PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Variation in changes in the incidence of colorectal cancer by age and association with screening uptake; an observational study.
AUTHORS	Clark, Gavin; Anderson, Annie; Godfrey, Thomas; Strachan, Judith; Fraser, Callum; Steele, Robert

VERSION 1 – REVIEW

REVIEWER	Amanda Cross Imperial College London
REVIEW RETURNED	24-Mar-2020

GENERAL COMMENTS	This manuscript was a pleasure to read. It addresses an important subject area with unique data, and is a very useful contribution to the literature. I only have three queries: 1. If possible, it would be good to include the data on mortality as well to give a complete picture. 2. Do the authors have any data from 2017 to 2020 to see if they are starting to see any changes in colorectal cancer incidence and mortality due to FIT? 3. Results, page 13-14 'In those aged 75 years and over (postscreening), a consistent drop in incidence was noted from 2009 (217.7 per 100,000) to 2017 (179.7 per 100,100) (Figure 2)…' The numbers given in the text do not appear to match the numbers in the figure. 4. Do the authors have an explanation for the marked dip in incidence in 2010 among those under age 50 years?

REVIEWER	Eric Miller National Cancer Institute, USA
REVIEW RETURNED	02-Apr-2020

GENERAL COMMENTS	The authors describe the trends of colorectal cancer incidence in relation to a pilot and full rollout of a gFOBT screening program in Scotland. While the research objective is not novel, it is still important to examine colorectal cancer rates in relation to screening programs and in different countries. The paper is well-written but has some notable limitations. The biggest shortcoming of the paper is the lack of statistical testing to determine if the trends are significant, if the rates and trends significantly differ by screening group, and if changes in trends are significant (e.g. using Joinpoint software). For example, the abstract

	mentions an increase in rates among those under 50 from 5.3 per 100,000 to 6.8 per 100,000 but it is unclear if this modest increase is statistically significant. In relation to this shortcoming, it would be helpful to see the number of cases diagnosed each year in the different age categories and screening categories. This issue is most important to Figure 3, where the annual rates are much less stable due to smaller numbers. There are confidence intervals presented in Figure 4 but they are not referred to in the text, either in the methods or results. Additional comments: I feel there is enough evidence in the literature demonstrating a difference in screening effectiveness by sex that warrants examining the rates separately by sex. The authors appropriately adjust for sex but this could mask important differences. If the results do not fit in the manuscript they could be included as supplemental material. In the discussion, the authors make comparisons of their results to other screening trials. The authors need to make clear that the results from those trials were analyzed as intention-to-screen whereas this analysis examined rates by compliance only among those invited to screening. When trying to interpret the figures, it would be helpful to know how many people were screened during the pilot phase versus the full rollout. In Figure 3 (under 50), there is a large drop in incidence from 2008-2009. This could be random year-to-year variation or a shift in resources to the older population eligible for screening. This is another example where the number of cases would be helpful and the authors may want to comment in the text. In Figure 4, incidence rates substantially increase in both groups (participation/no participation). The authors refer to the increase on page 13 (lines 35-37) but the explanation is unclear, especially since the increase occurred in both groups. While the focus of the paper is on incidence, I think the authors need to mention that the potential decrease in incidence rates found in the study or hypothesized in the future with the switch to the FIT does not guarantee a decrease in mortality rates, which is the primary purpose of screening. If the screening program is mostly identifying slow growing tumors, incidence may decrease without a corresponding decrease in mortality.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1: This manuscript was a pleasure to read. It addresses an important subject area with unique data and is a very useful contribution to the literature. I only have three queries:

Response: Thank you for these very complimentary comments.

Comment 2: If possible, it would be good to include the data on mortality as well to give a complete picture.

Response: Thank you for that suggestion. We have generated the data on mortality, with 95%CI, and added these in the Supplementary Material. Two new Figures show the change over the time of the study in the 50-74 years (screening) age range and in the under 50 years age range. These are explained briefly in the revised Methods and Results sections. In the Discussion section, we have added explanatory text.

Comment 3: Do the authors have any data from 2017 to 2020 to see if they are starting to see any changes in colorectal cancer incidence and mortality due to FIT?

Response: It is too early for the data collection methodology used in Scotland to allow us to examine this very interesting question. We have added a few words to the text of the Meaning of the study section of the Discussion: “and this will be examined when data become available”.

Comment 4: Results, page 13-14 ‘In those aged 75 years and over (post screening), a consistent drop in incidence was noted from 2009 (217.7 per 100,000) to 2017 (179.7 per 100,100) (Figure 2) …’ The numbers given in the text do not appear to match the numbers in the figure.

Response: This was an error in the original manuscript and has now been corrected.

Comment 5: Do the authors have an explanation for the marked dip in incidence in 2010 among those under age 50 years?

Response: We have now added the 95% CI to the Figures: these are wide for the under 50 years age range since the number with CRC is relatively small compared to the 50-75 and over 75 age ranges, as demonstrated in the revised Figures 1 and 2, which also now show the 95%CI. We are unaware of any logical reason why incidence would drop for this age range: the changes that seem to be present over time on visual inspection may be due to the large random variation.

Reviewer: 2

Comment 1: The authors describe the trends of colorectal cancer incidence in relation to a pilot and full rollout of a gFOBT screening program in Scotland. While the research objective is not novel, it is still important to examine colorectal cancer rates in relation to screening programs and in different countries. The paper is well-written but has some notable limitations.

Response: Thank you for the comments that subject of our paper was important and that the paper is well-written. We consider that our report does has a major novel aspect, since it reports, for the first time to our knowledge, that changes in incidence are linked to screening participation.

Comment 2: The biggest shortcoming of the paper is the lack of statistical testing to determine if the trends are significant, if the rates and trends significantly differ by screening group, and if changes in trends are significant (e.g. using Joinpoint software). For example, the abstract mentions an increase

in rates among those under 50 from 5.3 per 100,000 to 6.8 per 100,000 but it is unclear if this modest increase is statistically significant. In relation to this shortcoming, it would be helpful to see the number of cases diagnosed each year in the different age categories and screening categories. This issue is most important to Figure 3, where the annual rates are much less stable due to smaller numbers. There are confidence intervals presented in Figure 4 but they are not referred to in the text, either in the methods or results.

Response:

We have recast the Figures to include 95% CI where relevant to aid the visual interpretation of our data. This is now documented in the Methods section and reflected in the modified legends to the Figures. For the results of the Cox regression mode, we have now included p-values, in addition to the 95% CI included in the original manuscript. We have also included the number of cases by age range in the Supplementary Material.

Comment 3: I feel there is enough evidence in the literature demonstrating a difference in screening effectiveness by sex that warrants examining the rates separately by sex. The authors appropriately adjust for sex but this could mask important differences. If the results do not fit in the manuscript they could be included as supplemental material.

Response: We have now included crude cumulative incidence separated by sex and participation in the Supplementary Material.

Comment 4: In the discussion, the authors make comparisons of their results to other screening trials. The authors need to make clear that the results from those trials were analyzed as intention-to-screen whereas this analysis examined rates by compliance only among those invited to screening.

Response: It is true that results of RCT are properly analysed on an intention-to screen basis, and our analysis did the same; as the reviewer states, by examining incidence rates in the 50-74 years old age range, we analysed all those who were invited (i.e., in whom there was an intention to screen). We also separated the 50-74 years age range into participants and non-participants, but this was to examine the effect of participation, and intention to screen is not relevant in this context.

Comment 5: When trying to interpret the figures, it would be helpful to know how many people were screened during the pilot phase versus the full rollout.

Response: We have now included this in the first paragraph of the Results section

Comment 6: In Figure 3 (under 50), there is a large drop in incidence from 2008-2009. This could be random year-to-year variation or a shift in resources to the older population eligible for screening. This is another example where the number of cases would be helpful and the authors may want to comment in the text.

Response: This issue was also raised by Reviewer 1. We have added the 95%CI to all relevant figures to aid interpretation.

Comment 7: In Figure 4, incidence rates substantially increase in both groups (participation/no

participation). The authors refer to the increase on page 13 (lines 35-37) but the explanation is unclear, especially since the increase occurred in both groups.

Response: We have expanded on the original text and included a new Table (Table 2) in the Supplementary Material on the number of colorectal cancer cases by age range.

Comment 8: While the focus of the paper is on incidence, I think the authors need to mention that the potential decrease in incidence rates found in the study or hypothesized in the future with the switch to the FIT does not guarantee a decrease in mortality rates, which is the primary purpose of screening. If the screening program is mostly identifying slow growing tumors, incidence may decrease without a corresponding decrease in mortality.

Response: Selective detection of slow growing tumours (length bias) is one of the major confounding factors in screening and has been suggested as one of the ways that screening appears to decrease mortality. This is why population-based RCT analysed on an intention to screen basis are critical, and CRC screening is predicated on such trials. If screening is preventing only slowly growing tumours, then it could be argued that decreasing incidence may not be effective in reducing mortality. However, this is highly unlikely, especially given the significant mortality reduction in the flexible sigmoidoscopy randomised trials that were accompanied by significant incidence reductions. We have added text to this effect, and we have now added data on the mortality reduction seen in the 50-74 years age range.

We were pleased that no formatting amendments were required. Having carefully considered in detail the recommendations of the reviewers as far as we can at this time, and followed the cogent and constructive comments, we hope that our revision will be considered suitable for publication in BMJ Open. We have taken the opportunity to add a citation to very relevant recent paper (new reference 6) and to make some minor improvements to the text. We look forward to your feedback.

VERSION 2 – REVIEW

REVIEWER	Amanda Cross Imperial College London
REVIEW RETURNED	15-May-2020

GENERAL COMMENTS	The authors have addressed all of my concerns.

REVIEWER	Eric Miller National Cancer Institute United States of America
REVIEW RETURNED	19-May-2020

GENERAL COMMENTS	I appreciate the all the changes the authors have made to the manuscript. The main remaining issue I have is with what I feel is a somewhat overinterpretation of the increase in rates in the <50 age group. This is related to the lack of statistical testing for the change in rates. There appears to be essentially no change in rates from 1997 to 2010 (aside from some interesting changes within that time-period) but then a big increase in 2011 with fairly stable rates after that. This is not consistent with long-term changes in lifestyle factors and could potentially be an artifactual change in rates or due to increased endoscopy in this age group because of wider-spread use

	after 2009. Even with the confidence intervals it's hard to tell if the rate in 2017 is significantly higher than in 2000. The authors make important arguments against screening adults under 50 which apply regardless but I think the language concerning the increase in rates seen specifically in this analysis needs to be tempered unless the statistics demonstrate the rates have risen throughout the study period. This comment primarily applies to the abstract, results (page 13), and discussion (page 16). Other references to the increase appear to refer to the increase that has been observed generally and not specific to this analysis. Regarding my previous comment on Figure 4. I am still confused by the explanation for the increase in rates in 2005 for the no participation group. I understand that the inclusion of those >75 would increase the rates in those who participated in the screening program but why would there be a similar increase for those who did not participate? Is it possible there was some misclassification?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Comment: The authors have addressed all of my concerns.

Response: Thank you: we were pleased to learn that we had addressed the constructive comments of this reviewer.

Reviewer: 2

Comment 1: I appreciate the all the changes the authors have made to the manuscript. The main remaining issue I have is with what I feel is a somewhat overinterpretation of the increase in rates in the <50 age group. This is related to the lack of statistical testing for the change in rates. There appears to be essentially no change in rates from 1997 to 2010 (aside from some interesting changes within that time-period) but then a big increase in 2011 with fairly stable rates after that. This is not consistent with long-term changes in lifestyle factors and could potentially be an artefactual change in rates or due to increased endoscopy in this age group because of wider-spread use after 2009. Even with the confidence intervals it's hard to tell if the rate in 2017 is significantly higher than in 2000. The authors make important arguments against screening adults under 50 which apply regardless but I think the language concerning the increase in rates seen specifically in this analysis needs to be tempered unless the statistics demonstrate the rates have risen throughout the study period. This comment primarily applies to the abstract, results (page 13), and discussion (page 16). Other references to the increase appear to refer to the increase that has been observed generally and not specific to this analysis.

Response: We thank the reviewer for highlighting this important issue. We have now used Poisson regression to quantify and add a statistical significance estimate to the change in incidence in those under 50 years from 2000 to 2017. We have also included the text albeit with fluctuations when referencing this in the abstract and discussion (page 16), tempering our statements a little, as suggested by this reviewer.

Comment 2: Regarding my previous comment on Figure 4. I am still confused by the explanation for the increase in rates in 2005 for the no participation group. I understand that the inclusion of those >75 would increase the rates in those who participated in the screening program but why would there be a similar increase for those who did not participate? Is it possible there was some misclassification?

Response: Thank you for this comment. We have clarified this point by expanding on the wording in the Results section (page 13).