteristics, the number and type of physicians seen (e.g., primary care, gastrointestinal specialists, and obstetricians/gynecologists), type of physician in which the patient first reported symptoms, the practice type (clinic, emergency department, etc.), specific symptoms noted (abdominal pain, bowel changes, diarrhea, constipation, indigestion, weight loss, blood in stool, anemia, vomiting, rectal bleeding, and nausea), tests ordered and/or performed (colonoscopy, fecal occult blood test, sigmoidoscopy, barium enema, CT Scan, Magnetic Resonance Imaging, Positron emission tomography, blood work, urine analysis, digital rectal exam, other pelvic exams, endoscopy, and hemoccult), date of first symptom noted, date of diagnosis, date of tests, date and type of definitive diagnostic test, assessment of whether or not an MDO occurred, assessment of whether watchful waiting occurred (which was categorized under MDO), list of alternate diagnoses provided (if any), and stage and staging information.

2.3. Main Measures

2.3.1. Outcome

Missed Diagnostic Opportunity. The definition of MDO, adapted from the literature, is defined as a clinical encounter where, even in the presence of presumptive illness symptoms (in this case CRC), the diagnostic process is not started. Rather, alternative evaluations are initiated or an incorrect diagnosis is provided that ends the clinical evaluation process for CRC [25, 26]. All charts were rigorously reviewed and because we reviewed all visits for the CRC symptom cluster that often crossed many visits, we were able to contextualize the decisions made by physicians. Classification of an MDO, which included inappropriate watchful waiting, was reviewed by a board certified family physician (SHH). The outcome is binary—the absence of MDO refers to the commencement of a diagnostic process in response to symptoms while
the presence of MDO involves the offering of alternative evaluations or incorrect diagnoses that deviate from the diagnostic process of CRC.

2.3.2. Covariates

(1) Symptoms. Symptoms were documented if noted in the charts. Stomach or abdominal pain of any kind, bowel/stool changes, diarrhea, constipation, blood in stool, rectal bleeding, anemia/tiredness/weakness, weight loss, nausea, vomiting, and/or indigestion and additional, related symptoms, were summed to represent a total symptom count per patient.

(2) Physician Factors. The number and specialty of physicians consulted were recorded from the medical records.

(3) Patient Medcodemographic Characteristics. Age, gender, race, education, income, insurance status, and history of comorbid chronic disease were recorded. We also obtained information on prior diagnostic tests leading to CRC diagnosis including colonoscopy and other screening tests.

2.4. Statistical Analysis. SPSS version 20.0 was employed for analyses. Descriptive statistics were used to describe the sample, alternative diagnoses received, and time to diagnosis. Chi-square tests were used to determine significant bivariate relationships between the presence/absence of MDO and patient medicodemographic characteristics, physician characteristics, and presence/absence of specific symptoms. Independent t-tests were used to test the relationships between presence/absence of MDO and the three continuous variables measured: tumor size, number of total symptoms, and number of total physicians seen for symptoms prior to diagnosis. A stepwise logistic regression model was conducted to examine the independent predictors of MDO, controlling for sociodemographic characteristics. Sociodemographic characteristics shown to be significant in bivariate analyses at \( P < 0.05 \) were entered into the first block, followed by medical characteristics (including presence/absence of specific symptoms) and physician characteristics that were shown to be significant in bivariate analyses at \( P < 0.05 \). Independent variables in the logistic regression model were tested for significance using the Wald statistic at a \( P \) value level of 0.05. For summary purposes, Nagelkerke’s \( R^2 \) (analog to the \( R^2 \) in linear regression) was used to indicate the extent of variation explained and model fit.

3. Results

3.1. Patient Medcodemographic Characteristics. Of 495 patients screened, 66% (\( N = 303 \)) were eligible to participate, 84% (\( N = 256 \)) consented, and 252 completed the study. The patient population consisted of 47.6% (\( n = 120 \)) women and 53.6% (\( n = 135 \)) Caucasian. Twenty-five percent (\( n = 64; 25.4\% \)) were <50 years old, 47.6% (\( n = 120 \)) had a high school education or less, 44.0% (\( n = 111 \)) had private health insurance, and one-third of the sample (\( n = 84; 33.3\% \)) was diagnosed with earlier stage (I and II) disease. An MDO was ascertained from the medical records of 92 patients (36.5%). Table 1 shows the sociodemographic characteristics of CRC patients with and without an MDO.

CRC patients with an identified MDO were significantly more likely to be younger (less than age 50; \( X^2 = 6.74, P = 0.009 \)), female (\( X^2 = 11.94, P = 0.001 \)), and a race other than Caucasian (\( X^2 = 4.73, P = 0.03 \)) compared to those without MDOs. The groups were similar with respect to stage at time of diagnosis, tumor size, tumor depth, and presence of metastases. Patients with an MDO had an average of 2.7 nodes positive for cancer at diagnosis compared to 2.0 for those without an MDO and this difference was marginally significant (\( P = 0.05 \)).

Table 2 shows the patient and physician characteristics of the sample. Over half of the sample (57.1%; \( n = 144 \)) reported having a comorbid chronic condition at the time of diagnosis (e.g., hypertension, diabetes, and cardiac conditions). Although comorbidities were common in this sample, having at least one comorbidity was not associated with an MDO. A minority of patients (18.3%; \( n = 46 \)) had a colonoscopy or other CRC screening tests (18.9%; \( n = 47 \)) prior to receiving the diagnostic tests that led to the CRC diagnosis. Neither of these factors was associated with MDO.

3.2. Symptoms. The average participant reported their symptoms to two physicians at separate visits at outpatient primary care practices, emergency rooms (ER), and/or urgent care centers (range 0–10). Those patients with MDOs reported their symptoms to significantly more physicians than those who did not (3.8 versus 2.4 physicians; \( t = 7.00, P < 0.001 \)). Sixty-eight percent (\( n = 171; 67.9\% \)) of patients first communicated their symptoms to a primary care physician (PCP) and 21.0% (\( n = 53 \)) in the ER. Type of physician seen first was not associated with MDO. Patients with more symptoms were more likely to experience an MDO (4.7 versus 3.7; \( t = 3.29; P = 0.001 \)) (see Table 2). Compared to those without an MDO, those with an MDO were significantly more likely to have the following symptoms noted in their medical records: stomach pain (\( X^2 = 10.20, P = 0.001 \)), anemia (\( X^2 = 8.11, P = 0.004 \)), constipation (\( X^2 = 5.04, P = 0.03 \)), weight loss (\( X^2 = 4.40, P = 0.04 \)), and vomiting (\( X^2 = 4.19, P = 0.04 \)) (see Table 3). No differences between groups were noted with respect to other symptoms such as blood in stool and change in bowel habits. The percentage of individuals with each symptom who also experienced rectal bleeding was 35.3% of those with stomach pain, 24.7% of those with anemia, 34.7% of those with constipation, 32.6% of those with weight loss, and 20.5% of those with vomiting. Rectal bleeding was associated with anemia (\( X^2 = 5.70, P = 0.017 \)) and vomiting (\( X^2 = 4.20, P = 0.04 \)) such that individuals with anemia charted in their medical records were less likely to have rectal bleeding charted than those without anemia (24.7% versus 39.4%). Similarly, those with vomiting were less likely to have rectal bleeding reported (20.5% versus 36.5%).

3.3. Missed Diagnostic Opportunity, Alternative Diagnoses, and Time to Diagnosis. Diagnostic delay was defined based
<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients who had missed diagnostic opportunity</th>
<th>Patients who did not have missed diagnostic opportunity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 92; 36.5%)</td>
<td>(n = 160; 63.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57 (62.0%)</td>
<td>63 (39.4%)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>41 (44.6%)</td>
<td>94 (58.8%)</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Age**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>32 (34.8%)</td>
<td>32 (20.0%)</td>
<td>P = 0.009</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;High school</td>
<td>18 (19.6%)</td>
<td>32 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>30 (32.6%)</td>
<td>40 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>33 (35.9%)</td>
<td>50 (31.3%)</td>
<td>P = 0.10</td>
</tr>
<tr>
<td>Bachelor’s degree and beyond</td>
<td>11 (12.0%)</td>
<td>37 (23.1%)</td>
<td></td>
</tr>
<tr>
<td>Declined to answer/do not know</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$30,000</td>
<td>44 (47.8%)</td>
<td>61 (23.2%)</td>
<td></td>
</tr>
<tr>
<td>$30K–$75K</td>
<td>28 (30.4%)</td>
<td>44 (27.5%)</td>
<td>P = 0.22</td>
</tr>
<tr>
<td>&gt;$75K</td>
<td>18 (19.6%)</td>
<td>45 (28.1%)</td>
<td></td>
</tr>
<tr>
<td>Declined to answer/do not know</td>
<td>2 (2.3%)</td>
<td>10 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Health insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>41 (44.6%)</td>
<td>70 (43.8%)</td>
<td>P = 0.71</td>
</tr>
<tr>
<td>Medicare</td>
<td>28 (30.4%)</td>
<td>43 (26.9%)</td>
<td></td>
</tr>
<tr>
<td>Medicaid, state insurance, or uninsured</td>
<td>23 (25.0%)</td>
<td>47 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>25 (27.2%)</td>
<td>59 (36.9%)</td>
<td>P = 0.06</td>
</tr>
<tr>
<td>3-4</td>
<td>65 (70.7%)</td>
<td>101 (63.1%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>5.1 (2.1)</td>
<td>4.8 (2.0)</td>
<td>P = 0.14</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01.

**Table 2: Patient and physician factors associated with missed diagnostic opportunity.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients who had missed diagnostic opportunity</th>
<th>Patients who did not have missed diagnostic opportunity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of comorbid condition</td>
<td>57 (62.0%)</td>
<td>87 (54.4%)</td>
<td>P = 0.24</td>
</tr>
<tr>
<td>Colonoscopy prior to the one leading to CRC diagnosis</td>
<td>19 (20.7%)</td>
<td>27 (16.9%)</td>
<td>P = 0.46</td>
</tr>
<tr>
<td>Other CRC screening tests prior to one leading to diagnosis</td>
<td>14 (15.4%)</td>
<td>33 (20.9%)</td>
<td>P = 0.29</td>
</tr>
<tr>
<td>Number of symptoms**</td>
<td>4.7 (2.6)</td>
<td>3.7 (2.2)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Mean number of physicians seen***</td>
<td>3.8 (1.8)</td>
<td>2.4 (0.9)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Type of physician first seen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care physician</td>
<td>64 (69.6%)</td>
<td>107 (66.9%)</td>
<td>P = 0.81</td>
</tr>
<tr>
<td>Emergency room physician</td>
<td>21 (22.8%)</td>
<td>32 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>Other (specialist, nurse, etc.)</td>
<td>7 (7.6%)</td>
<td>21 (13.1%)</td>
<td></td>
</tr>
</tbody>
</table>

**P < 0.01, ***P < 0.001.**
on the recommended refinements to The General Model of Total Patient Delay [27] proposed by Andersen and colleagues (1995) [28] stemming from earlier work by Safer and colleagues (1979) [29]. Diagnostic delay was defined as the time in months from the date of the first consultation with a healthcare provider for symptoms to the date of diagnosis. Overall, the average diagnostic delay was 4.7 months (SD = 8.2).

Almost 80% of patients with an MDO were diagnosed with an alternate GI-GU disease (n = 73; 79.3%), including hemorrhoids (n = 26), diverticulitis (n = 15), urinary tract infection (UTI, n = 9), colitis/gastritis (n = 7), gastroesophageal reflux disease (GERD, n = 6), irritable bowel syndrome (IBS, n = 5), and/or gastroenteritis (n = 5) (see Table 3). All of the individuals with alternate diagnoses of UTI were women (100%, n = 9), two out of three of those diagnosed with diverticulitis were women (67%, n = 15), and the majority of those diagnosed with hemorrhoids (58%; n = 15) were women. Approximately one out of four received a non-GI-GU diagnosis (n = 21; 22.8%). For 26 patients (28.3%), the review of the medical records indicated that the physician engaged in watchful waiting, for example, when a patient's GI symptom complaints did not result in follow-up testing and/or the only treatment recommendations involved lifestyle or dietary changes.

Mean diagnostic delay for patients without an MDO was 2.0 months (SD = 4.0), significantly shorter than 9.4 months (SD = 11.0) for patients with a documented MDO (t = 8.21, P < 0.001). Patients whose physicians did not recommend watchful waiting averaged 3.7 months (SD = 6.6), significantly shorter than 13.6 months (SD = 13.6) for those whose physicians engaged in watchful waiting (t = 5.40, P < 0.001). Patients receiving a GI-GU related alternate diagnosis averaged 9.0 months (SD = 9.9) to diagnosis while those who received a non-GI-GU diagnosis needed 10.5 months (SD = 11.5) to be diagnosed (see Table 4).

3.4. Logistic Regression Model Predicting Missed Diagnostic Opportunity. The final model (Table 5) demonstrates that patients who had an MDO were more than twice as likely to be less than 50 years [OR = 2.29 (1.14–4.60), P = 0.02] and female [OR = 2.19 (1.16–4.16), P = 0.03]. For each physician seen, the likelihood of MDO more than doubled [OR = 2.05 (1.53–2.74), P < 0.001]. Number or type of symptoms was not independently predictive of MDO. Nagelkerke's R² of 0.36 indicates a moderate relationship between the set of predictors in the model and MDO.

4. Discussion

Routine screening is important for early diagnosis of CRC. However, many Americans are noncompliant with screening guidelines and screening is not perfect; only 65% of Americans, age 50 and older, have ever undergone any type of screening test for CRC [30]. Interestingly, screening compliance rates are similar in universal care and/or socialized health care systems [31]. For instance, only 55–60% of individuals aged 60 invited to participate in the Bowel Cancer Screening Programme in England returned their first FOBT [32]. Recent studies also estimate that colonoscopy may miss detecting lesions [33]. Moreover, routine testing is not recommended for those under 50 years of age; therefore, symptom recognition remains an important component of early detection and treatment. We found evidence that being younger (<50) and female, as well as being assessed by more than one physician, were independent risk factors for MDO. Furthermore, over the course of diagnosis, stomach pain, anemia, and constipation were more frequently documented in the group of patients with MDO. These, of course, are symptoms common to other illnesses and anemia is especially prevalent in menstruating women and associated with gynecological ailments. Lastly, almost 80% of misdiagnoses were alternate GI-GU diseases, most commonly, hemorrhoids
Table 4: Alternate diagnoses recorded in medical chart for symptoms indicative of CRC (n = 92).

<table>
<thead>
<tr>
<th>Alternate diagnosis†</th>
<th>n</th>
<th>Mean time to diagnosis in months</th>
<th>Median time to diagnosis in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diagnosis, missed opportunity/watchful waiting</td>
<td>26</td>
<td>13.6 (13.6)</td>
<td>9.2</td>
</tr>
<tr>
<td>GI-GU disease</td>
<td>73</td>
<td>9.0 (9.9)</td>
<td>6.3</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection (UTI)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis/Gastritis</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable bowel syndrome (IBS)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney stones</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OB/GYN disease (cyst, neoplasm, fibroids)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel disease (cancer, obstruction)</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Gallbladder</td>
<td>2</td>
<td></td>
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<tr>
<td>Crohn's disease</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Chronic dysphagia</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Chronic constipation</td>
<td>1</td>
<td></td>
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<tr>
<td>Hernia</td>
<td>1</td>
<td></td>
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<tr>
<td>Dyspepsia</td>
<td>1</td>
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<tr>
<td>H. pylori</td>
<td>1</td>
<td></td>
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<tr>
<td>Appendicitis</td>
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<td>Prostatitis</td>
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<tr>
<td>Anal fissure</td>
<td>1</td>
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<tr>
<td>Syphilis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-GI-GU diagnoses</td>
<td>21</td>
<td>10.5 (11.5)</td>
<td>9.3</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back/skeletal</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects of medications</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Some patients had more than one alternate diagnosis; 11 had both GI-GU and non-GI-GU alternate diagnoses. Because of this no tests of significance were performed.

and diverticulitis, and that diagnosis with a non-GI-GU disease was associated with even longer diagnostic delay. Individuals with an MDO experienced nearly double the time to diagnosis, and patients whose physicians chose watchful waiting experienced triple the time.

Few studies have simultaneously examined patient and physician factors influencing MDO in CRC; these studies have investigated physician delay in referring patients for further investigation of symptoms. Like this study, other studies indicate that older age leads to quicker referrals and more prereferral consultations are associated with younger age and ethnic minority status [11]. This supports the results of the present study in which those under age 50 are 2.3 times more likely to experience an MDO. In univariate analyses, patients of a race other than Caucasian were more likely than Caucasians to have an MDO, although these results were not significant in the multivariable model. Our findings strongly suggest that gender plays a significant role, as 62% of the MDO group were female. Follow-up analyses found that most of the alternate diagnoses of hemorrhoids, diverticulitis, and UTIs were made in females.
Some of this study’s findings are not consistent with previous work in the field, however. For instance, patients who experienced an MDO average one more documented symptom than those who did not experience an MDO. Mariscal et al. report that, as the number of symptoms presented increases, time from initial consultation to hospital admission for digestive tract cancers decreases [34]. The fact that higher number of symptoms are related to MDO but not stage suggests that patients who experienced an MDO in this study may be presenting with a more complex clinical picture. The types of symptoms these patients present with, and the time course of their multisymptom presentation, may account for this discrepancy, especially given that this sample excluded patients diagnosed through screening colonoscopy. These patients were excluded because of the study’s intent to examine the role that symptom presentation plays in the diagnostic process. Our study indicates that anemia, stomach pain, and constipation were the most common symptoms of the group with MDOs. In European cohorts, iron-deficiency anemia [26, 35] and rectal bleeding [26] were the primary symptoms most often associated with MDO for CRC diagnosis. In a US study, Singh et al. also found that anemia was the most common symptom associated with MDOs for CRC diagnosis and longest referral time for an endoscopic procedure [25]. It was also associated with two-thirds of MDOs for CRC in a Veterans Administration sample [36]. Of note in our study is that, in multivariable analyses, anemia was not a significant independent predictor of MDO. Finally, a systematic review of the diagnostic value of symptoms for CRC in primary care concluded that investigation of anemia in primary care patients is warranted, regardless of whether other symptoms are present [23].

Seeing an additional physician for CRC symptoms was associated with twice the risk of MDO. Although this finding may be intuitive, as increases in seeking consultations with new physicians provides more opportunity/risk for possible MDO, to our knowledge, the importance of this factor as related to MDO and/or diagnostic delay has not been previously documented. Our sample was comprised exclusively on those individuals who experienced symptoms prior to diagnosis who were primarily diagnosed with later stage disease, whereas many other studies examine all patients diagnosed with CRC and focus on physician screening behaviors and probably drove these results. We believe it is a strength, of this study, as those diagnoses through screening are a different segment of the CRC population. Furthermore, physician training, resources, and screening guideline incentives may differ across healthcare systems and regions, thus additional investigation of the factors related to MDO, in other contexts, is warranted.

It is possible that some physicians may have made verbal diagnoses or recommendations for follow-up that were not documented in the medical records and would not have been captured using the chart review methodology. Although we compiled lists of all possible physicians seen by patients and followed-up with practices identified via documented referrals, it is possible we may have missed some, thus influencing this study’s findings. Although every effort was taken to ensure that the case notes were rigorously reviewed, the timing of specific symptoms and symptom combinations in relation to the MDO was not extracted. Future studies, especially in the context of the U.S. healthcare system, and in context of the high variability in community practice, are warranted to fully explore these aspects.

In summary, our study suggests that greater training of physicians could be helpful for dispelling stereotypes about who is vulnerable to CRC. Within the population, men are only slightly more susceptible to CRC than women [1]; however, women were twice as likely to experience an MDO. Younger patients (<50 years) are also more likely to experience an MDO, giving rise to some concern that current CRC screening recommendations are leading physicians to erroneously discount the possibility of CRC in symptomatic younger patients. A recent study supports these findings, that, even lacking a family history, CRC is not insignificant [37]. Moreover, the incidence rate of CRC in this age group is increasing and now accounts for 12% of all cases of CRC [37, 38]. Given the fact that a physician has, on average, six to 18 minutes to conduct a clinical evaluation and provide follow-up recommendations (depending on the country) and that physicians feel they need more time to spend with their patients [39], future research and policy are needed to better understand and assist physicians with the demands placed on them that may result in rushed visits and ultimately an MDO.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Wald</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: female*</td>
<td>0.79</td>
<td>5.79</td>
<td>2.19 (1.16–4.16)</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Race: African American</td>
<td>0.31</td>
<td>0.96</td>
<td>1.37 (0.73–2.57)</td>
<td>P = 0.36</td>
</tr>
<tr>
<td>Age &lt; 50*</td>
<td>0.83</td>
<td>5.41</td>
<td>2.29 (1.14–4.60)</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Number of physicians seen***</td>
<td>0.72</td>
<td>23.31</td>
<td>2.05 (1.53–2.74)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Number of symptoms experienced</td>
<td>0.07</td>
<td>1.02</td>
<td>1.07 (0.94–1.23)</td>
<td>P = 0.31</td>
</tr>
<tr>
<td>Stomach pain</td>
<td>0.54</td>
<td>2.34</td>
<td>1.07 (0.86–3.41)</td>
<td>P = 0.26</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.11</td>
<td>0.11</td>
<td>1.12 (0.58–2.17)</td>
<td>P = 0.74</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.17</td>
<td>0.22</td>
<td>1.18 (0.59–2.35)</td>
<td>P = 0.64</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.17</td>
<td>0.23</td>
<td>1.18 (0.60–2.33)</td>
<td>P = 0.63</td>
</tr>
<tr>
<td>Vomiting</td>
<td>−0.26</td>
<td>0.32</td>
<td>0.77 (0.32–1.87)</td>
<td>P = 0.57</td>
</tr>
</tbody>
</table>

*P < 0.05, ***P < 0.001.
Looking at the results as a whole, there are potential lessons for clinical practice. First, although it is important to understand the average characteristics of a patient population, the focus in the physician-patient encounter is the patient and not his/her sociodemographic group. Although 90% of new cases of CRC are in patients over 50 years of age, over 14,000 individuals less than age 50 in the US alone will be diagnosed with CRC annually [40]. Therefore, some vigilance concerning patients under the age of 50 is warranted. In this study, younger patients were more likely to have greater times to diagnosis. In addition, women were also more likely to have greater diagnostic delay, perhaps because CRC is thought to be more prevalent in men. Another source of diagnostic difficulty was demonstrated by greater time to diagnosis for patients with more symptoms. Although intuitively it would seem that more symptoms would provide more sign posts leading toward the CRC diagnosis, the greater number of symptoms, coupled with the nonspecific nature of these symptoms, seemed to add complexity rather than clarity to making a diagnosis. We posit that when patients were seen by more physicians—perhaps because the patient was not satisfied with the treatment provided by the initial physician or because they did not have easy or regular access to the health system—the discontinuity in care led to greater time to diagnosis. This is an issue that bears further exploration.

It may be that some physicians are confronting a Hobson’s choice between interacting with the “whole” patient or just asking for the facts, although both pieces are likely important. This study is yet another indication that quality care takes time, skill, and the participation of both the patient and the physician.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References


Review Article

Developments in Screening Tests and Strategies for Colorectal Cancer

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Background. Worldwide, colorectal cancer (CRC) is the third most common cancer in men and second most common in women. It is the fourth most common cause of cancer mortality. In the United States, CRC is the third most common cause of cancer and second most common cause of cancer mortality. Incidence and mortality rates have steadily fallen, primarily due to widespread screening. Methods. We conducted keyword searches on PubMed in four categories of CRC screening: stool, endoscopic, radiologic, and serum, as well as news searches in Medscape and Google News. Results. Colonoscopy is the gold standard for CRC screening and the most common method in the United States. Technological improvements continue to be made, including the promising “third-eye retroscope.” Fecal occult blood remains widely used, particularly outside the United States. The first at-home screen, a fecal DNA screen, has also recently been approved. Radiological methods are effective but seldom used due to cost and other factors. Serum tests are largely experimental, although at least one is moving closer to market. Conclusions. Colonoscopy is likely to remain the most popular screening modality for the immediate future, although its shortcomings will continue to spur innovation in a variety of modalities.

1. Background

Worldwide, colorectal cancer (CRC) is the third most common cancer in men and second most common one in women [1]. It is also the fourth most common cause of cancer mortality [1]. Colorectal cancer (CRC) is the third most common cancer in the United States, as well as the second most common cause of cancer mortality [2, 3]. The lifetime prevalence of colorectal cancer in American men is 5% and only slightly lower in women [2]. Although those rankings have held steady in recent decades, incidence and mortality rates have steadily fallen [4].

The fall in CRC rates has not been even. Individuals over forty-nine years of age account for nearly the entire drop [5]. In fact, rates are rising in younger cohorts, although this population still accounts for a relatively low proportion of overall incidence (less than eight percent) [5]. Screening improvements, in methods and utilization rate, account for most of the drop in colorectal cancer burden [2]. Other important factors include changes in risk factors and improvements in treatment [2, 6].

Unfortunately, the primary risk factors for CRC remain poorly understood. The most compelling evidence for the role of lifestyle in CRC pathology is the stark difference in prevalence between developed and developing nations. Rates vary by factors of two and three, with higher disease burdens consistently limited to developed countries [1]. Rates in the United States are somewhat lower than in Europe and Australia but remain considerably higher than in other, less developed regions [1]. Moreover, immigrant populations experience a dramatic rise in colorectal cancer risk within one generation of moving to a developed economy [7].

Diet, fiber intake, and alcohol are all linked to colorectal cancer risk [8]. But the effect of each of these risk factors, alone and in the aggregate, is relatively subdued. They cannot account for disparities in colorectal cancer burden
Table 1: Screening recommendations (adapted from Short et al. [110]).

<table>
<thead>
<tr>
<th>Organization</th>
<th>Screen and interval</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Preventive Services Task Force (USPSTF)</td>
<td>(1) Fecal occult blood (1-year)</td>
<td>50+ years</td>
</tr>
<tr>
<td></td>
<td>(2) Flexible sigmoidoscopy (5-year) + high-sensitivity FOBT (3-year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) Colonoscopy (10-year)</td>
<td></td>
</tr>
<tr>
<td>Preferred</td>
<td>(1) Colonoscopy (10-year)</td>
<td>45+ years for blacks</td>
</tr>
<tr>
<td>American College of Gastroenterology</td>
<td>(2) FIT (1-year), if colonoscopy declined</td>
<td>50+ years everyone else</td>
</tr>
<tr>
<td>Alternative (prevention)</td>
<td>(3) Flexible sigmoidoscopy (5- to 10-year)</td>
<td></td>
</tr>
<tr>
<td>Alternative (cancer detection)</td>
<td>(4) CT colonography (5-year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5) gFOBT (1-year)</td>
<td></td>
</tr>
<tr>
<td>Alternative (prevention)</td>
<td>(6) Stool DNA (3-year)</td>
<td></td>
</tr>
<tr>
<td>American Cancer Society</td>
<td>Adenoma and cancer</td>
<td>50+ years</td>
</tr>
<tr>
<td></td>
<td>(1) Flexible sigmoidoscopy (5-year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2) Colonoscopy (10-year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) Double-contrast barium enema (5-year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4) CT colonography (5-year)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>(5) High-sensitivity FOBT (1-year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6) FIT (1-year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(7) Stool DNA (Cologuard) (uncertain)</td>
<td></td>
</tr>
</tbody>
</table>

across countries [8]. Nor is the link between increasing CRC incidence in younger people and increasing obesity clearly established [2].

With the environmental basis for CRC still cloudy, screening remains the basis for colorectal cancer prevention. As with most cancers, early detection vastly improves prognosis. Five-year survival is nearly 90% for localized lesions and 70% for regional ones, but plummetts to 13% with distant metastasis [4]. Depending on modality, the mortality benefit for CRC screening is somewhere between 25 and 50 percent of deaths prevented [9, 10]. Guaiac, endoscopic, and radiological methods are all available. Serum-based methods are advancing but remain investigative.

In the United States, there are at least three sets of screening guidelines (see Table 1). All three incorporate fecal occult blood, flexible sigmoidoscopy, or colonoscopy, alone or in combination. Colonoscopy is much more common in the United States than in other countries, even in other advanced economies. About two-thirds of Americans, 50 years and older, are compliant with USPSTF guidelines. A substantial majority meets those recommendations by colonoscopy [11, 12]. Lifetime colonoscopy prevalence in the United States is near 60% [13]. Data are sparser in Europe; lower GI endoscopy is only available as a primary screening tool in a handful of countries [13]. In Germany, about 3% of the eligible population appears to receive colonoscopy each year [9, 14]. Through 2008, 17.2% of eligible women and 15.5% of eligible men 55–74 years old had been screened [15].

Screening effectiveness also depends on rates of uptake and compliance. Intention-to-treat analysis and per-protocol effects often yield significantly different results [9]. Significant barriers discourage uptake of most of the major screening modalities, accounting in part for lower screening rates than in breast and cervical cancer. Embarrassment, lack of education, socioeconomic issues, concerns with masculinity, and cleanliness all play a role [3, 17]. Even the stool-based tests, considered less onerous by practitioners, seem unsanitary to the eyes of patients [17].

2. Stool-Based Screening

2.1. Guaiac-Based Fecal Occult-Blood Test (gFOBT). Guaiac-based fecal occult-blood testing (gFOBT) was the first stool-based laboratory test used to screen for CRC. Two stool samples are placed on a test card, and hydrogen peroxide is applied. Guaiac, a plant resin, turns blue in the presence of hydrogen peroxide and a catalyst, heme. The test is purely qualitative and therefore operator-dependent [18].

gFOBT is the only noninvasive screening method that has prospective, interventional evidence demonstrating decreased CRC mortality. There have been five such trials, four in Europe and one in the United States. In the European trials, screening with gFOBT led to a 24–39% reduction in mortality in the study population and a 16–18% reduction in the general population [19–22]. The Mandel study, from the United States, demonstrated a 33% decrease in mortality for the study population [23]. The results from these trials are presented in Table 2.

gFOBT is inexpensive, requires few resources, and is ideal for large-scale community intervention. However, it has the lowest sensitivity of the noninvasive screens, ranging from 33% to 50% for CRC [24, 25]. Rehydration of samples
prior to analysis, for instance, by the Hemocult II Sensa (Beckman Coulter, Inc., Fullerton, CA), increases sensitivity for colorectal neoplasm, [26] but not to the levels of newer noninvasive testing. gFOBT is less likely to detect small adenomas, flat or sessile adenomas, and proximal lesions than larger, pedunculated, or distal ones [27]. It does, however, detect a greater proportion of villous and tubulovillous structures [27]. Certain meats, fruits, and vegetables may give false positive results. And because heme remains intact through the gastrointestinal (GI) tract, the test cannot distinguish between upper and lower GI bleed.

These issues have contributed to the declining popularity of gFOBT as a screening tool. It remains in the USPSTF guidelines, though, either as a yearly, primary modality or every three years in combination with sigmoidoscopy every five.

2.2. Fecal Immunochemical Testing (FIT). Fecal immunochemical testing (FIT) also detects the presence of occult blood in stool but does so by agglutination of globin. Unlike heme, globin is degraded on its transit through the upper GI tract. This gives FIT increased specificity for lower GI bleed, without interference from dietary heme sources [28]. FIT is also more sensitive than gFOBT across all stages of CRC, from adenoma to advanced neoplasia [29–35]. Detection rates are 1.5–2.5 times higher than gFOBT for CRC and 2–4 times higher for advanced neoplasia.

A major advantage of FIT is its quantitative interpretation of globin levels. Unlike gFOBT, which is purely qualitative, FIT analysis can be automated and the results standardized, reducing operator error. Positive test result cutoff points have been well studied. Sensitivities at the lowest cutoff values, 20–50 ng/mL, range from 66% to 88% for CRC detection [34–36], while sensitivity at the highest cutoff value of 300 ng/mL is 56% for CRC [37]. The most common cutoff value studied is 100 ng/mL with sensitivities ranging from 60% to 82% for CRC [25, 38, 39]. As with most lab tests, specificity, and sensitivity correlate inversely, and the ideal cutoff number depends on population characteristics and the availability of confirmatory testing.

The performance of FIT as a function of polyp morphology appears broadly similar to gFOBT, [27, 40] despite an early study appearing to show similar performance across different polyp types [41].

The available evidence supports the superiority of FIT over gFOBT, but there are no interventional studies yet to demonstrate mortality reduction. Based on its predicted benefit, the American College of Gastroenterology recommends it over gFOBT for nonendoscopic screening of CRC.

2.3. Fecal DNA Testing (Cologuard®). Multitarget fecal DNA testing has been an area of increased research interest over the last several years. The FDA recently approved the first commercially available test, marketed as Cologuard® (Exact Sciences, Madison, WI). Exfoliated CRC cells turn over more quickly than healthy cells and are shed in the stool. Cologuard® targets gene mutations associated with these cancerous cells. These include aberrantly methylated BMP3 and NDRG4, seven different point mutations in KRAS, β-actin gene (a reference for human cells), and hemoglobin [42].

Imperiale et al. published the leading study on Cologuard® in the New England Journal of Medicine in 2014 [43]. The study randomized subjects to Cologuard® or FIT screening. Cologuard® sensitivities were superior to those of FIT for every type of pathologic lesion, albeit at somewhat lower specificity (Table 3).

Other studies have extended Imperiale’s findings to additional gene mutations, with sensitivities ranging from 85% to 100% for detection of CRC and 53% to 83% for high-grade dysplasias and adenomas [44–46]. And, in a subsequent paper, Imperiale et al. have demonstrated Cologuard® superiority to gFOBT [47].

Cologuard’s lower specificity relative to FIT and gFOBT could result in greater numbers of follow-on colonoscopy. The cost-benefit consequences are yet to be determined.

3. Endoscopic Screening

The three major endoscopic screening methods (see Table 4) differ chiefly in the extent of bowel visualized. So, for instance, the 45% sensitivity of flexible sigmoidoscopy for polyp detection reflects the fact that it cannot visualize the proximal colon, where nearly half of colorectal cancer arises.
### 3.1. Rigid and Flexible Sigmoidoscopy

Sigmoidoscopy is the oldest and most thoroughly researched of the endoscopic methods. Rigid sigmoidoscopy has existed for a century and flexible sigmoidoscopy for about half as long [48]. Its chief advantages are its simplicity and wide availability [49]. It can be performed by nonspecialists and, in some cases, nonphysicians, which makes it especially useful in the developing world [49]. Relative to colonoscopy, it requires less preparation, an enema, usually, instead of a thorough bowel cleanse [49, 50]. However, sigmoidoscopy is uncomfortable for the patient and, as its name implies, does not visualize the proximal colon.

Sigmoidoscopy appears to decrease colorectal cancer incidence by somewhere between twenty and thirty percent, by intent-to-treat analysis [49, 51]. This number increases to between forty and fifty percent for patients actually treated, demonstrating the prominent role of compliance in this type of screening [49]. In another quirk of compliance factors, patients screened by sigmoidoscopy have significantly poorer health habits after the screen than their unscreened counterparts [52].

### 3.2. Colonoscopy

Colonoscopy is both the gold standard for colorectal cancer screening and by far the most common means of colorectal cancer screening in the United States. Colonoscopy reduces the odds of colorectal cancer by somewhere between thirty and seventy-five percent [50]. Risk reduction remains unknown; the only major, randomized controlled studies are still in progress [50].

Colonoscopy is not without shortcomings. It misses about twenty to thirty percent of adenomas [16, 51]. The procedure is relatively complex, which introduces uncertainty. The quality of the colonoscopy depends on bowel preparation and operator characteristics [51]. Smaller, flatter lesions are more difficult to visualize and are missed more often than larger, pedunculated ones [53]. In a prospective study by Heresbach et al., 29% and 32% of sessile and flat polyps, respectively, were missed, compared with just 5% of pedunculated lesions [53]. Unfortunately, flat lesions are also particularly likely to be cancerous [54, 55]. Some studies have suggested that even though colonoscopy can visualize the proximal colon, it is less adept at finding lesions there than in the distal portion [55]. The complexity of colonoscopy leads to wide differences in operator proficiency. Adenoma detection rate, the best validated quality metric, ranges from 7% to 44% depending on the endoscopist [56].

### Table 4: Performance of endoscopic colonoscopy screens.

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigid sigmoidoscopy</td>
<td>~25% [54]*</td>
<td>Ease of operation</td>
<td>Patient discomfort</td>
<td>Rarely used in USA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be performed by clinician</td>
<td>Does not visualize proximal colon</td>
<td></td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>~45% [54, II]</td>
<td>More comfortable than rigid</td>
<td>Does not visualize proximal colon</td>
<td>Rarely used in USA</td>
</tr>
<tr>
<td>Colonsocopy</td>
<td>~80% [16, III]</td>
<td>Gold standard</td>
<td>Extensive bowel preparation</td>
<td>No randomized controlled prospective studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient discomfort</td>
<td></td>
</tr>
</tbody>
</table>

* Reported as polyps detected.

^ Sensitivity for ≤5 mm polyps; the figures for CRC are 60 and 95%, respectively.

The best-validated metric for colonoscopy effectiveness is the adenoma detection rate (ADR), the proportion of screened subjects in whom at least one adenomatous lesion is identified [16, 56]. Higher ADR correlates with fewer interval cancers [51]. Less is known about how ADR is related to incidence and mortality. However, most postcolonoscopy colorectal cancers are thought to be due to missed lesions, rather than new ones, which makes ADR a valuable measurement [16]. Current guidelines suggest that the ADR should be at least 25% in men and 15% in women [55]. Other, unverified metrics include endoscope withdrawal time, intubation rate, bowel preparation, patient comfort, sedation, and complication rates [16].

A long list of colonoscopy enhancements have been attempted, some with more promise than others. High-definition white-light colonoscopy does not appear to offer much benefit over standard methods [51, 55, 57]. Chromendooscopy is another advanced visualization technique that uses a dye spray to enhance contrast. It has shown more promise than high-definition imaging, but only in high-risk groups like IBD patients [51, 55, 58].

Another visualization method with doubtful benefit is cap-assisted colonoscopy. This technique uses a transparent cap at the tip of the colonoscope to improve visualization and depress mucosal folds. The balance of studies suggests no benefit to cap-assisted colonoscopy, or perhaps a small benefit confounded with the greater withdrawal times associated with this method [51, 55, 59, 60].

A more promising technical solution is the “third-eye retroscope,” a colonoscope with an elaborated camera giving simultaneous anterograde and retrograde views of the colon [51, 55, 61, 62]. Multiple studies have demonstrated improvements in polyp detection rates. At least one of these studies, though, also showed the TER withdrawal time was two minutes longer than control, a metric independently associated with higher adenoma detection rate. And no gadget comes free: a third-eye retroscope processor costs about $20,000 and the disposable catheter another $350 [51, 63].

While technology proceeds in fits and starts, several low-tech measures have proven effective at improving colonoscopy performance. A clean colon is an easy to inspect colon, so proper bowel preparation is essential [55]. The process is unpleasant; innovations that make it less unpleasant have value. Low-volume preparations are more effective than high-volume preparations, and it helps to split...
the preparation into two doses [55]. Finally, nurse assistance with spotting polyps increases the number of polyps found [55].

3.3. Capsule Endoscopy. In capsule endoscopy, the patient swallows a pill-sized camera that wirelessly transmits images as it tumbles through the gut. The patient’s bowel motility determines the capsule’s progress, and the capsule’s arbitrary orientation dictates the image captured by the camera. This lack of operator control currently limits capsule endoscopy to small bowel inspection, due to that segment’s relative inaccessibility to other endoscopic methods [64]. Research is ongoing, though, for its using as a CRC screening tool, particularly as the technology improves. The most recent research is limited to the second generation of the capsule, while the third generation has only been available since 2013. Successive generations have improved frame rates and resolution.

At least three studies have measured sensitivities and specificities for capsule endoscopy, typically only for medium- to larger-sized polyps, from ≥6 mm to ≥10 mm. These studies have found, for 6 mm polyps, sensitivities between 84% and 89% at 64% to 82% specificity [64–66]. Both numbers expectedly improve for larger polyps: 88% sensitivity at specificities ranging from 89% to 95% for polyps greater than 10 mm in size.

4. Radiology-Based Screening

4.1. Contrast Barium Enema. Contrast barium enema was the first radiological technique for examining the colon for structural lesions. There are two primary methods: single contrast and double contrast (SCBE and DCBE, resp.). SCBE uses barium alone, while DCBE relies on air contrast in addition to barium. An experienced radiologist must actively manipulate the colon during fluoroscopy to evenly distribute barium and provide imaging adequate for interpretation.

SCBE is 59% sensitive for polyps in a CRC screening population [67]. Barium contrast alone tends to obscure certain lesions, making study results more difficult to interpret. DCBE on the other hand is 87% sensitive for all polyps [67] and 96% sensitive for polyps >1 cm [68]. DCBE’s screening value is comparable to that of colonoscopy [69]. In fact, DCBE may detect more of the very proximal colon lesions that colonoscopy sometimes misses [70].

SCBE and DCBE have largely fallen out of favor despite the evidence supporting their utility, and many radiologists no longer perform this study. Newer imaging options, such as computed tomography (CT) and magnetic resonance imaging (MRI), offer similar or superior performance without operator dependence. Because of its effectiveness as a screening tool, Medicare still reimburses barium contrast fluoroscopy, and it still has a role for patients in whom other radiologic methods might be contraindicated.

4.2. CT Colonography. Computed tomography (CT) for CRC screening, known as CT colonography or virtual colonoscopy, is a newer use for a popular imaging tool. Computer software constructs 2D and 3D images of the colon from CT-scan data. Sensitivity for polyps >9 mm is between 85% and 93% with a specificity of 97%, according to two meta-analyses (see Table 5) [71–73]. This decreases to 70% for polyps 6–9 mm and 48% for polyps <6 mm [73]. An additional study by Macari et al. shows sensitivity to range from 12% for polyps of 5 mm or less but 70% and 93% for polyps 6–9 mm and greater than or equal to 10 mm, respectively [74]. Those figures are comparable to endoscopic colonoscopy and superior to DCBE [75].

Various radiological advances have improved the performance of CT colonography. Multidetector scanners are 7% more sensitive than single detectors [73]. They are also faster and less irradiating. Helical CT for colonography has been shown to be 100% sensitive for polyps of at least 10 mm, 83.3% sensitive for polyps 6–9 mm, and 51.3% sensitive for those 5 mm or less [76]. Tagging agents increase test performance by marking stool and fluid collections left over after preparatory colon cleanse. These collections can mimic polyps or obscure them, causing false negatives. Oral barium tags stool and residual solids, while oral iodine tags residual fluids. These oral agents have proven effective in clinical trials, the most notable being the ACRIN National CT Colonography Trial [72, 77].

With the routine use of multidetector scanners and oral tagging agents, CT colonography has become increasingly sensitive for polyps. However, radiologists and other healthcare providers must still interpret study results. Computer-aided diagnosis (CAD) is a useful interpretive adjunct in mammography and other radiological studies. Likewise, it increases test sensitivity for CT colonography when used in addition to radiologist interpretation, [78, 79] and is 90.1% sensitive for all polyps when used as the sole interpreter [80].

The performance of CT colonography relative to screening colonoscopy is not yet clearly established. A large-scale trial by Pickhardt et al. showed CT colonography to be superior to colonoscopy for polyps larger than 1 cm, with a sensitivity of 94% versus 88% [81]. However, colonoscopy was more sensitive for polyps 6 mm and larger, with a sensitivity of 92% versus 89% [81]. An additional study by Glueckner et al. demonstrates that multidetector CT colonography is 90% specific compared to gold standard colonoscopy [82]. Although the tests seem to have similar performance characteristics, one study by Pedersen et al. shows that CT colonography may be present more of a technical challenge since the study specific relies on absence on artifacts which are easily found in radiologic imaging [83]. The differences between the two tests appear to be small.

The relative sensitivity of CT colonography and other radiologic methods for flat and sessile polyps is also controversial. Intuitively, a screening modality that visualizes

<table>
<thead>
<tr>
<th>Table 5: Performance of CT colonography.</th>
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<tbody>
<tr>
<td>Single detector</td>
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<tr>
<td>Multidetector</td>
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<td>Pooled via meta-analyses</td>
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shapes should perform less well with lesions that have less shape. Lesion morphology is not considered in the Pickhardt trial mentioned above [81]. The Gluecker trial does not systematically consider flat lesions but does mention that a flat lesion was missed due to “perceptive error” [82]. Elsewhere, Pickhardt has found sensitivities of between 80% and 83% of CT colonography for flat lesions (for adenomas and flat lesions greater than 6 mm, resp.) [84]. Of course, these values were obtained against a reference standard of optical colonoscopy, which will itself miss a greater number of flat polyps than sessile or pedunculated ones. Other studies have found sensitivities as low as 50% [85]. Still, flat lesions are not usually entirely flat (they are typically defined as having height less than 1/2 or 1/3 of width), and they have a different attenuation than surrounding fat [82, 84]. Contrast coating the surface of these polyps increases the sensitivity of CT colonography for them [86]. But, including more suspected flat lesions also depresses the positive predictive value of CT colonography, from 96.5% and 92.5% for pedunculated and sessile polyps to 77.7% for flat [87].

Although CT colonography performance is comparable to colonoscopy, concerns over radiation exposure and cost have hindered its widespread adoption. The USPSTF cites radiation dosing for its decision not to recommend CT colonography. CT colonography remains, though, in the screening recommendations of the American College of Gastroenterology and the American Cancer Society. CT colonography is also more expensive than colonoscopy, and neither Medicare nor Medicaid covers the cost of the test. Without further improvements to these drawbacks or a clear demonstration of superior performance, CT colonography may remain merely promising or an alternative for appropriate patients.

4.3. MRI Colonography. MRI colonography works similarly to CT colonography. MRI data generates a virtual representation of the colon. Two techniques are used: light lumen and dark lumen. Light lumen MRI colonography uses liquid enema with gadolinium contrast, while the dark lumen method relies on air or gas contrast enema with IV contrast. Polyps appear as a filling defect on bright lumen MRI and as an enhancing lesion on dark lumen MRI. MRI colonography is relatively new, and the few studies that examine its performance vary widely in their criteria and results. In one study, sensitivities are 38% for polyps 6–9 mm, [88] while others show 84% and 100% for polyps of similar size [89, 90]. A meta-analysis by Zijta et al. concludes that MRI colonography has 88% sensitivity at 99% specificity for polyps 10 mm and larger [91]. Studies comparing MRI colonography to colonoscopy have shown sensitivities ranging from 93% to 100% for polyps 6–9 mm. [92–94]

The relative performance of MRI colonography for different polyp shapes is unknown. The trials listed above do not discriminate between lesion shapes, although Luboldt speculates that flat lesions “will likely remain obscure” on MRI [93]. Subsequent studies appear limited anecdotal accounts of missed flat lesions [95–97].

Unlike its CT counterpart, MRI colonography does not use radiation. However, MRI is more expensive and is contraindicated for patients with prostheses, pacemakers, or other metal implants. As with CT colonography, data supporting its superiority to the gold standard colonoscopy are lacking. More data are needed, though, before a definitive judgment can be rendered.

5. Serum-Based Screening

Currently, “serum-based screening” barely exists. The research is extensive, but little of it is validated and even less commercialized [18]. Indeed, most of the present literature is limited to colorectal cancer detection, instead of adenoma detection. But as with capsule endoscopy, the field is young, and at least some of the innovations are promising. In general, researchers have approached the problem from two directions: first, to try to identify novel, more powerful biomarkers, and second, to try to combine known biomarkers by algorithm to find patterns suggestive of colorectal cancer.

CEA is the traditional marker associated with colorectal cancer. Alone, its sensitivity for colorectal cancer disease is about 40%, too low to use as a screen, but valuable as a tool to monitor cancer recurrence, where its sensitivity doubles to 80% [98]. At least two groups have combined CEA with other markers associated with colorectal cancer, like ferritin and seprase, using multivariate analysis to yield sensitivities between 65.8% and 68% for colorectal cancer detection [32, 99]. This is comparable to FIT, although not yet as cost effective [99]. The adenoma detection rates for these multivariate analyses remain too low to be useful, 22.7% in the Wild study [99].

The most studied alternative to CEA is methylated septin-9, an epigenetic modification associated with colorectal cancer [18]. Studies vary widely on its predictive value, with numbers ranging from 48% to 90% sensitivity for colorectal cancer [18, 100]. Again, these values are considerably lower for adenomas (≥1 cm), ranging from 11% to 29%. These data were sufficient for approval from the European Medicines Agency (the Epigenomics Epi proColon), but an FDA advisory panel split 5–4 on the matter in early 2014, and the FDA itself has requested further data on screening compliance before granting approval [101].

Other DNA, RNA, and protein molecules under study tend to track the same markers studied in stool. For instance, guanylyl cyclase RNA has a sensitivity of 74% at 95% specificity for CRC [99]. And p53 autoantibodies have low sensitivity (around 25% at 95% specificity for CRC) but might be used in combination with other markers [102]. The full breadth of these efforts is outside the scope of this review: Imperiale gives a good summary [18]. An interesting issue will be whether it is more effective to measure these markers from stool or from blood. The most recent study, from Ahlquist et al., detected a greater number of adenomas from stool DNA than from plasma [103]. The few earlier studies are split [104, 105]. Even if plasma-based assays are less powerful, they may benefit from greater patient compliance. While Cologuard bills itself as the first “at home” screen, there
is at least some evidence that patients find sampling their own feces more objectionable than do physicians [17]. And, while patients may dislike needles, blood testing is a standard feature of medical practice.

Finally, it should be stressed that most of the research in serum-based markers has been for CRC detection, not adenoma detection. And, as noted above, the studies that have included adenoma in their data have showed a wide gap in the ability of serum-based markers to detect these early lesions.

6. Discussion and Conclusions

The European Commission set out its goals for cancer screening, including CRC screening, in a 2003 Council Recommendation, mentioning only fecal occult-blood testing [106]. Two subsequent reports on the implementation of these recommendations have identified shortcomings. The first, in 2008, found fewer than half the minimum number of screenings had taken place [107]. The second, in 2014, found that screening programs had only been implemented in 15 of 25 countries [108]. With the exception of Germany, at 54.2% of eligible people screened, no other country had more than a 26% screening rate for CRC [109]. Among the EU countries covered by the report, colonoscopy is available as a primary screening modality only in Germany, Austria, Poland, and the Czech Republic [13].

In the United States, the National Colorectal Cancer Screening Roundtable has a stated goal of an 80% colorectal cancer screening rate by 2018. In contrast to most of Europe, the screening rate in the United States already approaches two-thirds of the eligible population. Germany approaches this rate, but colonoscopy remains much more frequently used in the United States. Current guidelines give a range of options for effective screening, which this paper summarizes.

To a greater extent than with other cancers, barriers to screening alter the effectiveness of the various colorectal cancer screening methods. The best test is often the one that patients will do. In the United States, the CRC screening rate, although relatively high, may lag the cervical and breast cancer screening rates because of the relatively high barriers to existing modalities. Another shortcoming shared by all of the available screening methods is sensitivity for small, flat, and sessile polyps. There has been particular concern on this point with radiologic screening, but these types of polyps bleed less and are more difficult to see even under direct visualization, and all available screening modalities perform substantially less well.

Stool-based tests are less sensitive than colonoscopy, but improving. New advances, like the Cologuard test, catch significantly more polyps than occult-blood tests. Although less popular than colonoscopy, stool-based tests continue to be used as the primary screen in a substantial minority of patients. Their technical shortcomings are at least in part overcome by their practical ones: their simplicity and lower cost mean that they might be used by a greater part of the population more frequently than is possible with colonoscopy.

Colonoscopy is the gold standard colorectal cancer screen, the first, best option, and most common screen in the United States. As with cervical and breast cancer screening, its widespread implementation has substantially decreased the CRC burden in this country. But its utilization still lags the Pap smear and mammogram, and its costs and complexity are greater than either of those two tests. Barriers to colonoscopy uptake and shortcomings in the test itself continue to encourage research on alternative modalities.

The only screens that consistently rival colonoscopy in power are the radiological ones, CT and MRI colonography, in particular. Their problems reverse those of the stool-based tests: for all their technical merit, they remain expensive and, in the case of CT colonography, carry a small, but real radiation risk. Positive screens require follow-up colonoscopy to remove the identified polyps. Until ease of use improves or they show significantly better performance than colonoscopy, radiological screens may remain a minor alternative to endoscopic and noninvasive screens.

Disclosure

Justin L. Sovich and Zachary Sartor are the co-first authors.

Conflict of Interests

Dr. Subbasis Misra receives grant funding from the Cancer Prevention & Research Institute of Texas as principal investigator for the project “Get FIT to Stay Fit. Stepping Up to Fight Colorectal Cancer in the Panhandle.” Justin Sovich and Zachary Sartor have none to declare.

References


Research Article

Social Cognitive Mediators of Sociodemographic Differences in Colorectal Cancer Screening Uptake

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Background. This study examined if and how sociodemographic differences in colorectal cancer (CRC) screening uptake can be explained by social cognitive factors. Methods. Face-to-face interviews were conducted with individuals aged 60–70 years (n = 1309) living in England as part of a population-based omnibus survey. Results. There were differences in screening uptake by SES, marital status, ethnicity, and age but not by gender. Perceived barriers (stand. \( b = -0.40 \), \( p < 0.001 \)), social norms (stand. \( b = 0.33 \), \( p < 0.001 \)), and screening knowledge (stand. \( b = 0.17 \), \( p < 0.001 \)) had independent associations with uptake. SES differences in uptake were mediated through knowledge, social norms, and perceived barriers. Ethnic differences were mediated through knowledge. Differences in uptake by marital status were primarily mediated through social norms and to a lesser extent through knowledge. Age differences were largely unmediated, except for a small mediated effect via social norms. Conclusions. Sociodemographic differences in CRC screening uptake were largely mediated through social cognitive factors. Impact. Our findings suggest that multifaceted interventions might be needed to reduce socioeconomic inequalities. Ethnic differences might be reduced through improved screening knowledge. Normative interventions could emphasise screening as an activity endorsed by important others outside the immediate family to appeal to a wider audience.

1. Introduction

Colorectal cancer (CRC) screening using a guaiac-based faecal occult blood test (gFOBt) lowers CRC mortality by up to 25% among those who participate [1, 2]. The National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) sends all age-eligible (60–69, recently extended to 74) men and women living in England a free home-based gFOB test every two years, usually starting from their 60th birthday. Patient data from General Practitioner (GP) lists are used to approach eligible adults, so over 95% of the national population in the eligible age range is invited [3]. The test involves taking three stool samples and returning the kit to the laboratory in a freepost envelope. Despite the lack of financial barriers to screening, low and socially unequal uptake has been a persistent public health concern since the screening programme was introduced in 2006 [3, 4].

Socioeconomic status (SES) has consistently been associated with CRC screening uptake across healthcare systems [5, 6]. For instance, uptake of first-time screening invitations in England ranged from 35% in the most deprived quintile to 61% in the most affluent quintile of areas in the country [3]. Ethnic differences in CRC screening have also been frequently observed and appear to be independent of or only partially explained by other sociodemographic factors [7–9]. Although first-time gFOB test uptake is around 8% higher among women than men, gender differences in uptake are less persistent over time than SES effects [4, 10]. Being married has been related to higher uptake of other CRC screening modalities [11, 12], although few studies have examined the role of marital status in the context of gFOBt screening specifically [13].

In parallel with studies of the sociodemographic patterning of CRC screening behaviour, psychological models, such as the Health Belief Model (HBM) [14] and Theory of Planned Behaviour (TPB) [15], have been used to investigate social cognitive factors such as attitudes, knowledge, social norms, and perceived barriers to screening [5, 16, 17]. Social cognitive factors are typically measured using questions about relevant beliefs and are generally viewed as more
proximal and modifiable determinants of behaviour than sociodemographic factors [18]. Social cognitive factors would therefore be expected to mediate the association between sociodemographic factors and health behaviours [15].

General attitudes towards CRC screening in the population have been found to be very positive [19]. Nevertheless, there is relatively low awareness of CRC as a common cancer [20]. Misconceptions about the purpose of CRC screening, such as the belief that screening is only needed if one has symptoms, are also commonly reported among non-responders to screening [21–23]. The disgust, embarrassment and practicalities of stool sampling are well-documented barriers to gFOB screening [21, 23–25], and difficulty overcoming such perceived barriers is another common reason given for not taking part in CRC screening [13]. Furthermore, social norms have also been consistently related to CRC screening [16]. Due to the home-based nature of the gFOB test and the lack of direct contact with health professionals, it is plausible that any normative influence from nonmedical sources might be particularly relevant to CRC screening in the organised screening programme in England.

Although a framework has been developed to summarise potential social cognitive mediators of socioeconomic inequalities in screening uptake [26], few studies have empirically examined these pathways using mediation modelling. One study examining CRC and prostate screening in men showed that sociodemographic differences in screening uptake were largely attributable to the TPB-based social cognitive constructs (attitude, perceived norms, and perceived behavioural control) [27], but none has explored the specific pathways through which each sociodemographic variable affects uptake. Understanding these social cognitive pathways may help the development of effective and targeted interventions to reduce sociodemographic inequalities in cancer screening.

In this study, we aimed to explore social cognitive mediators of sociodemographic differences in gFOB screening uptake in England. The objectives were to explore the associations between sociodemographic factors and gFOB uptake in a cross-sectional dataset and to test mediation models exploring potential social cognitive mechanisms underlying sociodemographic differences in uptake, with a view to developing hypotheses to test in future prospective studies.

2. Methods

The data were collected as part of a TNS Research International population-based omnibus survey conducted in Great Britain between January and March 2014. Each week, up to 4000 people (aged 16+) are interviewed for the omnibus survey. The TNS omnibus survey defines sampling points using 2001 Census small-area statistics and the Postcode Address File (stratified by social grade and Government Office Region) for random location sampling selection. Response rates are not recorded. However, at each location, quotas are set for age, sex, children in the home, and working status to ensure a sample that reflects the demographic characteristics of the national population. Survey respondents were asked to take part in face-to-face interviews using computer-assisted personal interviewing (CAPI) on a voluntary basis. Only respondents aged 58–70 were included in the section of the omnibus survey about cancer screening.

2.1. Participants. Responses were collected from 1568 men and women living in England aged 58–70 years with no CRC history. One hundred eighty-seven respondents were excluded from the present analysis because they were aged between 58 and 59 and therefore not yet eligible for CRC screening at the time of the interview, leaving 1381 eligible respondents. This ensured that the included respondents should have been invited for CRC screening through the organised national programme, regardless of whether they remembered having been invited or not. Seventy-two respondents (5%) who had missing values (i.e., "refused" or "don't know") for the outcome variable "screening uptake" were also excluded. The final sample included 1309 respondents (95% of those eligible).

2.2. Measures

Screening Uptake. Respondents were asked if they had ever been invited to do a stool test for the NHS BCSP. If they had been invited, they were asked further questions about how many times they had been invited and how many times they had taken part. Self-report of not having been invited is likely due to reasons other than truly not having been sent a screening invitation (e.g., not remembering the invitation) because included respondents were eligible for screening through the national CRC screening programme in England. A dummy variable for screening uptake therefore coded respondents as nonresponders (not invited OR no test kits completed) or ever responders (≥1 test kit completed).

Social Cognitive Factors. Social cognitive measures were informed by previous literature on CRC screening uptake and social cognitive models of behaviour. Belief in the usefulness of asymptomatic screening [21–23] was measured in lieu of general attitude towards screening due to known ceiling effects in screening attitude [19]. An injunctive norm measure (i.e., what other people think one should do) and a descriptive norm measure (i.e., what other people do themselves) were included to be consistent with the social norms literature [28]. Finally, the most salient emotional [23–25] and time/delay [13, 21, 29] barriers known to be associated with poorer CRC screening uptake were used as measures of the perceived barriers factor. Respondents rated the extent of their (dis)agreement with a series of belief statements on a five-point scale (strongly agree/lightly agree/neither agree nor disagree/slightly disagree/strongly disagree).

Screening knowledge was measured with the statement “People only need to take part in bowel cancer screening if they have symptoms” and was reverse-coded.

Social norms were measured using one injunctive norm statement, “People who are important to me think that I should take part in bowel cancer screening,” and one descriptive norm statement, “People who are important to me take part in bowel cancer screening.”
Perceived barriers were measured with two statements measuring the respondent's ability to overcome emotional barriers: "It is difficult to overcome the disgust related to the stool test" and "It is difficult to overcome the embarrassment related to the stool test." A third statement was used to measure ability to overcome practical time barriers "It is difficult to get round to doing the stool test."

Sociodemographic Variables. Age, gender, marital status (married/divorced, separated, or widowed/single), ethnicity (white/nonwhite), and SES (A/B/C1/C2/D/E) were measured. The ordinal measure of SES was based on the National Readership Survey social grade classification system which ranks people according to occupation (or previous occupation if retired): A (higher managerial, administrative, or professional), B (intermediate managerial, administrative, or professional), C1 (supervisory, clerical or junior managerial, administrative, or professional), C2 (skilled manual), D (semiskilled or unskilled manual), or E (state pensioners, casual/lowest grade workers, or unemployed with state benefits only). The occupational status of the household's chief wage earner was used to assess SES if the respondent was not working.

2.3. Data Analysis. Screening uptake was first analysed by sociodemographic groups (Table 2) and by social cognitive beliefs (Table 3). The multivariable associations between sociodemographic variables and screening uptake were examined using logistic regression analysis (Table 2). Sociodemographic variables that were significantly associated with uptake ($p < 0.05$) were included in a multivariable analysis. Bivariate associations between social cognitive beliefs and uptake were also examined with logistic regression (Table 3). All logistic regression analyses were conducted using Stata SE13 [30].

Mediation of sociodemographic effects on screening uptake via social cognitive factors was then tested using Structural Equation Modelling (SEM) with MPlus 7.11 [31]. Hu and Bentler's guidelines for goodness-of-fit were used, with statistics around 0.95 and above for the Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI), and around 0.08 and below for the Root Mean Square Error of Approximation (RMSEA) and Standard Root Mean Residual (SRMR) deemed as indicators of good fit [32].

Before testing for mediation, two models were first tested to assess goodness-of-fit of the measurement model and the path model with social cognitive factors as predictors of uptake. The measurement model (Model I) of the social cognitive factors with measures grouped as described above was tested using Confirmatory Factor Analysis (CFA) (Table 4). As most indicators were nonnormally distributed MLM, a robust maximum likelihood estimator, was used to obtain estimates. The hypothesised measurement model showed adequate fit. The measurement model could therefore be extended into a SEM model by including uptake as the outcome variable. WLSMV, a robust weighted least squares estimator, which is the default estimator for binary outcome models in MPlus, was used for all SEM models. The first SEM model (Model II) tested for direct effects of social cognitive factors on uptake. Social cognitive factors were allowed to correlate freely with each other because they were strongly correlated and no hypotheses regarding the relationships between social cognitive factors needed to be tested. Similar to Model I, Model II had adequate goodness-of-fit statistics, indicating that all social cognitive factors had direct, independent effects on uptake as expected. Therefore, subsequent SEM models included direct paths from all social cognitive factors to uptake.

Model III aimed to test mediation of sociodemographic differences in uptake via social cognitive factors. The model included (1) direct paths from social cognitive factors to uptake; (2) direct paths from sociodemographic variables to uptake; and (3) indirect paths from sociodemographics via social cognitive factors to uptake. For the sake of parsimony, nonsignificant paths in Model III were removed using stepwise backward elimination to obtain the final model (Model IV, Figure 1). As in Model II, Models III and IV allowed all social cognitive factors to freely correlate with each other. Sociodemographic variables were not correlated, as they were largely independent predictors of uptake (Table 2).

To compare Model III with Model IV, the models were first run without bootstrapping to obtain chi-square statistics for a chi-square of difference test for models using the WLSMV estimator (DIFFTEST option in MPlus). The same models were estimated again with bootstrapping to obtain robust standard errors and confidence intervals of the point estimates. Bootstrapping is recommended for mediation analysis because the method tends to have the best statistical power and Type I error control [33]. Bootstrapping with 10,000 resamplings of the dataset was used to obtain bias-corrected confidence intervals. $p$ values from the bootstrapped model estimates were reported. Standardized path coefficients are reported for the final model (Model IV) to aid interpretation of the probit regression coefficients provided by the WLSMV estimator. Standardized indirect effects of sociodemographic variables on uptake are also reported.

3. Results

Of the total included samples, 50.7% were men (Table 1). The age range of the included sample was 60–70 with a mean age of 65 (SD = 3.2). The majority of respondents (65.0%) were married, 26.2% were divorced, separated, or widowed, and 8.8% were single. The socioeconomic distribution of the sample was as follows: 5.0% in A (the highest grade), 20.4% in B, 22.1% in C1, 18.3% in C2, 11.6% in D, and 22.5% in E (the lowest grade). Only 4.1% ($n = 53$) of respondents were nonwhite which reflects the low prevalence of ethnic minorities among older age groups in the national population of England [34].

Overall, 69.4% of respondents reported having taken part in screening at least once (Table 2). Of the respondents who had never participated ($n = 401$), 50.1% ($n = 201$) indicated they had never been invited.

3.1. Sociodemographics and Screening Uptake. Gender was not associated with screening uptake in the sample (Table 2). SES was associated with uptake in a graded fashion, from 59.3% in the lowest grade E to 74.2% in the highest grade A ($p < 0.001$). Nonwhite respondents were also less likely
ever to have responded to screening invitations than white respondents (41.5% versus 70.5%, \( p < 0.001 \)). Single people had lower uptake than those who were married (55.7% versus 71.7%, \( p < 0.001 \)). The difference in uptake rates between being divorced, separated, or widowed and being married was not statistically significant (68.2% versus 71.7%, ns.). Older age was also associated with higher uptake (60–64: 62.6% versus 65–70: 74.3%, \( p < 0.001 \)). A multivariable logistic regression analysis showed that all significant sociodemographic predictors were associated with uptake independently of one another (Table 2).

### 3.2 Social Cognitive Factors and Screening Uptake.

The prevalence of social cognitive beliefs and their association with uptake are described in Table 3. Bivariate analysis showed that all social cognitive measures were significantly associated with uptake (all \( p < 0.001 \)). A CFA analysis confirmed that the measurement model had a good fit (Model I, Table 4). This suggests that the belief statements were related to their respective social cognitive factor (screening knowledge, social norms, or perceived barriers) as described in Section 2.

All latent factors were correlated (screening knowledge with social norms: \( r = -0.43 \); screening knowledge with perceived barriers: \( r = 0.49 \); and social norms with perceived barriers: \( r = -0.41 \), all \( p < 0.001 \)). A SEM model with direct paths from each social cognitive factor to uptake (and correlated latent factors) also had an adequate fit (Model II).

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**Table 1: Sociodemographic characteristics of the included sample.**

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>% (n)</th>
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<tbody>
<tr>
<td><strong>Total</strong></td>
<td>100% (1309)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>50.7% (664)</td>
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<tr>
<td>Women</td>
<td>49.3% (645)</td>
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<tr>
<td><strong>Marital status</strong></td>
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<tr>
<td>Married</td>
<td>65.0% (851)</td>
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<tr>
<td>Divorced, separated, or widowed</td>
<td>26.2% (343)</td>
</tr>
<tr>
<td>Single</td>
<td>8.8% (115)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>95.9% (1256)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>4.1% (53)</td>
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<tr>
<td><strong>Socioeconomic status (A–E)</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>5.0% (66)</td>
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<tr>
<td>B</td>
<td>20.4% (267)</td>
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<tr>
<td>C1</td>
<td>22.1% (289)</td>
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<tr>
<td>C2</td>
<td>18.3% (240)</td>
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<tr>
<td>D</td>
<td>11.6% (152)</td>
</tr>
<tr>
<td>E</td>
<td>22.5% (295)</td>
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<tr>
<td><strong>Age (60–70)</strong></td>
<td></td>
</tr>
<tr>
<td>60–64</td>
<td>42.1% (551)</td>
</tr>
<tr>
<td>65–70</td>
<td>57.9% (758)</td>
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</tbody>
</table>
### Table 2: Sociodemographic characteristics and screening uptake: descriptive statistics and logistic regression results.

<table>
<thead>
<tr>
<th>Sociodemographic Group</th>
<th>Screening Uptake % (n)</th>
<th>Adjusted Odds Ratios (OR) With screening uptake as outcome</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Multivariable logistic regression results</td>
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<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Total</td>
<td>69.4% (1309)</td>
<td>(ref.)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>69.1% (664)</td>
<td>1.03</td>
</tr>
<tr>
<td>Women</td>
<td>69.6% (645)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>71.7% (851)</td>
<td>(ref.)</td>
</tr>
<tr>
<td>Divorced, separated, or widowed</td>
<td>68.2% (343)</td>
<td>0.97</td>
</tr>
<tr>
<td>Single</td>
<td>55.7% (115)</td>
<td>0.57**</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>70.5% (1256)</td>
<td>(ref.)</td>
</tr>
<tr>
<td>Non-white</td>
<td>41.5% (53)</td>
<td>0.34***</td>
</tr>
<tr>
<td><strong>Socioeconomic status (A–E)</strong></td>
<td></td>
<td>0.85***</td>
</tr>
<tr>
<td>A</td>
<td>74.2% (66)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>76.0% (267)</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>74.1% (289)</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>71.3% (240)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>63.2% (152)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>59.3% (295)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (60–70)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–64</td>
<td>62.6% (551)</td>
<td>1.08***</td>
</tr>
<tr>
<td>65–70</td>
<td>74.3% (758)</td>
<td></td>
</tr>
</tbody>
</table>

*a*bivariate regression results, b as a continuous variable in the logistic regression analysis. 
**p < 0.01; ***p < 0.001.

3.3. Social Cognitive Mediation of Sociodemographic Differences in Uptake. A SEM model with both direct and indirect paths from SES, ethnicity, marital status, and age showed adequate fit statistics. However, the direct paths from SES, ethnicity, and marital status to screening uptake were not statistically significant (Model III, Table 4). Age was the only sociodemographic variable with a significant direct path to screening uptake. A final SEM model preserved significant indirect paths from SES, ethnicity, marital status, and age to uptake and direct paths from social cognitive factors and age to uptake (Model IV, Table 4; Figure 1). A chi-square difference test for the WLSMV estimator showed that the more parsimonious Model IV did not have a significantly worse fit than Model III ($\Delta \chi^2 = 9.033, \Delta df = 9, p = 0.43$).

In the final model (Model IV, Figure 1), screening knowledge (d1), social norms (d2), perceived barriers (d3), and age (d4) had direct effects on uptake (all $p < 0.001$). Ethnicity had a significant indirect path to uptake via screening knowledge ([i1]: white: ref. cat.; nonwhite: stand. ind. effect = $-0.02$; 95% CI: $-0.045$–$-0.01$, $p < 0.01$). Marital status had a stronger indirect path to uptake via social norms (married: reference category; single [i3]: stand. ind. effect = $-0.047$, 95% CI: $-0.072$–$-0.021$, $p < 0.001$; divorced [i5]: stand. ind. effect = $-0.037$, 95% CI: $-0.062$–$-0.011$, $p < 0.01$) and a weaker indirect path via screening knowledge (single [i2]: stand. ind. effect = $-0.012$, 95% CI: $-0.024$–$-0.001$, $p < 0.05$) and perceived barriers (single [i4]: stand. ind. effect = 0.032, 95% CI: $-0.063$–$-0.001$, $p < 0.05$). SES had significant indirect paths to uptake via screening knowledge ([i6] stand. ind. effect = $-0.026$, 95% CI: $-0.041$–$-0.011$, $p < 0.001$), social norms ([i7] stand. ind. effect = $-0.025$, 95% CI: $-0.049$–$-0.001$, $p < 0.05$), and perceived barriers ([i8] stand. ind. effect = $-0.040$, 95% CI: $-0.070$–$-0.009$, $p < 0.05$). Age had a significant indirect path to uptake via social norms ([i9] stand. ind. effect = $0.027$, 95% CI: $0.005$–$0.049$, $p < 0.05$).

4. Discussion

The present study explored social cognitive mechanisms underlying sociodemographic differences in uptake of CRC screening using gFOBt in England. Of the three social cognitive factors, perceived barriers and social norms were most strongly associated with uptake, while screening knowledge showed a weaker association. The relatively strong associations of perceived barriers and social norms with uptake suggest that changes in beliefs related to these social cognitive factors might result in the largest impact on overall screening uptake.
Table 3: Social cognitive beliefs and screening uptake: descriptive statistics and logistic regression results.

<table>
<thead>
<tr>
<th>Social cognitive beliefs</th>
<th>Screening uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (n)</td>
<td>By agreement with social cognitive beliefs</td>
</tr>
<tr>
<td>People only need to take part if they have symptoms</td>
<td></td>
</tr>
<tr>
<td>Neither agree nor disagree, slightly or strongly disagree</td>
<td>86.0% (1091)</td>
</tr>
<tr>
<td>Slightly or strongly agree</td>
<td>14.0% (178)</td>
</tr>
<tr>
<td>Difficult to get round to doing the test</td>
<td></td>
</tr>
<tr>
<td>Neither agree nor disagree, slightly or strongly disagree</td>
<td>84.7% (1072)</td>
</tr>
<tr>
<td>Slightly or strongly agree</td>
<td>15.3% (193)</td>
</tr>
<tr>
<td>Difficult to overcome the embarrassment</td>
<td></td>
</tr>
<tr>
<td>Neither agree nor disagree, slightly or strongly disagree</td>
<td>87.3% (1110)</td>
</tr>
<tr>
<td>Slightly or strongly agree</td>
<td>12.7% (161)</td>
</tr>
<tr>
<td>Difficult to overcome the disgust</td>
<td></td>
</tr>
<tr>
<td>Neither agree nor disagree, slightly or strongly disagree</td>
<td>88.5% (1124)</td>
</tr>
<tr>
<td>Slightly or strongly agree</td>
<td>11.5% (146)</td>
</tr>
<tr>
<td>People who are important to me think I should take part</td>
<td></td>
</tr>
<tr>
<td>Neither agree nor disagree, slightly or strongly disagree</td>
<td>30.3% (367)</td>
</tr>
<tr>
<td>Slightly or strongly agree</td>
<td>69.7% (846)</td>
</tr>
<tr>
<td>People who are important to me take part</td>
<td></td>
</tr>
<tr>
<td>Neither agree nor disagree, slightly or strongly disagree</td>
<td>32.5% (384)</td>
</tr>
<tr>
<td>Slightly or strongly agree</td>
<td>67.5% (797)</td>
</tr>
</tbody>
</table>

*reverse coded for the logistic regression analysis.

***p < 0.001.
4.1. Social Cognitive Mediators of Sociodemographic Differences. Mediation of sociodemographic differences in uptake via screening knowledge, social norms, and perceived barriers was tested. SES differences in uptake were mediated through all three social cognitive factors, while ethnic differences in uptake were mediated via screening knowledge alone. Differences in uptake by marital status were primarily mediated through social norms and to a lesser extent through screening knowledge and perceived barriers. Age had a direct, positive effect on uptake and a smaller indirect effect via social norms. Overall, these findings indicate that, with the exception of age, sociodemographic differences in uptake may be largely mediated via social cognitive factors derived from psychological models such as the TPB [15] and the HBM [14].

4.1.1. Mediation of Socioeconomic Differences in Screening Uptake. The current findings also suggest that socioeconomic inequalities in screening uptake are multidimensional and are unlikely to be entirely resolved through changes in one or a few key beliefs. This study suggests that social cognitive factors derived from common psychological models are mediators of socioeconomic difference in CRC screening uptake. This extends on previous research, which has demonstrated mediation of socioeconomic differences in screening uptake via cancer-specific social cognitive constructs, such as cancer worry [35] and fatalism [36]. If our findings are confirmed in longitudinal studies, interventions may need to target a range of beliefs, including those related to perceived barriers, screening knowledge, and social norms. However, a single, well-designed intervention might be able to target several relevant beliefs simultaneously, given that they tend to be correlated. Stepped interventions which offer generic educational material and advice to all and more tailored assistance for persistent nonresponders seem a promising intervention format for this purpose [37, 38].

4.1.2. Mediation of Ethnic Differences in Screening Uptake. In line with previous research on cervical screening uptake among ethnic minority women [39], ethnic differences in CRC screening uptake were solely mediated via screening knowledge. Awareness campaigns targeted towards specific ethnic minority groups could therefore be useful. Although the English CRC screening programme already provides written translations of their information booklet, more could be done to engage people from ethnic groups who do not respond well to written information, even if provided in their native tongue [40].

4.1.3. Mediation of Differences in Screening Uptake by Marital Status. Marital status appears to influence screening uptake primarily through social norms, possibly due to the availability of a clearly defined referent group for married people (i.e., their spouse) and by implication more salient social norms. Differences in uptake by marital status could be caused or inadvertently aggravated if normative messages focus on partners or children as a reason to take part in screening. Public communication should acknowledge that roughly one-third of the target group for cancer screening do not or no longer have a life partner or children. Other potential sources of normative messages, such as health care providers and community leaders, could appeal to a wider audience, including those without a partner or children. The overall findings for marital status suggest that a life partner can highlight the social relevance of screening as well as increasing relevant knowledge and reducing perceived barriers to screening, albeit to a lesser extent. This is consistent with previous qualitative findings which emphasised the influence of talking about screening and being aware of one’s partner’s or friends’ screening participation on uptake [21].

4.1.4. Mediation of Age Differences in Screening Uptake. Although age differences in screening uptake were largely unmediated via social cognitive factors in the tested model, a small indirect effect via social norms might indicate that people are gradually exposed to more positive norms as they age (although it could also be a cohort effect). This might have a positive impact on screening uptake among those who have not responded to earlier screening invitations [21]. In the
present study, the outcome measure was whether respondents had “ever” participated in screening, which is likely to be associated with age, simply by virtue of the fact that older people will have received more invitations and therefore had more opportunities to participate. Future research should examine if these observed age effects on uptake also extend to other screening uptake outcomes (e.g., regular uptake over time).

4.2. Study Limitations. The present study results should be interpreted in the light of widely discussed limitations of using cross-sectional data for mediation analyses [41, 42]. Although our findings are plausible and are consistent with psychological theory and a number of previous findings, it is essential that they are replicated using longitudinal methods in order to confirm the mediation effects. This survey provided the opportunity to explore associations in a large population-based sample, but our findings must be treated with caution and should be used to develop hypotheses for future studies.

Another study limitation was that screening knowledge was measured with a single item (“People only need to take part in bowel cancer screening if they have symptoms”). Although the measure taps into a common misconception about screening which has direct implications for screening participation, the results might not generalise to other knowledge measures. Findings regarding ethnic differences in uptake should also be replicated in studies with a larger sample of nonwhite respondents, as the ethnic minority sample was small and is unlikely to have been representative of all ethnic minority groups in England.

A final limitation is our inability to report a response rate due to the methods used by the survey company that carried out the fieldwork. Although this means that we cannot rule out participation bias, it is unlikely that attitudes to screening would have been associated with participation, as the survey was part of an omnibus, including questions on a wide range of subjects. The sampling method ensured that the demographic profile of the sample was broadly similar to the national population.

5. Conclusion

In conclusion, the present study has identified possible social cognitive pathways through which sociodemographic factors could affect colorectal cancer screening uptake. A range of social cognitive factors seem to be associated with socioeconomic inequalities, whereas only lack of screening knowledge was associated with ethnic inequalities. Social norms were the main mediator of uptake differences by marital status. The study findings could inform the development of hypotheses to be tested in future longitudinal studies, with a view to developing interventions aimed at reducing sociodemographic differences in CRC screening uptake.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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