BMJ Open

Variation in changes in the incidence of colorectal cancer by age and association with screening uptake; an observational study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037925
Article Type:	Original research
Date Submitted by the Author:	24-Feb-2020
Complete List of Authors:	Clark, Gavin; NHS Scotland National Services Division Anderson, Annie; university of dundee, Centre for public health nutrition research Godfrey, Thomas; NHS Scotland National Services Division Strachan, Judith; NHS Tayside, Blood Sciences Fraser, Callum; University of Dundee, Centre for Research into Cancer Prevention and Screening Steele, Robert; University of Dundee, Centre for Research into Cancer Prevention and Screening
Keywords:	GASTROENTEROLOGY, ONCOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Variation in changes in the incidence of colorectal cancer by age and association with screening uptake; an observational study.

Gavin RC Clark, Annie S Anderson (0000-0002-0047-4500), Thomas G Godfrey, Judith A Strachan, Callum G Fraser (0000-0002-1333-7994), Robert JC Steele (0000-0003-4248-6785)

Information Services Division, NHS National Services Scotland, Edinburgh EH12 9EB, Scotland, UK

Gavin RC Clark senior information analyst

Thomas G Godfrey information analyst

Centre for Public Health Nutrition, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Annie S Anderson professor

Department of Blood Sciences and Scottish Bowel Screening Laboratory, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Judith A Strachan consultant clinical scientist

Centre for Research into Cancer Prevention and Screening, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Callum G Fraser, honorary professor,

Robert JC Steele, senior research professor

Emails:

Gavin RC Clark, gavin.clark2@nhs.net

Annie S Anderson, a.s.anderson@dundee.ac.uk

Thomas G Godfrey, thomas.godfrey@nhs.net

Judith A Strachan, judith.strachan@nhs.net

Callum G Fraser, callum.fraser@nhs.net

Robert JC Steele, r.j.c.steele@dundee.ac.uk

Corresponding author: Professor Robert JC Steele, Mailbox 4, Level 7, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK.

Email: r.j.c.steele@dundee.ac.uk

Telephone: + 44 (0)1382 3835444

Short title: Incidence of colorectal cancer

No of words (abstract): 293

No of words (text): 2527

No of references: 19

No of Tables: 0

No of Figures: 5

No of Supplementary Tables: 1

Keywords: adenoma, colorectal cancer, faecal occult blood test, incidence, screening

Abbreviations: CRC: colorectal cancer, FIT: faecal immunochemical test for haemoglobin, gFOBT: guaiac faecal occult blood testing, HDI: human development index, RCT: randomised controlled trial, SBSD: Scottish Bowel Screening Database, SCR: Scottish Cancer Registry, SEER: Surveillance, Epidemiology and End Results, UK: United Kingdom, USA: United States of America

Abstract

Objectives - In developed countries, the incidence of colorectal cancer (CRC) has declined in the over 50 years age group, but increased in younger people. We studied incidence by age and the influence of screening uptake on CRC incidence.

Design - Age and sex-standardised incidence data for CRC from 1997 to 2017 were obtained from the Scottish Cancer Registry (SCR). In addition, linkage between the Scottish Bowel Screening Database (SBSD) and the SCR allowed investigation of any association between screening participation and CRC incidence.

Setting – Scotland and the Scottish Bowel Screening Programme, in which guaiac faecal occult blood test screening was piloted from March 2000 and fully rolled by December 2009**.**

Participants – From the introduction of screening in 2000 through to 2017, 2,395,172 were invited to participate, of whom 1,487,999 participated at least once.

Main outcome measures – Incidence of CRC.

Results - In the screening age range (50-74 years), CRC incidence peaked at 156.5 cases per 100,000 in 2010 after full roll-out of screening across Scotland but fell to 123.9 per 100,000 in 2017. However, under 50 years, there was a rise of from 5.3 cases per 100,000 in 2000 to 6.8 per 100,000 in 2017. When CRC incidence was examined in those who had been offered screening, incidence fell in the participant group more than in the non-participant group after roll-out of screening was complete. Analysis of cumulative incidence demonstrated that CRC incidence in the participant group remained consistently below that of the non-participant from around seven years of follow-up.

Conclusions - The incidence of colorectal cancer (CRC) in Scotland has declined in the over 50 years age groups, but increased in younger people. Population screening has likely contributed to the reduction in CRC incidence in the over 50 years age group.

Strengths and limitations of this study

- We examine age and sex-standardised incidence data for colorectal cancer for the years 1997 to 2017 obtained from the Scottish Cancer Registry and linkage between the Registry and the Scottish Bowel Screening Database.

- We are able to show previously unreported changes in the incidence of colorectal cancer in Scotland in all age groups.

- We are able to examine in detail, for the first time, if population-based screening using faecal occult blood tests affects incidence of colorectal cancer.

- Associations between incidence and plausible reasons for the changes over time will help establish future helpful interventions.

- Although this was a large study, we did not examine incidence by yearly age, only in three large groups.

.

Introduction

Colorectal cancer (CRC) is a major health problem worldwide. In Scotland, it is currently the third most commonly diagnosed non-cutaneous cancer and the second most common cause of cancer-related deaths.[1] However, the incidence of CRC varies widely across the world and it is estimated that 60% of CRC deaths occur in those countries with a high or very high human development index (HDI).[2] Western lifestyle factors including obesity, lack of physical exercise, a diet rich in red and processed meat, smoking, and alcohol have all been linked to the risk of developing CRC,[3] and marked increases in both incidence and mortality have been observed in many medium-high HDI countries, especially in Asia, South America and Eastern Europe.[2] However, both incidence and mortality have either stabilised or declined in countries with the highest HDI, e.g., Australia, New Zealand, United States of America (USA), and several Western European countries.[4] At least in part, these reductions in mortality may be attributed to improved access to high quality treatment and earlier diagnosis through both screening and through prompt investigation of those presenting with symptoms.

The declines in incidence are not so easy to explain, especially since the frequency of obesity continues to rise in all high HDI countries.[5] However, there is now good

evidence, largely from the USA and particularly from the Surveillance, Epidemiology and End Results (SEER) database that, while incidence has been falling since around 1985 in those aged 50 years and over, it has been rising in those under 50 years since the mid-1990s.[3] It has been postulated that screening may be responsible for the reduction in incidence in the group aged over 50 years, especially where this is associated with high rates of large bowel endoscopy, which facilitates the diagnosis and removal of pre-malignant adenoma.[3] Since there is now robust evidence from randomised trials of endoscopic screening that removal of adenoma leads to a reduction in CRC incidence,[6] this is an attractive hypothesis, but one that is difficult to test.

In Scotland, CRC screening, initially using biennial guaiac faecal occult blood tests (gFOBT), was rolled out to the whole of the population aged 50-74 years in 2007 after a three screening rounds pilot which started in 2000.[7,8] In addition, Scotland, along with the rest of the United Kingdom (UK), is ranked as having a very high HDI,[2] has a high incidence of CRC,[1] and lifestyle factors associated with CRC are prevalent in the population.[9] We therefore examined the incidence of CRC between 1997 and 2017 in the 50-74 years screening age range, the post-screening age range, and the pre-screening age range. In addition, the effect of screening participation was assessed.

Methods

In Scotland, screening for CRC using biennial gFOBT, offered to everyone in the 50-69 years age range and registered with a general practitioner, commenced in March 2000 with a pilot involving three of the fourteen NHS Boards responsible for routine health care. Roll-out to the rest of Scotland began in July 2007 and was completed by December 2009. The age range was also extended up to age 74 years for the whole of Scotland during roll-out. Details of the pilot, roll-out and descriptions of the screening algorithms have been published previously.[7,8] Data are collected centrally by the Information Services Division of NHS National Services Scotland and held in the Scottish Bowel Screening Database (SBSD).

To assess changes in the incidence of CRC in different age ranges around the time of the introduction of screening, data were obtained from the Scottish Cancer Registry (SCR) for the years 1997 to 2017. Crude incidence rates were calculated by sex and five-year age group using mid-year population estimates from the National Records of Scotland (NRS). These rates were then directly standardised using the 2013 European Standard Population. Age-sex standardised rates were calculated separately for the screening (50-74 years), post-screening (75 years and higher), and pre-screening (under 50 years) age ranges.

To investigate the impact of screening participation on incidence, linkage was carried out between the SBSD, the SCR and NRS deaths. The SBSD allowed identification of those invited for screening and those who participated. Participants who received a

positive or negative screening test result at any point were included in the participant cohort. Those who did not receive a positive or negative test result, or never returned a completed test, were included in the non-participant cohort. Data were included from the pilot through to national roll-out, with the data on invites available from March 2000. Linkage with the SCR allowed CRC incidence to be calculated for the participant and non-participant groups and linkage with the NRS deaths records allowed removal of participants from study at the point of death. Follow-up data were available to 31 December 2017. Age-sex standardised rates were calculated for participant and non-participant groups as described above.

The age structure of the screening population changed a great deal in the early years of the study period (see Supplementary Table 1). The ageing of the original pilot cohort, in addition to the expansion of the age-range on national rollout, influence the annual CRC incidence rate, despite adjustment through standardisation. In addition, any reduction seen in annual CRC incidence could be influenced by a shortening time to diagnosis. That is, since cancers are detected earlier, the years after roll-out see a reduction in incidence exclusively due to early detection rather than to prevention of disease. To better analyse these issues, time-to-event analysis was used in addition to the descriptive time-series analysis. This facilitated better understanding of the relationship between participation in screening and how it affects an individual's risk over time. Cumulative incidence was estimated using the Kaplan-Meier method. Cox regression was also used to estimate the impact of screening participation on time from invite to

CRC diagnosis, adjusting for age at first invite, sex, and level of socioeconomic status as determined by the Scottish Index of Multiple Deprivation.

An underlying assumption of Cox regression is that of proportional hazards, i.e., that the ratio of the hazards between treatment and non-treatment groups remains constant over time. This assumption was not met for the participation status variable, since the CRC hazard increases at biennial intervals for the participant group, consistent with screening participation. In consequence, an alternative analytical approach is also presented, with separate hazard ratios reported for less than, and more than, seven years of follow-up. Seven years was chosen as the cut-off because participant cumulative incidence is consistently lower than non-participant (and the proportional hazards assumption is met) from this point. All analyses were performed using R statistical software, version 3.5.1.

Neither patients, participants in screening, nor the public were involved in any way in development of the research question, the design of the study, or any other aspect of this research. Dissemination to these groups is not possible nor applicable.

The Scottish Government, funders of the study, 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 requests for data sharing should be discussed, in the first instance, with RJCS at r.j.c.steele@dundee.ac.uk

Results

77,262 CRC were diagnosed in Scotland between 1997 and 2017. From the introduction of screening in 2000 through to 2017, 2,395,172 were invited to participate, of whom 1,487,999 participated at least once. There were 24,817 CRC diagnosed within the population invited to screen (15,663 in participants, 9,154 in non-participants) in the same period. These CRC were detected through both screening and non-screening pathways.

In the 50-74 years (screening) age range, a slight drop in incidence was observed, from 154.4 cases per 100,000 in 2000, the first year of the demonstration pilot, to 137.8 in 2005. Then, coinciding with commencement of roll-out of screening across the country in 2007, an increase was noted, which peaked at 156.5 cases per 100,000 in 2010 and began to fall to levels well below those seen in the immediate pre-screening period, reaching 123.9 per 100,000 in 2017 (Figure 1). 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) whereas, in those aged under 50 years (pre-screening) a rise throughout the study period from 5.3 cases per 100,000 in 2000 to 6.8 per 100,000 in 2017 was seen, albeit with fluctuations (Figure 3).

When CRC incidence in the population who had been offered screening was examined, there was a distinct difference between those who had participated at least once and those who never participated. The data shown are age and sex-standardised since these variables influence both CRC incidence and uptake of screening, with both uptake and incidence increasing with age, and with uptake being lower, but incidence higher, in men than in women.[10] Figure 4 shows that incidence increased more in the participant group than in the non-participant group as national roll-out of screening started but that, after roll-out had been completed, incidence fell in the participant group to a greater extent than in the non-participant group, with participant incidence 13.9% below non-participant in 2017. Data obtained prior to 2005 was still influenced by the age structure of the invited population despite adjustment.

Analysis of cumulative incidence shown in Figure 5 demonstrates the risk of developing CRC over time. Fluctuations can be seen initially in the participant group, consistent with the biennial screening interval. The participant group then remains consistently below that of the non-participant from around seven years of follow-up.

Cox regression analysis adjusted for age, sex and socioeconomic deprivation gave a hazard ratio of 0.92 for participants, relative to non-participants (95% CI: 0.90-0.95). The hazard ratios, when separating the follow-up period at seven years, were 0.95 (95% CI: 0.92-0.98) in the period up to seven years and 0.87 (95% CI: 0.83-0.91) in the period seven years or more.

Discussion

Statement of principal findings - The findings in this study have similarities with those reported in from other high-income countries,[4] namely that the incidence of CRC is falling in older age groups but increasing in people under the age of 50 years. However, in this study, we were not only able to examine the changes in CRC incidence by age, but also by screening participation, and this demonstrated that the fall in incidence was more evident in those who had participated in screening.

Strengths and weaknesses in relation to other studies - The Minnesota randomised controlled trial (RCT), which employed mostly rehydrated Hemoccult II giving a positivity of 9.8 %, did demonstrate a modest reduction in the groups offered screening after 18 years of follow-up,[11] but the Nottingham RCT, which used gFOBT in un-rehydrated form (the same approach that was adopted in Scotland) and reported a 2% positivity, showed no effect on CRC incidence after 11 years.[12] Overall, previous studies of the effect of gFOBT screening on CRC incidence have not shown a substantial effect. In Scotland,

from December 2009, biennial gFOBT screening was being offered to the whole of the eligible population. This resulted in a positivity of around 2%, so that, with an average uptake at this time of 55%, only around 1% of people being offered screening actually underwent colonoscopy.[8] Of those that did, the average positive predictive value of gFOBT for CRC was 10% and 40% for adenoma,[8] so that less than 0.5% of the population offered screening (the 50-74 year age range) would have had removal of adenoma. However, in the present study, the groups were much bigger than in the RCT and the reduction in incidence seen in the 50-74 years age range is likely to have been due, at least in part, to polypectomy following a positive screening test result. The rise in incidence immediately after roll-out and preceding the consistent fall is likely to have been due to the well-described screening effect caused by a combination of early and over-diagnosis.[13] This would not explain the later fall in incidence, however, since the incidence of disease after the introduction of screening tends not to fall back to baseline because of over-diagnosis (i.e., some people with screen-detected disease would have never presented clinically) as is the case in breast cancer screening.[14]

Meaning of the study - In November 2017, the Scottish Bowel Screening Programme changed the screening test from gFOBT to a quantitative faecal immunochemical test (FIT) at a threshold of 80 µg haemoglobin/g faeces. At this threshold, in the first year of screening with FIT, there was a 100% relative increase in the number of participants with adenomas identified,[14] so that, going forward, screening using FIT can be expected to bring about a greater reduction in CRC incidence than has been seen to date. The other very important consideration is the increase in CRC incidence seen in younger

people. One approach to this could be to extend screening to those aged under 50 years, but it must be borne in mind that, under the age of 50 years, although incidence is increasing,[15] it is still much lower than in the current screening age range.

Unanswered questions and future research - There is no objective evidence yet to support screening under the age of 50 years, and other approaches, including improved awareness of symptoms, increased use of FIT to triage patients presenting in primary care with symptoms[16] and addressing lifestyle issues in the Scottish population must be part of the solution. We cannot necessarily screen our way out of this problem. Observational data such as these cannot prove that screening is the only cause of reduced incidence. Over the age of 50 years, individuals are much more likely to undergo colonoscopy because of lower bowel symptoms than those under 50 years, and this may explain at least part of the incidence reduction in those aged over 50 years. It is interesting that, in the over 75 years age group, a consistent decline in incidence was seen from 2009 onwards. Some of this cohort will have had the opportunity to return screening tests, but by no means all, and it is likely that colonoscopy for the investigation of symptoms is performed even more frequently in this age range.

The reasons underlying the marked increase in incidence in those aged under 50 years is not clear, but may relate to lifestyle factors, particularly around diet, body weight and physical activity, all of which are associated with increased risk of CRC.[17,18] Rising rates

of obesity in younger life (which are indicators of diet and physical activity) are of particular interest because excess adiposity is now experienced by more people at earlier life stages and a recent study has demonstrated a relationship between body mass index in childhood and risk of adult CRC.[19]

However, the clear separation of yearly and cumulative incidence by participation lends persuasive evidence to the hypothesis that screening is at least in part responsible for the observed incidence patterns in the population. It could still be argued that the people who participated in screening were healthier than those who did not, and that lifestyle factors were also responsible for this observation but, given the clear effect of removal of adenomas on CRC incidence,[6] it is highly likely that screening played an important role.

Contributor statement

GRCC collected and analysed the data, participated in data interpretation, and contributed to writing the paper. AAS contributed on dietary issues, participated in data interpretation, and contributed to writing the paper. TGG assisted with analysing and validating the data, participated in data interpretation, and contributed to writing the paper. JAS directed the laboratories that analysed the faecal tests in the SBoSP from 2010, participated in data interpretation, and contributed to writing the paper. CGF directed the SBoSP laboratories to 2010, participated in data interpretation, and

provided significant input into the writing of the paper. RJCS is Clinical Director of the SBoSP, initiated the study, led the data interpretation, and wrote first and final drafts of the paper, and is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; CGF did consultancy for Immunostics Inc, Ocean, NJ, USA, and does

for Hitachi Chemical Diagnostic Systems Co., Ltd, Tokyo, Japan; no other relationships or activities that could appear to have influenced the submitted work have been done.

Acknowledgements

We acknowledge the support of Scottish Government and the NHS National Services and Information Services Divisions.

Patient and public involvement statement

Neither patients, participants in screening, nor the public were involved in any way in development of the research question, the design of the study, or any other aspect of this research. Dissemination to these groups is not possible nor applicable.

Funding

The Scottish Government, funders of the study, 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.

Data sharing

All requests for data sharing should be discussed, in the first instance, with RJCS at r.j.c.steele@dundee.ac.uk

References

1. Cancer in Scotland. Information Services Division, NHS National Services Scotland 2019 https://www.isdscotland.org/Health-Topics/Cancer/Publications/2019-04-30/Cancer_in_Scotland_summary_m.pdf (Accessed 30 January 2020)

2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017 66:683-91. doi: 10.1136/gutjnl-2015-310912.

3. Connell LC, Mota JM, Braghiroli MI, Hoff PM. The rising incidence of younger patients with colorectal cancer: questions about screening, biology, and treatment. *Curr Treat Options Oncol* 2017;18:23. doi: 10.1007/s11864-017-0463-3.

4. Araghi M, Soerjomataram I, Bardot A, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. *Lancet Gastroenterol Hepatol* 2019;4:511-8. doi: 10.1016/S2468-1253(19)30147-5.

5. GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 24 years. *N Engl J Med* 2017;377:13-27. doi: 10.1056/NEJMoa1614362.

6. Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet* [2017;389:1299-1311. doi: 10.1016/S0140-6736(17)30396-3.

7. Steele RJC. McClements PL, Libby G, et al. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. *Gut* 2009;58:530-5. doi:10.1136/gut.2008.162883

8. Fraser CG, Digby J, McDonald PJ, Strachan JA, Carey FA, Steele RJC. Experience with a two-tier reflex gFOBT/FIT strategy in a national bowel screening programme. *J Med Screen* 2012;19:8-13. doi:10.1258/jms.2011.011098

9. *Scottish Health Survey.* https://www.gov.scot/publications/scottish-health-survey-2018-volume-1-main-report/ (Accessed 30 January 2020).

10. Steele RJC, Kostourou I, McClements P, et al. Effect of gender, age and deprivation on key performance indicators in a FOBT based colorectal screening programme. *J Med Screen* 2010;17:68-74. doi:10.1258/jms.2010.009120.

11. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000;343:1603-7. doi:10.1056/NEJM200011303432203.

12. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut* 2012;61:1036-40. doi: 10.1136/gutjnl-2011-300774.

13. Grey M, Raffle A. Screening. Evidence and Practice. Oxford University Press 2007. Scottish Bowel Screening Programme Key Performance Indicators report, Information Services Division, NHS National Services Scotland, https://www.isdscotland.org/Health-Topics/Cancer/Publications/2019-08-06/2019-08-06-Bowel-Screening-KPI-Report.xlsx (Accessed 30 January 2020)

14. Information Services Division (ISD) Scotland. Bowel Cancer Screening. https://www.isdscotland.org/Health-Topics/Cancer/Bowel-Screening/ (Accessed 30 January 2020).

15. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut 2019;68:1820–6. doi:10.1136/gutjnl-2018-317592

16. Mowat C, Digby J, Strachan JA, et al. Impact of introducing a faecal immunochemical test (FIT) for haemoglobin into primary care on the outcome of patients with new bowel symptoms: a prospective cohort study. BMJ Open Gastroenterol 2019;6:e000293. doi: 10.1136/bmjgast-2019-000293. eCollection 2019.

17. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening; an independent review. *Lancet* 2012;380:1778-86. doi:10.1016/S0140-6736(12)61611-0.

18. Potter JD. Rising rates of colorectal cancer in younger adults. *BMJ* 2019; 365:l4280. doi: 10.1136/bmj.l4280.

19. Jensen BW, Gamborg M, Gögenur I, Renehan AG, Sørensen TIA, Baker JL. Childhood body mass index and height in relation to site-specific risks of

colorectal cancers in adult life. *Eur J Epidemiol* 2017;32:1097-1106. doi: 10.1007/s10654-017-0289-0.

Legends to Figures

Figure 1. Age-sex standardised colorectal cancer incidence, ages 50-74 years, from 1997 to 2017

Figure 2. Age-sex standardised colorectal cancer incidence, ages 75 years and over, from 1997 to 2017

Figure 3. Age-sex standardised colorectal cancer incidence, ages less than 50 years, from 1997 to 2017

Figure 4. Age-sex standardised colorectal cancer incidence for the screening population, by screening participation status (95% confidence intervals shown)

Figure 5. Cumulative colorectal cancer incidence, by screening participation status

Legend to Supplementary Table 1

Supplementary Table 1: Age distribution of screening and post-screening population, by year

Figure 1. Age-sex standardised colorectal cancer incidence, ages 50-74 years, from 1997 to 2017

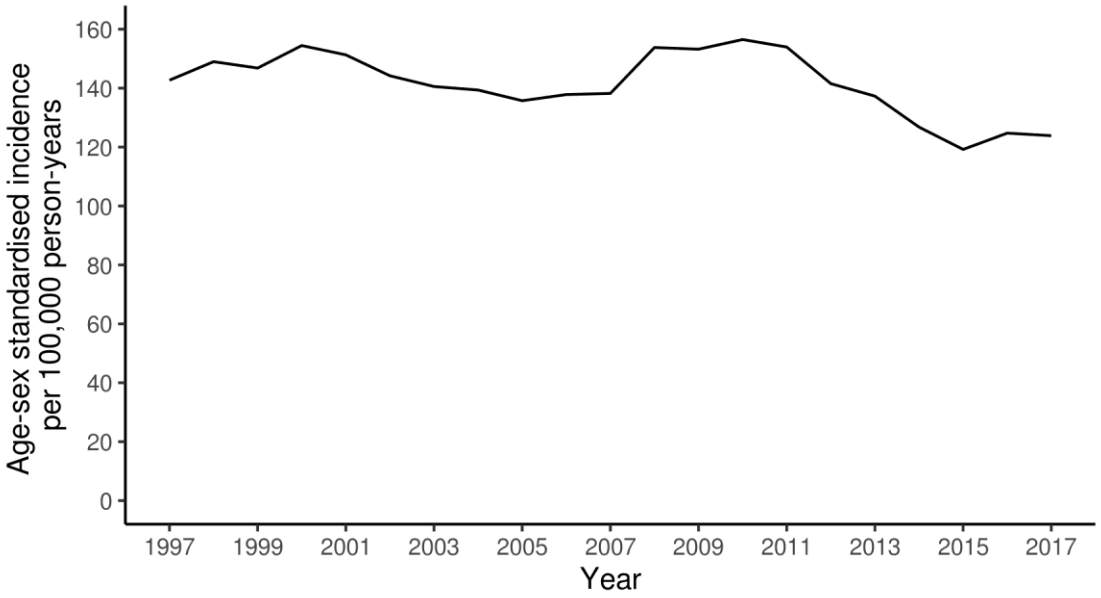


Figure 2. Age-sex standardised colorectal cancer incidence, ages 75 years and over, from 1997 to 2017

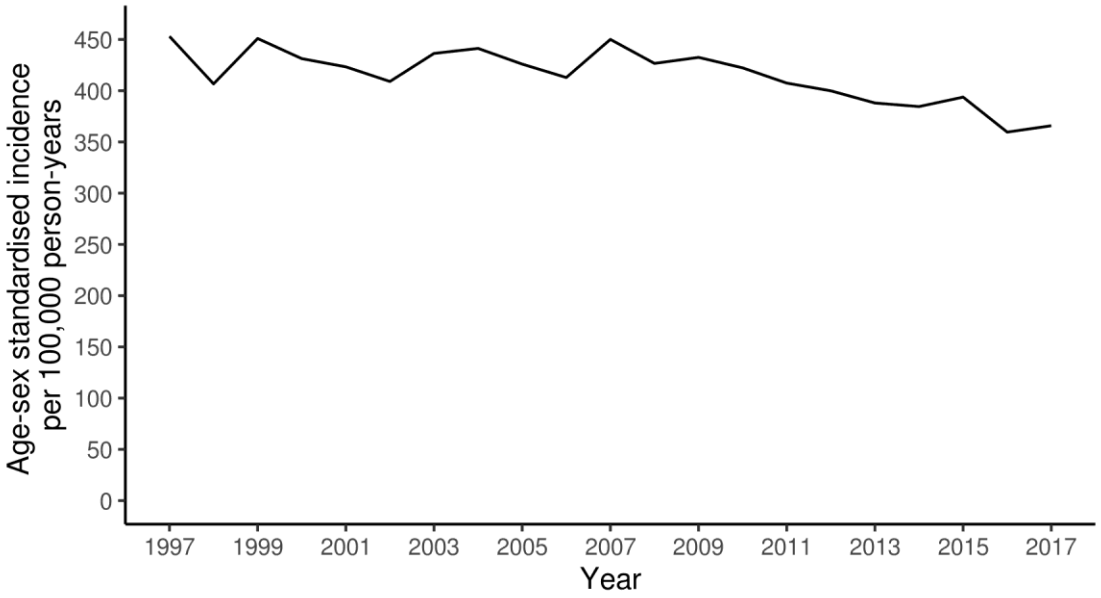


Figure 3. Age-sex standardised colorectal cancer incidence, ages less than 50 years, from 1997 to 2017

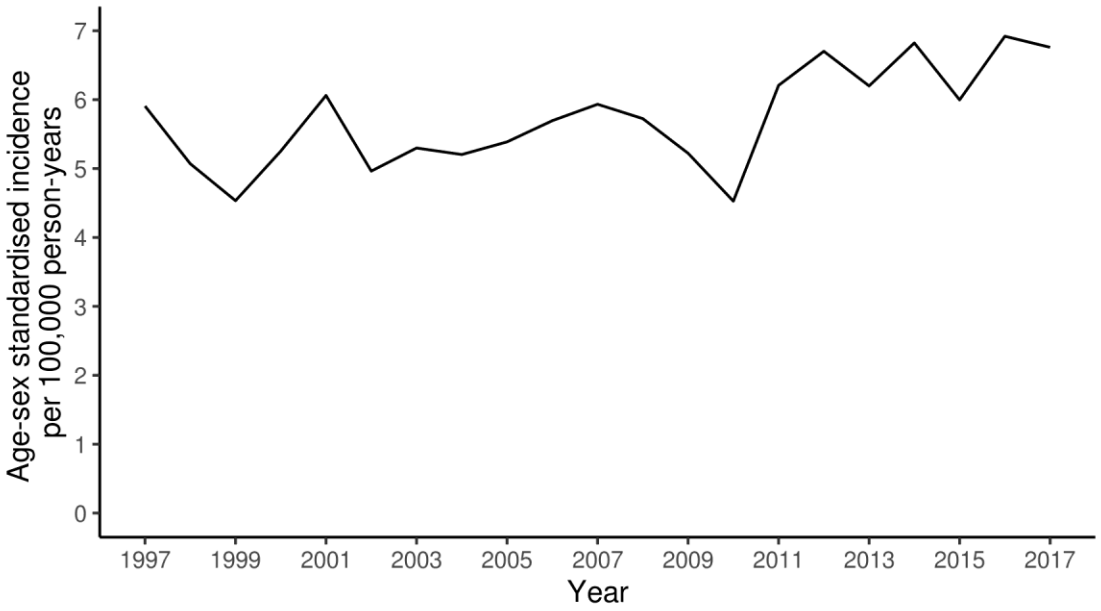


Figure 4. Age-sex standardised colorectal cancer incidence for the screening population, by screening participation status (95% confidence intervals shown)

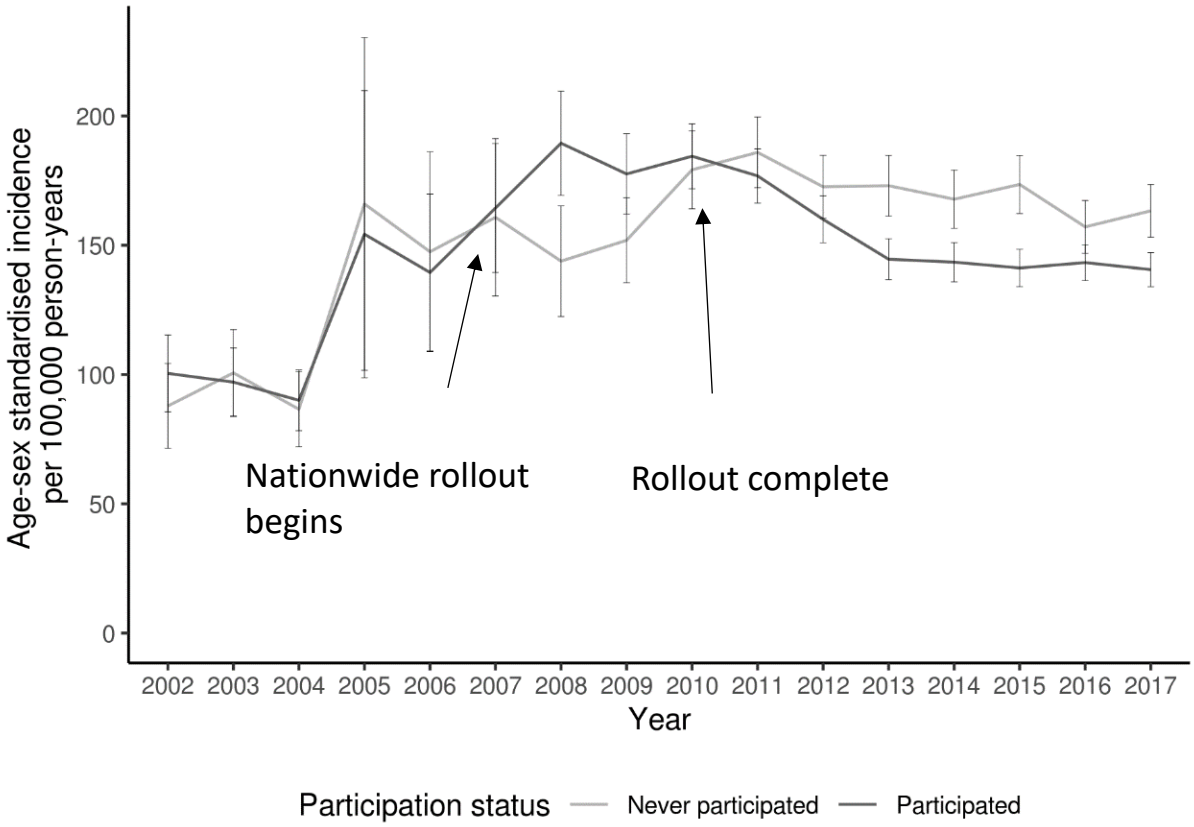
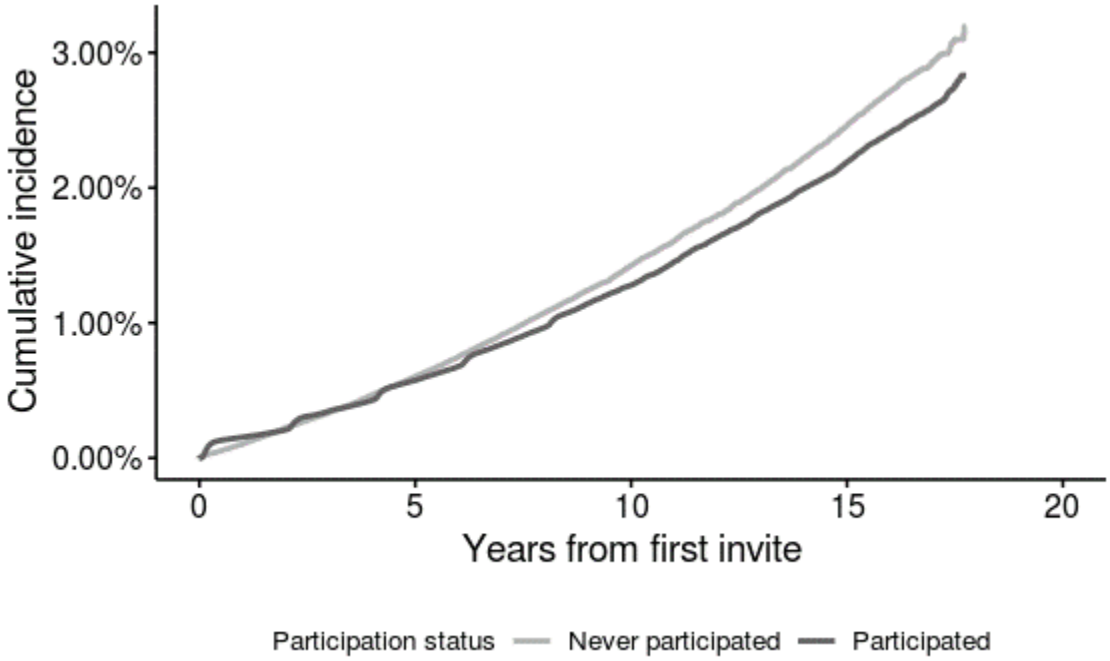


Figure 5. Cumulative colorectal cancer incidence, by screening participation status



Supplementary Table 1: Age distribution of screening and post-screening population, by year

	Age distribution of population, n (%),											
	50-54		55-59		60-64		65-69		70-74		75+	
Year												
2001	54,240	(26.4%)	51,239	(25.0%)	44,137	(21.5%)	42,905	(20.9%)	12,679	(6.2%)	-	(0.0%)
2002	61,490	(22.2%)	74,204	(26.8%)	60,079	(21.7%)	57,307	(20.7%)	23,851	(8.6%)	-	(0.0%)
2003	65,241	(21.5%)	81,141	(26.7%)	63,410	(20.9%)	59,472	(19.6%)	34,581	(11.4%)	-	(0.0%)
2004	67,571	(20.5%)	87,062	(26.4%)	68,088	(20.6%)	61,739	(18.7%)	45,561	(13.8%)	-	(0.0%)
2005	62,874	(18.2%)	92,267	(26.7%)	70,813	(20.5%)	62,646	(18.2%)	52,651	(15.3%)	3,829	(1.1%)
2006	76,947	(20.2%)	93,881	(24.6%)	78,362	(20.6%)	64,371	(16.9%)	56,093	(14.7%)	11,204	(2.9%)
2007	82,678	(19.7%)	96,401	(23.0%)	88,775	(21.2%)	70,209	(16.7%)	59,571	(14.2%)	21,890	(5.2%)
2008	124,768	(20.9%)	130,326	(21.8%)	120,431	(20.1%)	100,736	(16.8%)	81,370	(13.6%)	40,230	(6.7%)
2009	207,433	(21.4%)	203,613	(21.0%)	192,470	(19.8%)	164,107	(16.9%)	132,759	(13.7%)	70,838	(7.3%)
2010	298,073	(21.6%)	279,971	(20.3%)	279,627	(20.2%)	225,020	(16.3%)	189,222	(13.7%)	109,061	(7.9%)
2011	339,145	(21.0%)	321,494	(20.0%)	317,497	(19.7%)	267,034	(16.6%)	218,456	(13.6%)	147,739	(9.2%)
2012		(20.8%)		(19.8%)		(18.4%)		(17.1%)		(13.1%)		(10.7%)

	357,830		339,212		316,700		293,561		225,389		184,587	
2013	376,959	(20.7%)	357,825	(19.6%)	323,931	(17.8%)	310,399	(17.0%)	233,617	(12.8%)	221,685	(12.2%)
2014	398,197	(20.6%)	375,480	(19.5%)	332,956	(17.3%)	323,005	(16.7%)	244,065	(12.6%)	256,410	(13.3%)
2015	411,856	(20.3%)	393,919	(19.5%)	342,353	(16.9%)	337,714	(16.7%)	249,651	(12.3%)	289,123	(14.3%)
2016	425,191	(20.1%)	408,845	(19.3%)	354,588	(16.8%)	338,041	(16.0%)	267,472	(12.7%)	320,149	(15.1%)
2017	422,301	(19.3%)	423,926	(19.4%)	367,652	(16.8%)	331,431	(15.2%)	290,065	(13.3%)	352,178	(16.1%)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9-10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9 -10
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	12-14
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-14
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Variation in changes in the incidence of colorectal cancer by age and association with screening uptake; an observational study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037925.R1
Article Type:	Original research
Date Submitted by the Author:	13-May-2020
Complete List of Authors:	Clark, Gavin; NHS Scotland National Services Division Anderson, Annie; university of dundee, Centre for public health nutrition research Godfrey, Thomas; NHS Scotland National Services Division Strachan, Judith; NHS Tayside, Blood Sciences Fraser, Callum; University of Dundee, Centre for Research into Cancer Prevention and Screening Steele, Robert; University of Dundee, Centre for Research into Cancer Prevention and Screening
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Oncology, Public health
Keywords:	GASTROENTEROLOGY, ONCOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Variation in changes in the incidence of colorectal cancer by age and association with screening uptake; an observational study.

Gavin RC Clark, Annie S Anderson (0000-0002-0047-4500), Thomas G Godfrey, Judith A Strachan, Callum G Fraser (0000-0002-1333-7994), Robert JC Steele (0000-0003-4248-6785)

Information Services Division, NHS National Services Scotland, Edinburgh EH12 9EB, Scotland, UK

Gavin RC Clark senior information analyst

Thomas G Godfrey information analyst

Centre for Public Health Nutrition, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Annie S Anderson professor

Department of Blood Sciences and Scottish Bowel Screening Laboratory, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Judith A Strachan consultant clinical scientist

Centre for Research into Cancer Prevention and Screening, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Callum G Fraser, honorary professor,

Robert JC Steele, senior research professor

Emails:

Gavin RC Clark, gavin.clark2@nhs.net

Annie S Anderson, a.s.anderson@dundee.ac.uk

Thomas G Godfrey, thomas.godfrey@nhs.net

Judith A Strachan, judith.strachan@nhs.net

Callum G Fraser, callum.fraser@nhs.net

Robert JC Steele, r.j.c.steele@dundee.ac.uk

Corresponding author: Professor Robert JC Steele, Mailbox 4, Level 7, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK.

Email: r.j.c.steele@dundee.ac.uk

Telephone: + 44 (0)1382 3835444

Short title: Incidence of colorectal cancer

No of words (abstract): 296

No of words (text): 2938

No of references: 21

No of Tables: 0

No of Figures: 5

No of Supplementary Tables: 2

No of Supplementary Figures: 3

Keywords: adenoma, colorectal cancer, faecal occult blood test, incidence, mortality, screening

Abbreviations: CRC: colorectal cancer, FIT: faecal immunochemical test for haemoglobin, gFOBT: guaiac faecal occult blood testing, HDI: human development index, NRS: National Records Scotland, RCT: randomised controlled trial, SBSD: Scottish Bowel Screening Database, SCR: Scottish Cancer Registry, SEER: Surveillance, Epidemiology and End Results, UK: United Kingdom, USA: United States of America

Abstract

Objectives - In developed countries, the incidence of colorectal cancer (CRC) has declined in the over 50 years age group but increased in younger people. We studied CRC incidence by age and the influence of screening uptake.

Design - Age and sex-standardised incidence for CRC from 1997 to 2017 were obtained from the Scottish Cancer Registry (SCR). In addition, linkage between the Scottish Bowel Screening Database (SBSD) and the SCR allowed investigation of any association between screening participation and CRC incidence.

Setting – Scotland and the Scottish Bowel Screening Programme, in which guaiac faecal occult blood test screening was piloted from March 2000 and fully rolled by December 2009**.**

Participants – From the introduction of screening in 2000 through to 2017, 2,395,172 were invited to participate, of whom 1,487,999 participated at least once.

Main outcome measures – Incidence of CRC.

Results - In the screening age range (50-74 years), CRC incidence peaked at 156.5 cases per 100,000 in 2010 after full roll-out of screening across Scotland but fell to 123.9 per 100,000 in 2017. However, under 50 years, there was a rise of from 5.3

cases per 100,000 in 2000 to 6.8 per 100,000 in 2017. When CRC incidence was examined in those who had been offered screening, incidence fell in the participant group more than in the non-participant group after roll-out of screening was complete. Analysis of cumulative incidence demonstrated that CRC incidence in the participant group remained consistently below that of the non-participant from around seven years of follow-up.

Conclusions - The incidence of colorectal cancer (CRC) in Scotland has declined in the over 50 years age groups but increased in younger people. It is likely that population screening has contributed to the reduction in CRC incidence in the over 50 years age group.

Strengths and limitations of this study

- We examine age and sex-standardised incidence data for colorectal cancer for the years 1997 to 2017 obtained from the Scottish Cancer Registry and linkage between the Registry and the Scottish Bowel Screening Database.

- We are able to show previously unreported changes in the incidence of colorectal cancer in Scotland in all age groups.

- We are able to examine in detail, for the first time, if population-based screening using faecal occult blood tests is associated with incidence of colorectal cancer.

- Associations between incidence and plausible reasons for the changes over time will help the development of future interventions.

- Although this was a large study, we did not examine incidence by yearly age, only in three large groups.

.

Introduction

Colorectal cancer (CRC) is a major health problem worldwide. In Scotland, it is currently the third most commonly diagnosed non-cutaneous cancer and the second most common cause of cancer-related deaths.[1] However, the incidence of CRC varies widely across the world and it is estimated that 60% of CRC deaths occur in those countries with a high or very high human development index (HDI).[2] Western lifestyle factors, including obesity, lack of physical exercise, a diet rich in red and processed meat, smoking, and alcohol, have all been linked to the risk of developing CRC,[3] and marked increases in both incidence and mortality have been observed in many medium-high HDI countries, especially in Asia, South America and Eastern Europe.[2] However, both incidence and mortality have either stabilised or declined in countries with the highest HDI, e.g., Australia, New Zealand, United States of America (USA), and several Western European countries.[4] These reductions in mortality are likely to be attributable to improved access to high quality treatment and earlier diagnosis through both screening and through prompt investigation of those presenting with symptoms.

The declines in incidence are not so easy to explain, especially since the frequency of obesity continues to rise in all high HDI countries.[5] However, there is now good evidence, largely from the USA and particularly from the Surveillance, Epidemiology and End Results (SEER) database that, while incidence has been falling since around 1985 in those aged 50 years and over, it has been rising in those under 50 years since the mid-1990s.[3] In a recent analysis of incidence and mortality databases from 39

countries, it was confirmed that countries with the highest HDI had a decrease in CRC incidence, but that incidence of colon and rectal cancers has continued to increase in countries with medium–high HDI, and in younger populations.[6] It has been postulated that screening may be responsible for the reduction in incidence in the group aged over 50 years, especially where this is associated with high rates of large bowel endoscopy, which facilitates the diagnosis and removal of pre-malignant adenomas.[3] Since there is now robust evidence from randomised trials of endoscopic screening that removal of adenoma leads to a reduction in CRC incidence,[7] this is an attractive hypothesis, but one that is difficult to test.

In Scotland, CRC screening, initially using biennial guaiac faecal occult blood tests (gFOBT), was rolled out to the whole of the population aged 50-74 years in 2007 after a three screening rounds pilot which started in 2000.[8,9] In addition, Scotland, along with the rest of the United Kingdom (UK), is ranked as having a very high HDI,[2] and although the incidence has fallen by 18.6% from 2007 to 2017,[1] it still has a high incidence of CRC,[1] and lifestyle factors associated with CRC are prevalent in the population.[10] We therefore examined the incidence of CRC between 1997 and 2017 in the 50-74 years screening age range, the post-screening age range, and the pre-screening age range. In addition, the effect of screening participation on CRC incidence was assessed.

Methods

In Scotland, screening for CRC using biennial gFOBT, offered to everyone in the 50-69 years age range and registered with a general practitioner, commenced in March 2000 with a pilot involving three of the fourteen NHS Boards responsible for routine health care. Roll-out to the rest of Scotland began in July 2007 and was completed by December 2009. The age range was also extended up to age 74 years for the whole of Scotland during roll-out. Details of the pilot, roll-out and descriptions of the screening algorithms have been published previously.[8,9] Data are collected centrally by the Information Services Division of NHS National Services Scotland and held in the Scottish Bowel Screening Database (SBSD).

To assess changes in the incidence of CRC in different age ranges around the time of the introduction of screening, data were obtained from the Scottish Cancer Registry (SCR) for the years 1997 to 2017. Crude incidence rates were calculated by sex and five-year age group using mid-year population estimates from the National Records of Scotland (NRS). These rates were then directly standardised using the 2013 European Standard Population. Age-sex standardised rates were calculated separately for the screening (50-74 years), post-screening (75 years and higher), and pre-screening (under 50 years) age ranges. Age-sex standardised CRC mortality rates were also calculated for the screening (50-74 years) and pre-screening (under 50 years) age ranges using death registration data from NRS.

To investigate the impact of screening participation on incidence, linkage was carried out between the SBSD, the SCR and NRS deaths. The SBSD allowed identification of those invited for screening and those who participated. Participants who received a positive or negative screening test result at any point were included in the participant cohort. Those who did not receive a positive or negative test result, or never returned a completed test, were included in the non-participant cohort. Data were included from the pilot through to national roll-out, with the data on invites available from March 2000. Linkage with the SCR allowed CRC incidence to be calculated for the participant and non-participant groups and linkage with the NRS deaths records allowed removal of participants from study at the point of death. Follow-up data were available to 31 December 2017. Age-sex standardised rates were calculated for participant and non-participant groups as described above.

The age structure of the screening population changed a great deal in the early years of the study period (see Supplementary Table 1). The ageing of the original pilot cohort, in addition to the expansion of the age-range on national rollout, influence the annual CRC incidence rate, despite adjustment through standardisation. In addition, any reduction seen in annual CRC incidence could be influenced by a shortening time to diagnosis. That is, since cancers are detected earlier, the years after roll-out see a reduction in incidence exclusively due to early detection rather than to prevention of disease. To better analyse these issues, time-to-event analysis was used in addition to the descriptive time-series analysis. This facilitated better understanding of the relationship

between participation in screening and how it affects an individual's risk over time. Cumulative incidence was estimated using the Kaplan-Meier method. Cox regression was also used to estimate the impact of screening participation on time from invite to CRC diagnosis, adjusting for age at first invite, sex, and level of socioeconomic status as determined by the Scottish Index of Multiple Deprivation.

An underlying assumption of Cox regression is that of proportional hazards, i.e., that the ratio of the hazards between treatment and non-treatment groups remains constant over time. This assumption was not met for the participation status variable, since the CRC hazard increases at biennial intervals for the participant group, consistent with screening participation. In consequence, an alternative analytical approach is also presented, with separate hazard ratios reported for less than, and more than, seven years of follow-up. Seven years was chosen as the cut-off because participant cumulative incidence is consistently lower than non-participant (and the proportional hazards assumption is met) from this point. All analyses were performed using R statistical software, version 3.5.1 and 95% confidence intervals (CI) are shown as bars in the Figures, when relevant.

Neither patients, participants in screening, nor the public were involved in any way in development of the research question, the design of the study, or any other aspect of this research. Dissemination to these groups is not possible nor applicable. Formal ethical approval for the study was not required because individual participants were not approached and only routinely collected population-based data were used.

The Scottish Government, funders of the study, 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 requests for data sharing should be discussed, in the first instance, with RJCS at r.j.c.steele@dundee.ac.uk

Results

77,262 CRC were diagnosed in Scotland between 1997 and 2017. From the introduction of screening in 2000 through to 2017, 2,395,172 individuals were invited to participate (409,255 in the Pilot, 1,985,917 in the Programme), of whom 1,487,999 participated at least once. There were 24,817 CRC diagnosed within the population invited to screen (15,663 in participants, 9,154 in non-participants) in the same period. These CRC were detected through both screening and non-screening pathways.

In the 50-74 years (screening) age range, a slight drop in incidence was observed, from 154.4 cases per 100,000 in 2000, the first year of the demonstration pilot, to 137.8 in 2006. Then, coinciding with commencement of roll-out of screening across the country in 2007, an increase was noted, which peaked at 156.5 cases per 100,000 in 2010 and began to fall to levels well below those seen in the immediate pre-screening period, reaching 123.9 per 100,000 in 2017 (Figure 1). In those aged 75 years and over (post-

screening), a consistent drop in incidence was noted from 2009 (432.5 per 100,000) to 2017 (366.8 per 100,100) (Figure 2) whereas, in those aged under 50 years (pre-screening) a rise throughout the study period from 5.3 cases per 100,000 in 2000 to 6.8 per 100,000 in 2017 was seen, albeit with fluctuations (Figure 3).

When CRC incidence in the population who had been offered screening was examined, there was a distinct difference between those who had participated at least once and those who never participated. The data shown are age and sex-standardised since these variables influence both CRC incidence and uptake of screening, with both uptake and incidence increasing with age, and with uptake being lower, but incidence higher, in men than in women.[11] Figure 4 shows that incidence increased more in the participant group than in the non-participant group as national roll-out of screening started but that, after roll-out had been completed, incidence fell in the participant group to a greater extent than in the non-participant group, with participant incidence 13.9% below non-participant in 2017. The large increase in incidence in 2005 was due to there being no invitees in the over 75 years age range prior to this point (see Supplementary Table 2). Since the CRC risk in the over 75 years age range is higher than in those aged below 75 years, the age-standardised rates are influenced by this ageing of the invited population.

Analysis of cumulative incidence shown in Figure 5 demonstrates the risk of developing CRC over time. Fluctuations can be seen initially in the participant group, consistent with the biennial screening interval. The participant group then remains consistently

below that of the non-participant group from around seven years of follow-up. Cox regression analysis adjusted for age at first invite, sex and socioeconomic deprivation gave a hazard ratio of 0.92 for participants, relative to non-participants (95% CI: 0.90-0.95*, p < 0.001*). The hazard ratios, when separating the follow-up period at seven years, were 0.95 (95% CI: 0.92-0.98*, p < 0.001*) in the period up to seven years and 0.87 (95% CI: 0.83-0.91*, p < 0.001*) in the period seven years or more. These data are shown separately for males and females in Supplementary Figure 1.

We also examined mortality in the 50-74 years (screening) and the under 50 years (pre-screening) age groups. These data, with 95%CI, are given as Supplementary Figures 2 and 3, and show a substantial reduction in mortality since the introduction of screening in the 50-74 years range, but not in the under 50 years range.

Discussion

Statement of principal findings - The findings in this study have similarities with those reported in from other high-income countries,[4,6] namely that the incidence of CRC is falling in older age groups but increasing in people under the age of 50 years. However, in this study, we were not only able to examine the changes in CRC incidence by age, but also by screening participation, and this demonstrated, for the first time to our knowledge, that the fall in incidence was more evident in those who had participated in screening.

Strengths and weaknesses in relation to other studies - The Minnesota randomised controlled trial (RCT), which employed mostly rehydrated Hemoccult II giving a positivity of 9.8 %, did demonstrate a modest reduction in the groups offered screening after 18 years of follow-up,[12] but the Nottingham RCT, which used gFOBT in un-rehydrated form (the same approach that was adopted in Scotland) and reported a 2% positivity, showed no effect on CRC incidence after 11 years.[13] Overall, previous studies of the effect of gFOBT screening on CRC incidence have not shown a substantial effect. In Scotland, from December 2009, biennial gFOBT screening was being offered to the whole of the eligible population. This resulted in a positivity of around 2%, so that, with an average uptake at this time of 55%, only around 1% of people being offered screening actually underwent colonoscopy.[9] Of those that did, the average positive predictive value of gFOBT for CRC was 10% and 40% for adenoma,[9] so that less than 0.5% of the population offered screening (the 50-74 year age range) would have had removal of adenoma. However, in the present study, the groups were much bigger than in the RCT and the reduction in incidence seen in the 50-74 years age range is likely to have been due, at least in part, to polypectomy following a positive screening test result. The rise in incidence immediately after roll-out and preceding the consistent fall is likely to have been due to the well-described screening effect caused by a combination of early and over-diagnosis.[14] This would not explain the later fall in incidence, however, since the incidence of disease after the introduction of screening tends not to fall back to baseline because of over-diagnosis (i.e., some people with screen-detected disease would have never presented clinically) as is the case in breast cancer screening.[15]

It could be argued that a fall in incidence would not necessarily translate into a fall in mortality, if only indolent cancers were being prevented. However, this is highly unlikely, given that the fall in incidence seen in the flexible sigmoidoscopy screening trials was accompanied by reductions in mortality.[7] In addition, just as North America, Oceania and most European countries,[6] CRC mortality in the 50-74 years age range in Scotland has fallen over time and it is likely that part of this effect can be attributed to early detection and prevention of disease as a result of screening.[16] It is also interesting that we did not observe a fall in CRC mortality in the under 50 years age range, lending further strength to the argument that screening has contributed to this trend.

Meaning of the study - In November 2017, the Scottish Bowel Screening Programme changed the screening test from gFOBT to a quantitative faecal immunochemical test (FIT) at a threshold of 80 µg haemoglobin/g faeces. At this threshold, in the first year of screening with FIT, there was a 100% relative increase in the number of participants with adenomas identified,[17] so that, going forward, screening using FIT can be expected to bring about a greater reduction in CRC incidence than has been seen to date and this will be examined when the data become available. The other very important consideration is the increase in CRC incidence seen in younger people. One approach to this could be to extend screening to those aged under 50 years, but it must be borne in mind that, under the age of 50 years, although incidence is increasing,[18] it is still much lower than in the current screening age range.

Unanswered questions and future research - There is no objective evidence yet to support screening under the age of 50 years, and other approaches, including improved awareness of symptoms, increased use of FIT to triage patients presenting in primary care with symptoms[19] and addressing lifestyle issues in the Scottish population must be part of the solution. The reasons underlying the marked increase in incidence in those aged under 50 years are not clear, but may relate to lifestyle factors, particularly around diet, body weight and physical activity, all of which are associated with increased risk of CRC.[20] Rising rates of obesity in younger life (which are indicators of diet and physical activity) are of particular interest, because excess adiposity is now experienced by more people at earlier life stages and a recent study has demonstrated a relationship between body mass index in childhood and risk of adult CRC.[21] We cannot necessarily screen our way out of this problem

Observational data such as these cannot prove definitively that screening is the only cause of reduced incidence. Over the age of 50 years, individuals are much more likely to undergo colonoscopy because of lower bowel symptoms than those under 50 years, and this may explain at least part of the incidence reduction in those aged over 50 years. It is interesting that, in the over 75 years age range, a consistent decline in incidence was seen from 2009 onwards. Some of this cohort will have had the opportunity to return screening tests, but by no means all, and it is likely that colonoscopy for the investigation of symptoms is performed even more frequently in this age range.

However, the clear separation of yearly and cumulative incidence by participation in screening lends persuasive evidence to the hypothesis that screening is at least in part responsible for the observed incidence patterns in the population. It could still be argued that the people who participated in screening were healthier than those who did not, and that lifestyle factors were also responsible for this observation but, given the clear effect of removal of adenomas on CRC incidence,[7] it is highly likely that screening played an important role.

Contributor statement

GRCC collected and analysed the data, participated in data interpretation, and contributed to writing the paper. AAS contributed on dietary issues, participated in data interpretation, and contributed to writing the paper. TGG assisted with analysing and validating the data, participated in data interpretation, and contributed to writing the paper. JAS directed the laboratories that analysed the faecal tests in the SBoSP from 2010, participated in data interpretation, and contributed to writing the paper. CGF directed the SBoSP laboratories to 2010, participated in data interpretation, and provided significant input into the writing of the paper. RJCS is Clinical Director of the SBoSP, initiated the study, led the data interpretation, and wrote first and final drafts of the paper, and is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: CGF did consultancy for Immunostics Inc, Ocean, NJ, USA, and does for Hitachi Chemical Diagnostic Systems Co., Ltd, Tokyo, Japan; no other relationships or activities that could appear to have influenced the submitted work have been done.

Acknowledgements

We acknowledge the support of Scottish Government and the NHS National Services and Information Services Divisions.

Patient and public involvement statement

Neither patients, participants in screening, nor the public were involved in any way in development of the research question, the design of the study, or any other aspect of this research. Dissemination to these groups is not possible nor applicable.

Funding

The Scottish Government, funders of the study, 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.

Data sharing

All requests for data sharing should be discussed, in the first instance, with RJCS at r.j.c.steele@dundee.ac.uk

References

1. NHS National Services Scotland. Information Services Division. Cancer in Scotland April 2019. https://www.isdscotland.org/Health-Topics/Cancer/Publications/2019-04-30/Cancer_in_Scotland_summary_m.pdf (Accessed 30 April 2020)

2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017 66:683-91. doi: 10.1136/gutjnl-2015-310912.

3. Connell LC, Mota JM, Braghiroli MI, Hoff PM. The rising incidence of younger patients with colorectal cancer: questions about screening, biology, and treatment. *Curr Treat Options Oncol* 2017;18:23. doi: 10.1007/s11864-017-0463-3.

4. Araghi M, Soerjomataram I, Bardot A, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. *Lancet Gastroenterol Hepatol* 2019;4:511-8. doi: 10.1016/S2468-1253(19)30147-5.

5. GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 24 years. *N Engl J Med* 2017;377:13-27. doi: 10.1056/NEJMoa1614362.

6. Wong MCS, Huang J, Huang JLW, et al. Global prevalence of colorectal neoplasia: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020;18:553-61. e10. doi:10.1016/j.cgh.2019.07.016.

7. Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet* 2017;389:1299-1311. doi: 10.1016/S0140-6736(17)30396-3.

8. Steele RJC. McClements PL, Libby G, et al. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. *Gut* 2009;58:530-5. doi:10.1136/gut.2008.162883

9. Fraser CG, Digby J, McDonald PJ, Strachan JA, Carey FA, Steele RJC. Experience with a two-tier reflex gFOBT/FIT strategy in a national bowel screening programme. *J Med Screen* 2012;19:8-13. doi:10.1258/jms.2011.011098

10. Scottish Health Survey. https://www.gov.scot/publications/scottish-health-survey-2018-volume-1-main-report/ (Accessed 30 January 2020).

11. Steele RJC, Kostourou I, McClements P, et al. Effect of gender, age and deprivation on key performance indicators in a FOBT based colorectal screening programme. *J Med Screen* 2010;17:68-74. doi:10.1258/jms.2010.009120.

12. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000;343:1603-7. doi:10.1056/NEJM200011303432203.

13. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut* 2012;61:1036-40. doi: 10.1136/gutjnl-2011-300774.

14. Grey M, Raffle A. Screening. Evidence and Practice. Oxford University Press 2007. Scottish Bowel Screening Programme Key Performance Indicators report, Information Services Division, NHS National Services Scotland, https://www.isdscotland.org/Health-Topics/Cancer/Publications/2019-08-06/2019-08-06-Bowel-Screening-KPI-Report.xlsx (Accessed 30 January 2020)

15. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening; an independent review. Lancet 2012;380:1778-86. doi:10.1016/S0140-6736(12)61611-0.

16. Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2018 with focus on colorectal cancer. *Ann Oncol* 2018;29:1016-22. doi:10.1093/annonc/mdy033.

17. Information Services Division (ISD) Scotland. Bowel Cancer Screening. https://www.isdscotland.org/Health-Topics/Cancer/Bowel-Screening/ (Accessed 30 January 2020).

18. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* 2019;68:1820–6. doi:10.1136/gutjnl-2018-317592

19. Mowat C, Digby J, Strachan JA, et al. Impact of introducing a faecal immunochemical test (FIT) for haemoglobin into primary care on the outcome of patients with new bowel symptoms: a prospective cohort study. *BMJ Open Gastroenterol* 2019;6:e000293. doi: 10.1136/bmjgast-2019-000293. eCollection 2019.

20. Potter JD. Rising rates of colorectal cancer in younger adults. *BMJ* 2019; 365:l4280. doi: 10.1136/bmj.l4280.

21. Jensen BW, Gamborg M, Gögenur I, Renehan AG, Sørensen TIA, Baker JL. Childhood body mass index and height in relation to site-specific risks of

colorectal cancers in adult life. *Eur J Epidemiol* 2017;32:1097-1106. doi: 10.1007/s10654-017-0289-0.

Legends to Figures

Figure 1. Age-sex standardised colorectal cancer incidence, ages 50-74 years, from 1997 to 2017 (95% confidence intervals shown)

Figure 2. Age-sex standardised colorectal cancer incidence, ages 75 years and over, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown)

Figure 3. Age-sex standardised colorectal cancer incidence, ages less than 50 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown)

Figure 4. Age-sex standardised colorectal cancer incidence for the screening population per 100,000 person-years, by screening participation status (95% confidence intervals shown)

Figure 5. Cumulative colorectal cancer incidence, by screening participation status

Legends to Supplementary Tables and Figures

Supplementary Table 1

Age distribution of screening and post-screening population, by year, in six age groups (years)

Supplementary Table 2.

Age distribution of colorectal cancers, by year, in six age groups (years)

Supplementary figure 1.

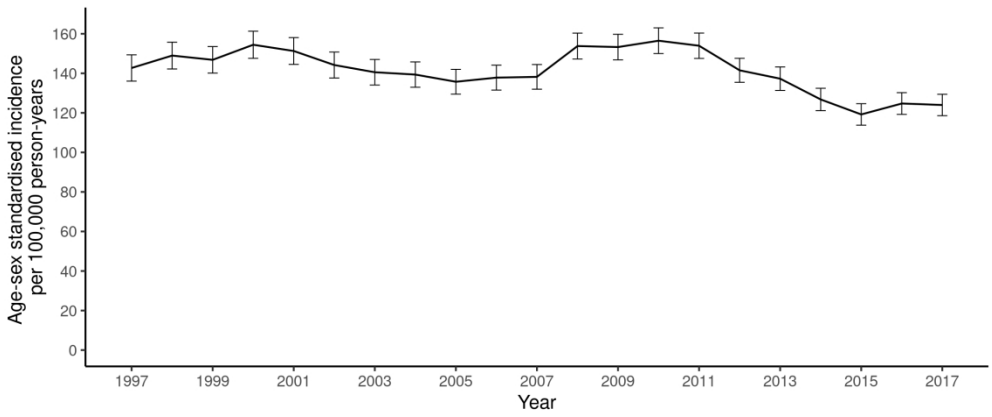
Cumulative colorectal cancer incidence, by sex and screening participation status

Supplementary Figure 2.

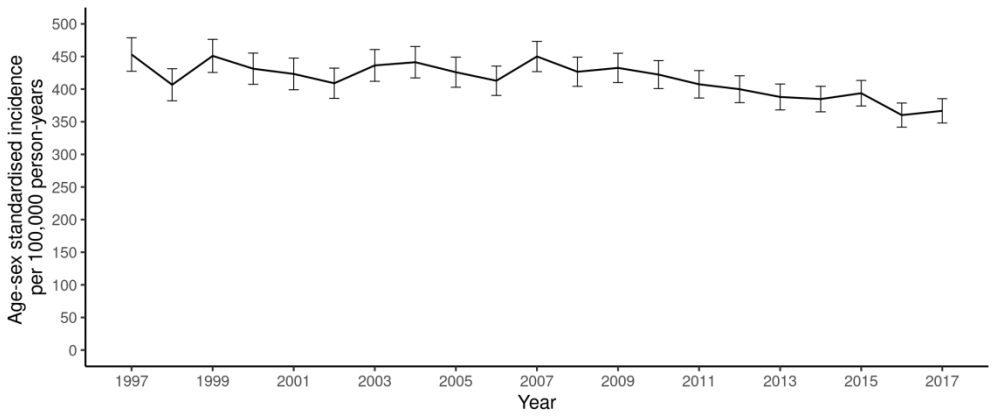
Age-sex standardised colorectal cancer mortality, ages 50-74 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown).

Supplementary Figure 3.

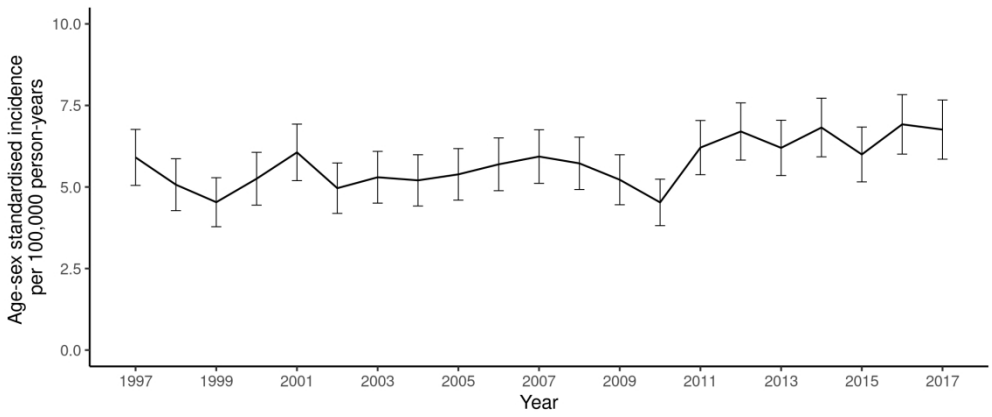
Age-sex standardised colorectal cancer mortality, ages under 50 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown).



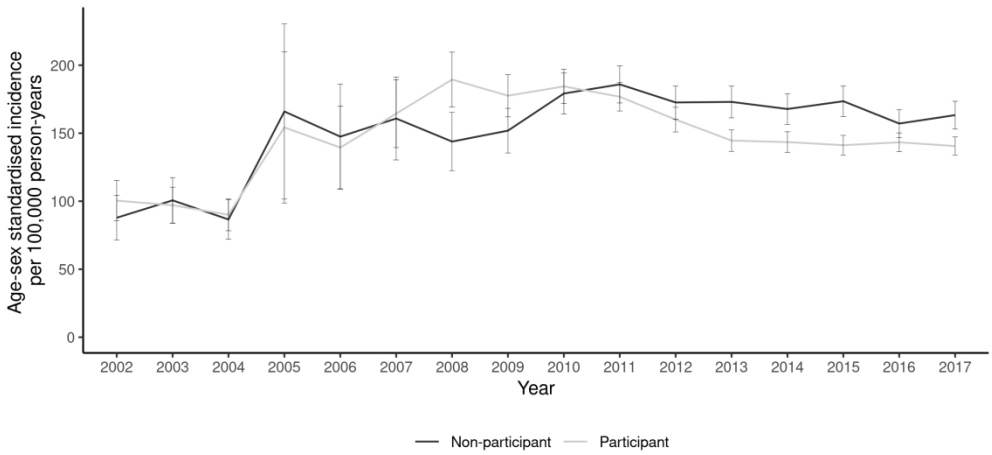
Age-sex standardised colorectal cancer incidence, ages 50-74 years, from 1997 to 2017 (95% confidence intervals shown)



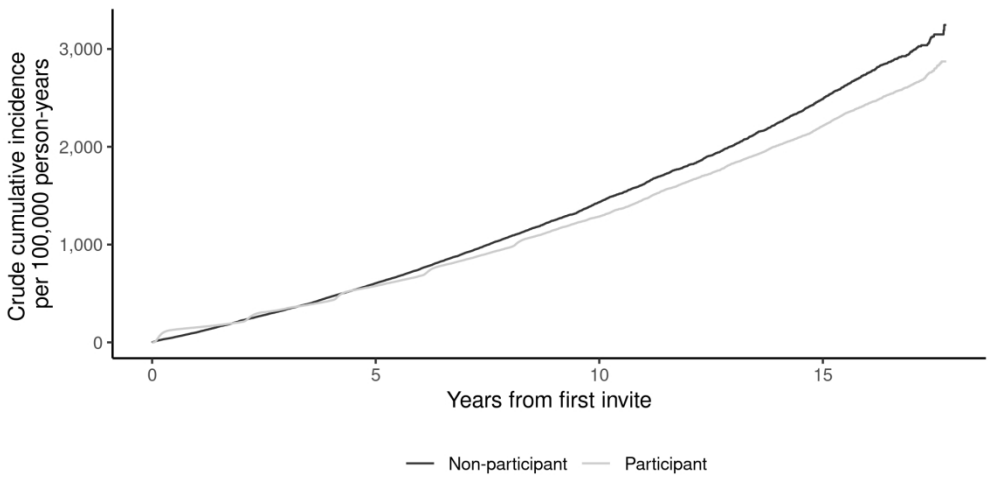
Age-sex standardised colorectal cancer incidence, ages 75 years and over, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown)



Age-sex standardised colorectal cancer incidence, ages less than 50 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown)



Age-sex standardised colorectal cancer incidence for the screening population per 100,000 person-years, by screening participation status (95% confidence intervals shown)



Cumulative colorectal cancer incidence, by screening participation status

Supplementary Table 1: Age distribution of screening and post-screening population, by year, in six age groups (years)

	Age distribution of population, n (%),											
	50-54		55-59		60-64		65-69		70-74		75+	
Year												
2001	54,240	(26.4%)	51,239	(25.0%)	44,137	(21.5%)	42,905	(20.9%)	12,679	(6.2%)	-	(0.0%)
2002	61,490	(22.2%)	74,204	(26.8%)	60,079	(21.7%)	57,307	(20.7%)	23,851	(8.6%)	-	(0.0%)
2003	65,241	(21.5%)	81,141	(26.7%)	63,410	(20.9%)	59,472	(19.6%)	34,581	(11.4%)	-	(0.0%)
2004	67,571	(20.5%)	87,062	(26.4%)	68,088	(20.6%)	61,739	(18.7%)	45,561	(13.8%)	-	(0.0%)
2005	62,874	(18.2%)	92,267	(26.7%)	70,813	(20.5%)	62,646	(18.2%)	52,651	(15.3%)	3,829	(1.1%)
2006	76,947	(20.2%)	93,881	(24.6%)	78,362	(20.6%)	64,371	(16.9%)	56,093	(14.7%)	11,204	(2.9%)
2007	82,678	(19.7%)	96,401	(23.0%)	88,775	(21.2%)	70,209	(16.7%)	59,571	(14.2%)	21,890	(5.2%)
2008	124,768	(20.9%)	130,326	(21.8%)	120,431	(20.1%)	100,736	(16.8%)	81,370	(13.6%)	40,230	(6.7%)
2009	207,433	(21.4%)	203,613	(21.0%)	192,470	(19.8%)	164,107	(16.9%)	132,759	(13.7%)	70,838	(7.3%)
2010	298,073	(21.6%)	279,971	(20.3%)	279,627	(20.2%)	225,020	(16.3%)	189,222	(13.7%)	109,061	(7.9%)
2011		(21.0%)		(20.0%)		(19.7%)		(16.6%)		(13.6%)		(9.2%)

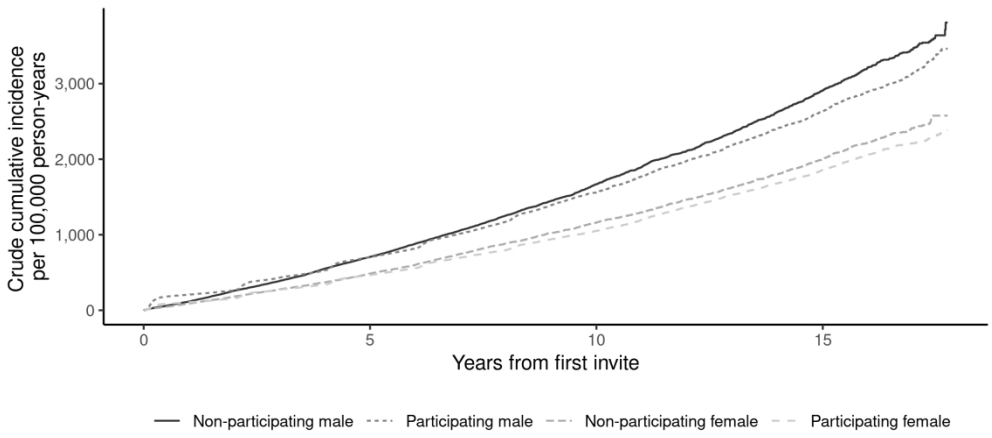
	339,145		321,494		317,497		267,034		218,456		147,739	
2012	357,830	(20.8%)	339,212	(19.8%)	316,700	(18.4%)	293,561	(17.1%)	225,389	(13.1%)	184,587	(10.7%)
2013	376,959	(20.7%)	357,825	(19.6%)	323,931	(17.8%)	310,399	(17.0%)	233,617	(12.8%)	221,685	(12.2%)
2014	398,197	(20.6%)	375,480	(19.5%)	332,956	(17.3%)	323,005	(16.7%)	244,065	(12.6%)	256,410	(13.3%)
2015	411,856	(20.3%)	393,919	(19.5%)	342,353	(16.9%)	337,714	(16.7%)	249,651	(12.3%)	289,123	(14.3%)
2016	425,191	(20.1%)	408,845	(19.3%)	354,588	(16.8%)	338,041	(16.0%)	267,472	(12.7%)	320,149	(15.1%)
2017	422,301	(19.3%)	423,926	(19.4%)	367,652	(16.8%)	331,431	(15.2%)	290,065	(13.3%)	352,178	(16.1%)

Supplementary Table 2: Age distribution of colorectal cancers, by year, in six age groups (years)

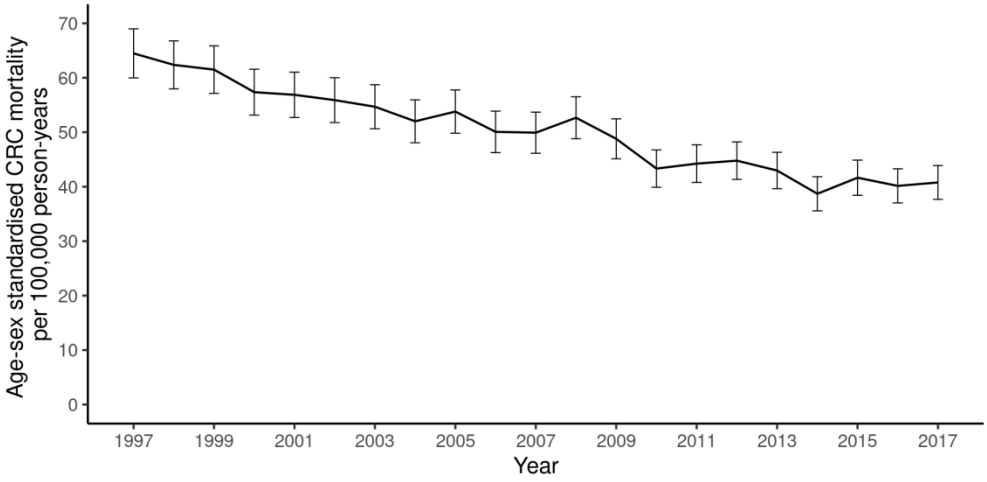
Age distribution of colorectal cancers detected in screening population, n (%)

Year	50-54		55-59		60-64		65-69		70-74		75+	
2001	18	(8.2%)	44	(20.0%)	49	(22.3%)	77	(35.0%)	32	(14.5%)	-	(0.0%)
2002	28	(8.6%)	48	(14.8%)	100	(30.9%)	102	(31.5%)	46	(14.2%)	-	(0.0%)
2003	25	(6.8%)	67	(18.3%)	80	(21.9%)	112	(30.6%)	82	(22.4%)	-	(0.0%)
2004	26	(7.0%)	60	(16.1%)	90	(24.1%)	117	(31.4%)	80	(21.4%)	-	(0.0%)
2005	21	(5.2%)	68	(16.7%)	71	(17.4%)	110	(27.0%)	126	(31.0%)	11	(2.7%)
2006	21	(5.1%)	50	(12.0%)	82	(19.8%)	117	(28.2%)	116	(28.0%)	29	(7.0%)
2007	42	(8.1%)	68	(13.1%)	101	(19.4%)	113	(21.7%)	127	(24.4%)	69	(13.3%)
2008	56	(6.8%)	84	(10.2%)	152	(18.5%)	184	(22.4%)	222	(27.1%)	122	(14.9%)
2009	93	(7.3%)	144	(11.3%)	217	(17.1%)	277	(21.8%)	318	(25.0%)	222	(17.5%)
2010	132	(6.6%)	212	(10.6%)	351	(17.6%)	423	(21.2%)	505	(25.3%)	372	(18.6%)
2011	160	(6.7%)	247	(10.3%)	394	(16.4%)	539	(22.4%)	593	(24.7%)	470	(19.6%)
2012	158	(6.5%)	243	(10.0%)	391	(16.1%)	530	(21.8%)	579	(23.9%)	525	(21.6%)

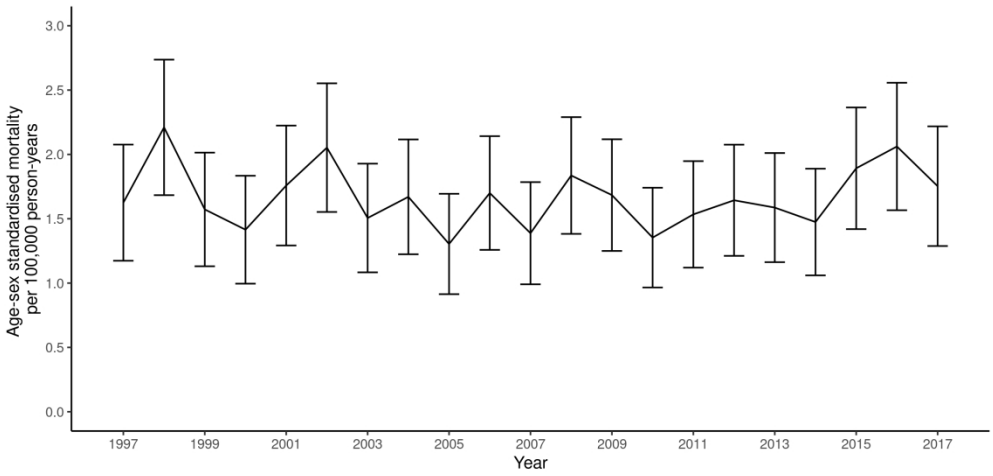
2013	160	(6.5%)	266	(10.8%)	355	(14.4%)	531	(21.6%)	556	(22.6%)	594	(24.1%)
2014	152	(6.0%)	248	(9.9%)	319	(12.7%)	532	(21.1%)	523	(20.8%)	743	(29.5%)
2015	172	(6.6%)	212	(8.1%)	361	(13.8%)	468	(17.9%)	502	(19.2%)	899	(34.4%)
2016	183	(6.6%)	270	(9.8%)	350	(12.7%)	490	(17.8%)	574	(20.8%)	887	(32.2%)
2017	165	(5.7%)	267	(9.2%)	375	(13.0%)	492	(17.0%)	596	(20.6%)	993	(34.4%)



Supplementary Figure 1. Cumulative colorectal cancer incidence, by sex and screening participation status



Supplementary Figure 2. Age-sex standardised colorectal cancer mortality, ages 50-74 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown).



Supplementary Figure 3. Age-sex standardised colorectal cancer mortality, ages under 50 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9-10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9 -10
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	12-14
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-14
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Variation in changes in the incidence of colorectal cancer by age and association with screening uptake; an observational study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037925.R2
Article Type:	Original research
Date Submitted by the Author:	27-Jul-2020
Complete List of Authors:	Clark, Gavin; NHS Scotland National Services Division Anderson, Annie; university of dundee, Centre for public health nutrition research Godfrey, Thomas; NHS Scotland National Services Division Strachan, Judith; NHS Tayside, Blood Sciences Fraser, Callum; University of Dundee, Centre for Research into Cancer Prevention and Screening Steele, Robert; University of Dundee, Centre for Research into Cancer Prevention and Screening
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Oncology, Public health
Keywords:	GASTROENTEROLOGY, ONCOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Variation in changes in the incidence of colorectal cancer by age and association with screening uptake; an observational study.

Gavin RC Clark, Annie S Anderson (0000-0002-0047-4500), Thomas G Godfrey, Judith A Strachan, Callum G Fraser (0000-0002-1333-7994), Robert JC Steele (0000-0003-4248-6785)

Information Services Division, NHS National Services Scotland, Edinburgh EH12 9EB, Scotland, UK

Gavin RC Clark senior information analyst

Thomas G Godfrey information analyst

Centre for Public Health Nutrition, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Annie S Anderson professor

Department of Blood Sciences and Scottish Bowel Screening Laboratory, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Judith A Strachan consultant clinical scientist

Centre for Research into Cancer Prevention and Screening, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK

Callum G Fraser, honorary professor,

Robert JC Steele, senior research professor

Emails:

Gavin RC Clark, gavin.clark2@nhs.net

Annie S Anderson, a.s.anderson@dundee.ac.uk

Thomas G Godfrey, thomas.godfrey@nhs.net

Judith A Strachan, judith.strachan@nhs.net

Callum G Fraser, callum.fraser@nhs.net

Robert JC Steele, r.j.c.steele@dundee.ac.uk

Corresponding author: Professor Robert JC Steele, Mailbox 4, Level 7, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, UK.

Email: r.j.c.steele@dundee.ac.uk

Telephone: + 44 (0)1382 3835444

Short title: Incidence of colorectal cancer

No of words (abstract): 296

No of words (text): 2938

No of references: 21

No of Tables: 0

No of Figures: 5

No of Supplementary Tables: 2

No of Supplementary Figures: 3

Keywords: adenoma, colorectal cancer, faecal occult blood test, incidence, mortality, screening

Abbreviations: CRC: colorectal cancer, FIT: faecal immunochemical test for haemoglobin, gFOBT: guaiac faecal occult blood testing, HDI: human development index, NRS: National Records Scotland, RCT: randomised controlled trial, SBSD: Scottish Bowel Screening Database, SCR: Scottish Cancer Registry, SEER: Surveillance, Epidemiology and End Results, UK: United Kingdom, USA: United States of America

Abstract

Objectives - In developed countries, the incidence of colorectal cancer (CRC) has declined in the over 50 years age group but increased in younger people. We studied CRC incidence by age and the influence of screening uptake.

Design - Age and sex-standardised incidence for CRC from 1997 to 2017 were obtained from the Scottish Cancer Registry (SCR). In addition, linkage between the Scottish Bowel Screening Database (SBSD) and the SCR allowed investigation of any association between screening participation and CRC incidence.

Setting – Scotland and the Scottish Bowel Screening Programme, in which guaiac faecal occult blood test screening was piloted from March 2000 and fully rolled by December 2009**.**

Participants – From the introduction of screening in 2000 through to 2017, 2,395,172 were invited to participate, of whom 1,487,999 participated at least once.

Main outcome measures – Incidence of CRC.

Results - In the screening age range (50-74 years), CRC incidence peaked at 156.5 cases per 100,000 in 2010 after full roll-out of screening across Scotland but fell to 123.9 per 100,000 in 2017. However, under 50 years, there was a rise of from 5.3

cases per 100,000 in 2000 to 6.8 per 100,000 in 2017. When CRC incidence was examined in those who had been offered screening, incidence fell in the participant group more than in the non-participant group after roll-out of screening was complete. Analysis of cumulative incidence demonstrated that CRC incidence in the participant group remained consistently below that of the non-participant from around seven years of follow-up.

Conclusions - The incidence of colorectal cancer (CRC) in Scotland has declined in the over 50 years age groups but increased in younger people. It is likely that population screening has contributed to the reduction in CRC incidence in the over 50 years age group.

Strengths and limitations of this study

- We examine age and sex-standardised incidence data for colorectal cancer for the years 1997 to 2017 obtained from the Scottish Cancer Registry and linkage between the Registry and the Scottish Bowel Screening Database.

- We are able to show previously unreported changes in the incidence of colorectal cancer in Scotland in all age groups.

- We are able to examine in detail, for the first time, if population-based screening using faecal occult blood tests is associated with incidence of colorectal cancer.

- Associations between incidence and plausible reasons for the changes over time will help the development of future interventions.

- Although this was a large study, we did not examine incidence by yearly age, only in three large groups.

.

Introduction

Colorectal cancer (CRC) is a major health problem worldwide. In Scotland, it is currently the third most commonly diagnosed non-cutaneous cancer and the second most common cause of cancer-related deaths.[1] However, the incidence of CRC varies widely across the world and it is estimated that 60% of CRC deaths occur in those countries with a high or very high human development index (HDI).[2] Western lifestyle factors, including obesity, lack of physical exercise, a diet rich in red and processed meat, smoking, and alcohol, have all been linked to the risk of developing CRC,[3] and marked increases in both incidence and mortality have been observed in many medium-high HDI countries, especially in Asia, South America and Eastern Europe.[2] However, both incidence and mortality have either stabilised or declined in countries with the highest HDI, e.g., Australia, New Zealand, United States of America (USA), and several Western European countries.[4] These reductions in mortality are likely to be attributable to improved access to high quality treatment and earlier diagnosis through both screening and through prompt investigation of those presenting with symptoms.

The declines in incidence are not so easy to explain, especially since the frequency of obesity continues to rise in all high HDI countries.[5] However, there is now good evidence, largely from the USA and particularly from the Surveillance, Epidemiology and End Results (SEER) database that, while incidence has been falling since around 1985 in those aged 50 years and over, it has been rising in those under 50 years since the mid-1990s.[3] In a recent analysis of incidence and mortality databases from 39

countries, it was confirmed that countries with the highest HDI had a decrease in CRC incidence, but that incidence of colon and rectal cancers has continued to increase in countries with medium–high HDI, and in younger populations.[6] It has been postulated that screening may be responsible for the reduction in incidence in the group aged over 50 years, especially where this is associated with high rates of large bowel endoscopy, which facilitates the diagnosis and removal of pre-malignant adenomas.[3] Since there is now robust evidence from randomised trials of endoscopic screening that removal of adenoma leads to a reduction in CRC incidence,[7] this is an attractive hypothesis, but one that is difficult to test.

In Scotland, CRC screening, initially using biennial guaiac faecal occult blood tests (gFOBT), was rolled out to the whole of the population aged 50-74 years in 2007 after a three screening rounds pilot which started in 2000.[8,9] In addition, Scotland, along with the rest of the United Kingdom (UK), is ranked as having a very high HDI,[2] and although the incidence has fallen by 18.6% from 2007 to 2017,[1] it still has a high incidence of CRC,[1] and lifestyle factors associated with CRC are prevalent in the population.[10] We therefore examined the incidence of CRC between 1997 and 2017 in the 50-74 years screening age range, the post-screening age range, and the pre-screening age range. In addition, the effect of screening participation on CRC incidence was assessed.

Methods

In Scotland, screening for CRC using biennial gFOBT, offered to everyone in the 50-69 years age range and registered with a general practitioner, commenced in March 2000 with a pilot involving three of the fourteen NHS Boards responsible for routine health care. Roll-out to the rest of Scotland began in July 2007 and was completed by December 2009. The age range was also extended up to age 74 years for the whole of Scotland during roll-out. Details of the pilot, roll-out and descriptions of the screening algorithms have been published previously.[8,9] Data are collected centrally by the Information Services Division of NHS National Services Scotland and held in the Scottish Bowel Screening Database (SBSD).

To assess changes in the incidence of CRC in different age ranges around the time of the introduction of screening, data were obtained from the Scottish Cancer Registry (SCR) for the years 1997 to 2017. Crude incidence rates were calculated by sex and five-year age group using mid-year population estimates from the National Records of Scotland (NRS). These rates were then directly standardised using the 2013 European Standard Population. Age-sex standardised rates were calculated separately for the screening (50-74 years), post-screening (75 years and higher), and pre-screening (under 50 years) age ranges. Age-sex standardised CRC mortality rates were also calculated for the screening (50-74 years) and pre-screening (under 50 years) age ranges using death registration data from NRS.

To investigate the impact of screening participation on incidence, linkage was carried out between the SBSD, the SCR and NRS deaths. The SBSD allowed identification of those invited for screening and those who participated. Participants who received a positive or negative screening test result at any point were included in the participant cohort. Those who did not receive a positive or negative test result, or never returned a completed test, were included in the non-participant cohort. Data were included from the pilot through to national roll-out, with the data on invites available from March 2000. Linkage with the SCR allowed CRC incidence to be calculated for the participant and non-participant groups and linkage with the NRS deaths records allowed removal of participants from study at the point of death. Follow-up data were available to 31 December 2017. Age-sex standardised rates were calculated for participant and non-participant groups as described above.

The age structure of the screening population changed a great deal in the early years of the study period (see Supplementary Table 1). The ageing of the original pilot cohort, in addition to the expansion of the age-range on national rollout, influence the annual CRC incidence rate, despite adjustment through standardisation. In addition, any reduction seen in annual CRC incidence could be influenced by a shortening time to diagnosis. That is, since cancers are detected earlier, the years after roll-out see a reduction in incidence exclusively due to early detection rather than to prevention of disease. To better analyse these issues, time-to-event analysis was used in addition to the descriptive time-series analysis. This facilitated better understanding of the relationship

between participation in screening and how it affects an individual's risk over time. Cumulative incidence was estimated using the Kaplan-Meier method. Cox regression was also used to estimate the impact of screening participation on time from invite to CRC diagnosis, adjusting for age at first invite, sex, and level of socioeconomic status as determined by the Scottish Index of Multiple Deprivation.

An underlying assumption of Cox regression is that of proportional hazards, i.e., that the ratio of the hazards between treatment and non-treatment groups remains constant over time. This assumption was not met for the participation status variable, since the CRC hazard increases at biennial intervals for the participant group, consistent with screening participation. In consequence, an alternative analytical approach is also presented, with separate hazard ratios reported for less than, and more than, seven years of follow-up. Seven years was chosen as the cut-off because participant cumulative incidence is consistently lower than non-participant (and the proportional hazards assumption is met) from this point. All analyses were performed using R statistical software, version 3.5.1 and 95% confidence intervals (CI) are shown as bars in the Figures, when relevant.

Neither patients, participants in screening, nor the public were involved in any way in development of the research question, the design of the study, or any other aspect of this research. Dissemination to these groups is not possible nor applicable. Formal ethical approval for the study was not required because individual participants were not approached and only routinely collected population-based data were used.

The Scottish Government, funders of the study, 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 requests for data sharing should be discussed, in the first instance, with RJCS at r.j.c.steele@dundee.ac.uk

Results

77,262 CRC were diagnosed in Scotland between 1997 and 2017. From the introduction of screening in 2000 through to 2017, 2,395,172 individuals were invited to participate (409,255 in the Pilot, 1,985,917 in the Programme), of whom 1,487,999 participated at least once. There were 24,817 CRC diagnosed within the population invited to screen (15,663 in participants, 9,154 in non-participants) in the same period. These CRC were detected through both screening and non-screening pathways.

In the 50-74 years (screening) age range, a slight drop in incidence was observed, from 154.4 cases per 100,000 in 2000, the first year of the demonstration pilot, to 137.8 in 2006. Then, coinciding with commencement of roll-out of screening across the country in 2007, an increase was noted, which peaked at 156.5 cases per 100,000 in 2010 and began to fall to levels well below those seen in the immediate pre-screening period, reaching 123.9 per 100,000 in 2017 (Figure 1). In those aged 75 years and over (post-

screening), a consistent drop in incidence was noted from 2009 (432.5 per 100,000) to 2017 (366.8 per 100,100) (Figure 2) whereas, in those aged under 50 years (pre-screening) a rise throughout the study period from 5.3 cases per 100,000 in 2000 to 6.8 per 100,000 in 2017 was seen, albeit with fluctuations (Figure 3).

When CRC incidence in the population who had been offered screening was examined, there was a distinct difference between those who had participated at least once and those who never participated. The data shown are age and sex-standardised since these variables influence both CRC incidence and uptake of screening, with both uptake and incidence increasing with age, and with uptake being lower, but incidence higher, in men than in women.[11] Figure 4 shows that incidence increased more in the participant group than in the non-participant group as national roll-out of screening started but that, after roll-out had been completed, incidence fell in the participant group to a greater extent than in the non-participant group, with participant incidence 13.9% below non-participant in 2017. The large increase in incidence in 2005 was due to there being no invitees in the over 75 years age range prior to this point (see Supplementary Table 2). Since the CRC risk in the over 75 years age range is higher than in those aged below 75 years, the age-standardised rates are influenced by this ageing of the invited population.

Analysis of cumulative incidence shown in Figure 5 demonstrates the risk of developing CRC over time. Fluctuations can be seen initially in the participant group, consistent with the biennial screening interval. The participant group then remains consistently

below that of the non-participant group from around seven years of follow-up. Cox regression analysis adjusted for age at first invite, sex and socioeconomic deprivation gave a hazard ratio of 0.92 for participants, relative to non-participants (95% CI: 0.90-0.95*, p < 0.001*). The hazard ratios, when separating the follow-up period at seven years, were 0.95 (95% CI: 0.92-0.98*, p < 0.001*) in the period up to seven years and 0.87 (95% CI: 0.83-0.91*, p < 0.001*) in the period seven years or more. These data are shown separately for males and females in Supplementary Figure 1.

We also examined mortality in the 50-74 years (screening) and the under 50 years (pre-screening) age groups. These data, with 95%CI, are given as Supplementary Figures 2 and 3, and show a substantial reduction in mortality since the introduction of screening in the 50-74 years range, but not in the under 50 years range.

Discussion

Statement of principal findings - The findings in this study have similarities with those reported in from other high-income countries,[4,6] namely that the incidence of CRC is falling in older age groups but increasing in people under the age of 50 years. However, in this study, we were not only able to examine the changes in CRC incidence by age, but also by screening participation, and this demonstrated, for the first time to our knowledge, that the fall in incidence was more evident in those who had participated in screening.

Strengths and weaknesses in relation to other studies - The Minnesota randomised controlled trial (RCT), which employed mostly rehydrated Hemoccult II giving a positivity of 9.8 %, did demonstrate a modest reduction in the groups offered screening after 18 years of follow-up,[12] but the Nottingham RCT, which used gFOBT in un-rehydrated form (the same approach that was adopted in Scotland) and reported a 2% positivity, showed no effect on CRC incidence after 11 years.[13] Overall, previous studies of the effect of gFOBT screening on CRC incidence have not shown a substantial effect. In Scotland, from December 2009, biennial gFOBT screening was being offered to the whole of the eligible population. This resulted in a positivity of around 2%, so that, with an average uptake at this time of 55%, only around 1% of people being offered screening actually underwent colonoscopy.[9] Of those that did, the average positive predictive value of gFOBT for CRC was 10% and 40% for adenoma,[9] so that less than 0.5% of the population offered screening (the 50-74 year age range) would have had removal of adenoma. However, in the present study, the groups were much bigger than in the RCT and the reduction in incidence seen in the 50-74 years age range is likely to have been due, at least in part, to polypectomy following a positive screening test result. The rise in incidence immediately after roll-out and preceding the consistent fall is likely to have been due to the well-described screening effect caused by a combination of early and over-diagnosis.[14] This would not explain the later fall in incidence, however, since the incidence of disease after the introduction of screening tends not to fall back to baseline because of over-diagnosis (i.e., some people with screen-detected disease would have never presented clinically) as is the case in breast cancer screening.[15]

It could be argued that a fall in incidence would not necessarily translate into a fall in mortality, if only indolent cancers were being prevented. However, this is highly unlikely, given that the fall in incidence seen in the flexible sigmoidoscopy screening trials was accompanied by reductions in mortality.[7] In addition, just as North America, Oceania and most European countries,[6] CRC mortality in the 50-74 years age range in Scotland has fallen over time and it is likely that part of this effect can be attributed to early detection and prevention of disease as a result of screening.[16] It is also interesting that we did not observe a fall in CRC mortality in the under 50 years age range, lending further strength to the argument that screening has contributed to this trend.

Meaning of the study - In November 2017, the Scottish Bowel Screening Programme changed the screening test from gFOBT to a quantitative faecal immunochemical test (FIT) at a threshold of 80 µg haemoglobin/g faeces. At this threshold, in the first year of screening with FIT, there was a 100% relative increase in the number of participants with adenomas identified,[17] so that, going forward, screening using FIT can be expected to bring about a greater reduction in CRC incidence than has been seen to date and this will be examined when the data become available. The other very important consideration is the increase in CRC incidence seen in younger people. One approach to this could be to extend screening to those aged under 50 years, but it must be borne in mind that, under the age of 50 years, although incidence is increasing,[18] it is still much lower than in the current screening age range.

Unanswered questions and future research - There is no objective evidence yet to support screening under the age of 50 years, and other approaches, including improved awareness of symptoms, increased use of FIT to triage patients presenting in primary care with symptoms[19] and addressing lifestyle issues in the Scottish population must be part of the solution. The reasons underlying the marked increase in incidence in those aged under 50 years are not clear, but may relate to lifestyle factors, particularly around diet, body weight and physical activity, all of which are associated with increased risk of CRC.[20] Rising rates of obesity in younger life (which are indicators of diet and physical activity) are of particular interest, because excess adiposity is now experienced by more people at earlier life stages and a recent study has demonstrated a relationship between body mass index in childhood and risk of adult CRC.[21] We cannot necessarily screen our way out of this problem

Observational data such as these cannot prove definitively that screening is the only cause of reduced incidence. Over the age of 50 years, individuals are much more likely to undergo colonoscopy because of lower bowel symptoms than those under 50 years, and this may explain at least part of the incidence reduction in those aged over 50 years. It is interesting that, in the over 75 years age range, a consistent decline in incidence was seen from 2009 onwards. Some of this cohort will have had the opportunity to return screening tests, but by no means all, and it is likely that colonoscopy for the investigation of symptoms is performed even more frequently in this age range.

However, the clear separation of yearly and cumulative incidence by participation in screening lends persuasive evidence to the hypothesis that screening is at least in part responsible for the observed incidence patterns in the population. It could still be argued that the people who participated in screening were healthier than those who did not, and that lifestyle factors were also responsible for this observation but, given the clear effect of removal of adenomas on CRC incidence,[7] it is highly likely that screening played an important role.

Contributor statement

GRCC collected and analysed the data, participated in data interpretation, and contributed to writing the paper. AAS contributed on dietary issues, participated in data interpretation, and contributed to writing the paper. TGG assisted with analysing and validating the data, participated in data interpretation, and contributed to writing the paper. JAS directed the laboratories that analysed the faecal tests in the SBoSP from 2010, participated in data interpretation, and contributed to writing the paper. CGF directed the SBoSP laboratories to 2010, participated in data interpretation, and provided significant input into the writing of the paper. RJCS is Clinical Director of the SBoSP, initiated the study, led the data interpretation, and wrote first and final drafts of the paper, and is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: CGF did consultancy for Immunostics Inc, Ocean, NJ, USA, and does for Hitachi Chemical Diagnostic Systems Co., Ltd, Tokyo, Japan; no other relationships or activities that could appear to have influenced the submitted work have been done.

Acknowledgements

We acknowledge the support of Scottish Government and the NHS National Services and Information Services Divisions.

Patient and public involvement statement

Neither patients, participants in screening, nor the public were involved in any way in development of the research question, the design of the study, or any other aspect of this research. Dissemination to these groups is not possible nor applicable.

Funding

The Scottish Government, funders of the study, 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. Award/Grant number not applicable.

Data sharing

All requests for data sharing should be discussed, in the first instance, with RJCS at r.j.c.steele@dundee.ac.uk

References

1. NHS National Services Scotland. Information Services Division. Cancer in Scotland April 2019. https://www.isdscotland.org/Health-Topics/Cancer/Publications/2019-04-30/Cancer_in_Scotland_summary_m.pdf (Accessed 30 April 2020)

2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017 66:683-91. doi: 10.1136/gutjnl-2015-310912.

3. Connell LC, Mota JM, Braghiroli MI, Hoff PM. The rising incidence of younger patients with colorectal cancer: questions about screening, biology, and treatment. *Curr Treat Options Oncol* 2017;18:23. doi: 10.1007/s11864-017-0463-3.

4. Araghi M, Soerjomataram I, Bardot A, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. *Lancet Gastroenterol Hepatol* 2019;4:511-8. doi: 10.1016/S2468-1253(19)30147-5.

5. GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 24 years. *N Engl J Med* 2017;377:13-27. doi: 10.1056/NEJMoa1614362.

6. Wong MCS, Huang J, Huang JLW, et al. Global prevalence of colorectal neoplasia: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020;18:553-61. e10. doi:10.1016/j.cgh.2019.07.016.

7. Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet* 2017;389:1299-1311. doi: 10.1016/S0140-6736(17)30396-3.

8. Steele RJC. McClements PL, Libby G, et al. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. *Gut* 2009;58:530-5. doi:10.1136/gut.2008.162883

9. Fraser CG, Digby J, McDonald PJ, Strachan JA, Carey FA, Steele RJC. Experience with a two-tier reflex gFOBT/FIT strategy in a national bowel screening programme. *J Med Screen* 2012;19:8-13. doi:10.1258/jms.2011.011098

10. Scottish Health Survey. https://www.gov.scot/publications/scottish-health-survey-2018-volume-1-main-report/ (Accessed 30 January 2020).

11. Steele RJC, Kostourou I, McClements P, et al. Effect of gender, age and deprivation on key performance indicators in a FOBT based colorectal screening programme. *J Med Screen* 2010;17:68-74. doi:10.1258/jms.2010.009120.

12. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000;343:1603-7. doi:10.1056/NEJM200011303432203.

13. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut* 2012;61:1036-40. doi: 10.1136/gutjnl-2011-300774.

14. Grey M, Raffle A. Screening. Evidence and Practice. Oxford University Press 2007. Scottish Bowel Screening Programme Key Performance Indicators report, Information Services Division, NHS National Services Scotland, https://www.isdscotland.org/Health-Topics/Cancer/Publications/2019-08-06/2019-08-06-Bowel-Screening-KPI-Report.xlsx (Accessed 30 January 2020)

15. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening; an independent review. Lancet 2012;380:1778-86. doi:10.1016/S0140-6736(12)61611-0.

16. Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2018 with focus on colorectal cancer. *Ann Oncol* 2018;29:1016-22. doi:10.1093/annonc/mdy033.

17. Information Services Division (ISD) Scotland. Bowel Cancer Screening. https://www.isdscotland.org/Health-Topics/Cancer/Bowel-Screening/ (Accessed 30 January 2020).

18. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* 2019;68:1820–6. doi:10.1136/gutjnl-2018-317592

19. Mowat C, Digby J, Strachan JA, et al. Impact of introducing a faecal immunochemical test (FIT) for haemoglobin into primary care on the outcome of patients with new bowel symptoms: a prospective cohort study. *BMJ Open Gastroenterol* 2019;6:e000293. doi: 10.1136/bmjgast-2019-000293. eCollection 2019.

20. Potter JD. Rising rates of colorectal cancer in younger adults. *BMJ* 2019; 365:l4280. doi: 10.1136/bmj.l4280.

21. Jensen BW, Gamborg M, Gögenur I, Renehan AG, Sørensen TIA, Baker JL. Childhood body mass index and height in relation to site-specific risks of

colorectal cancers in adult life. *Eur J Epidemiol* 2017;32:1097-1106. doi: 10.1007/s10654-017-0289-0.

Legends to Figures

Figure 1. Age-sex standardised colorectal cancer incidence, ages 50-74 years, from 1997 to 2017 (95% confidence intervals shown)

Figure 2. Age-sex standardised colorectal cancer incidence, ages 75 years and over, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown)

Figure 3. Age-sex standardised colorectal cancer incidence, ages less than 50 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown)

Figure 4. Age-sex standardised colorectal cancer incidence for the screening population per 100,000 person-years, by screening participation status (95% confidence intervals shown)

Figure 5. Cumulative colorectal cancer incidence, by screening participation status

Legends to Supplementary Tables and Figures

Supplementary Table 1

Age distribution of screening and post-screening population, by year, in six age groups (years)

Supplementary Table 2.

Age distribution of colorectal cancers, by year, in six age groups (years)

Supplementary Figure 1.

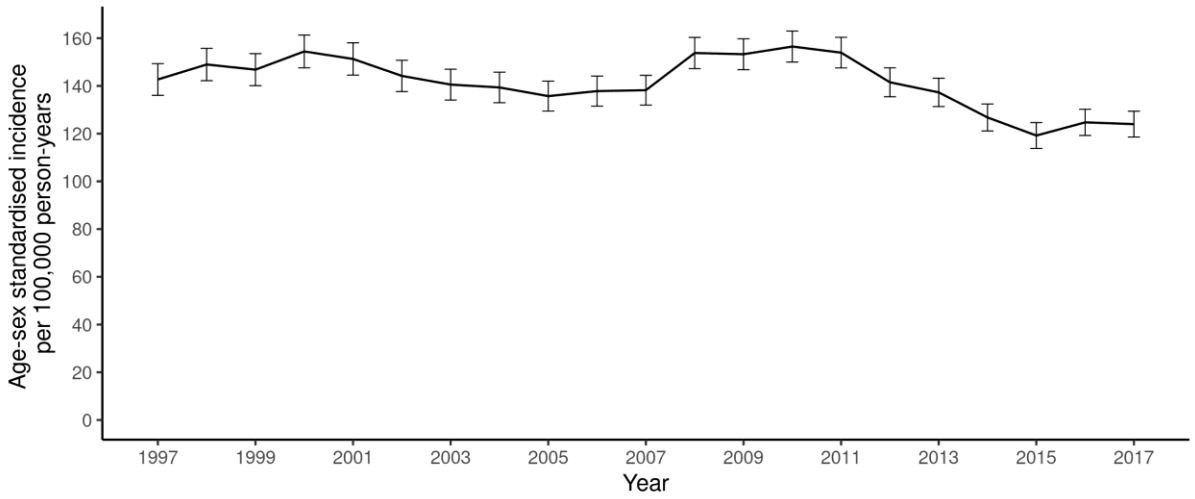
Cumulative colorectal cancer incidence, by sex and screening participation status

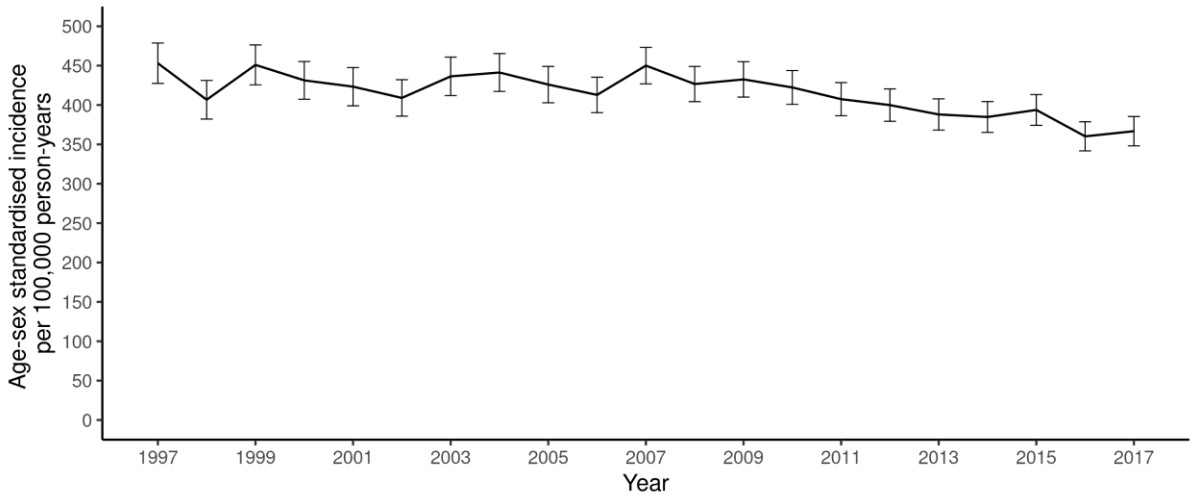
Supplementary Figure 2.

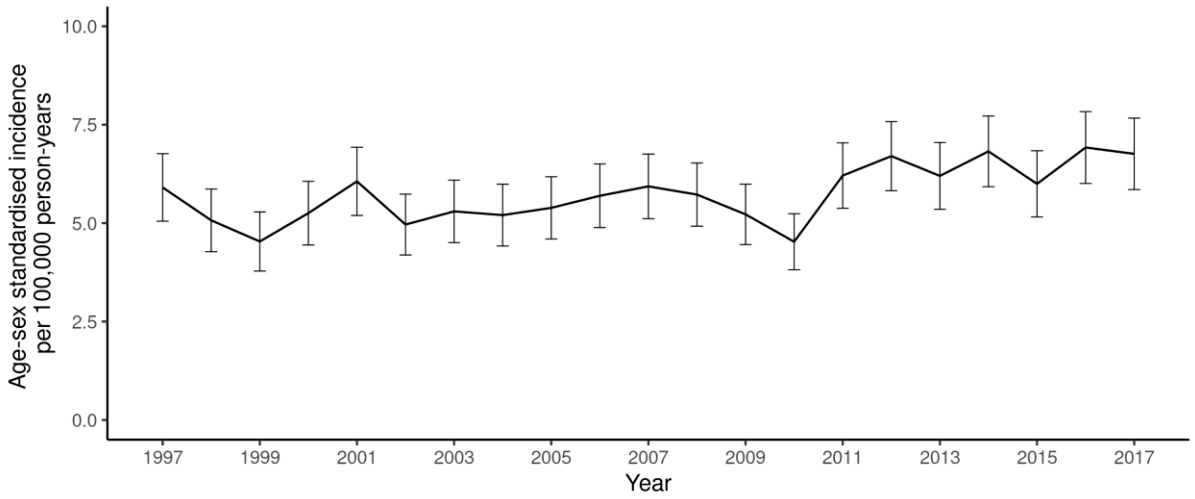
Age-sex standardised colorectal cancer mortality, ages 50-74 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown).

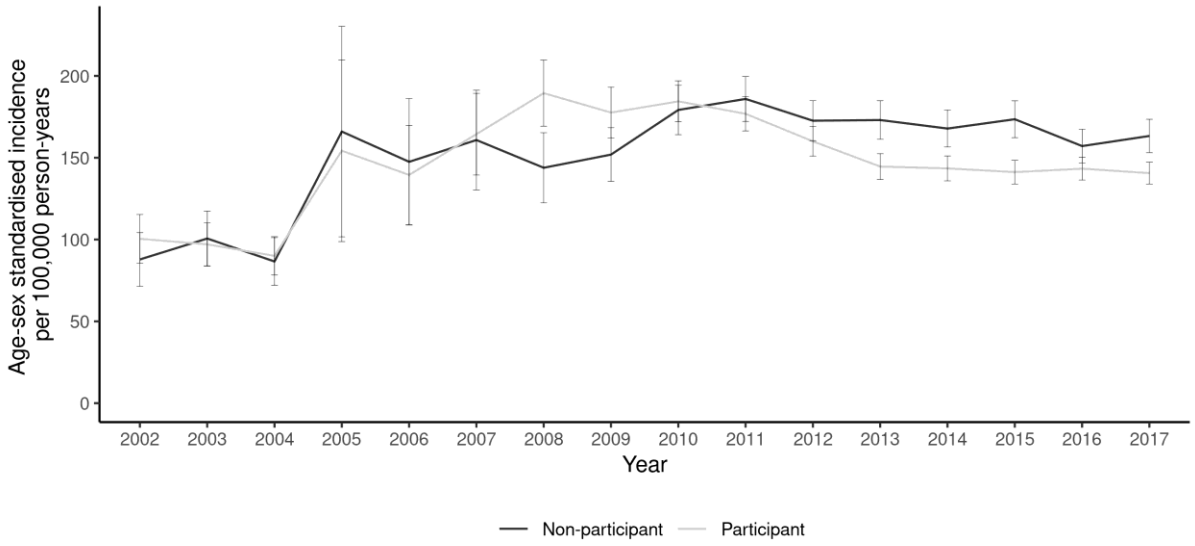
Supplementary Figure 3.

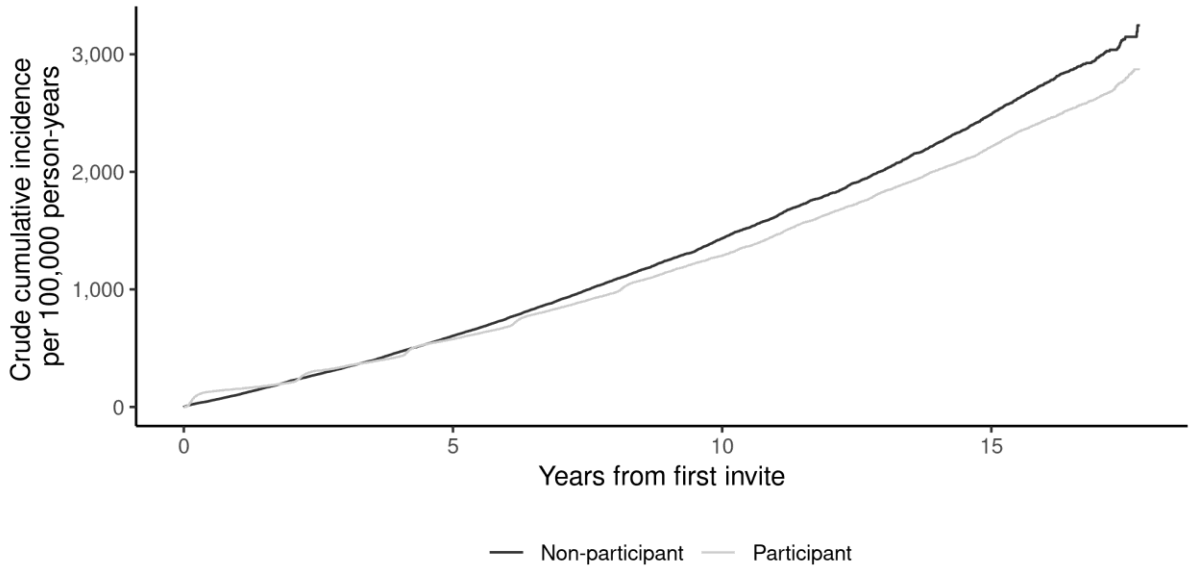
Age-sex standardised colorectal cancer mortality, ages under 50 years, from 1997 to 2017 per 100,000 person-years (95% confidence intervals shown).











Supplementary Table 1: Age distribution of screening and post-screening population, by year, in six age groups (years)

	Age distribution of population, n (%),											
	50-54		55-59		60-64		65-69		70-74		75+	
Year												
2001	54,240	(26.4%)	51,239	(25.0%)	44,137	(21.5%)	42,905	(20.9%)	12,679	(6.2%)	-	(0.0%)
2002	61,490	(22.2%)	74,204	(26.8%)	60,079	(21.7%)	57,307	(20.7%)	23,851	(8.6%)	-	(0.0%)
2003	65,241	(21.5%)	81,141	(26.7%)	63,410	(20.9%)	59,472	(19.6%)	34,581	(11.4%)	-	(0.0%)
2004	67,571	(20.5%)	87,062	(26.4%)	68,088	(20.6%)	61,739	(18.7%)	45,561	(13.8%)	-	(0.0%)
2005	62,874	(18.2%)	92,267	(26.7%)	70,813	(20.5%)	62,646	(18.2%)	52,651	(15.3%)	3,829	(1.1%)
2006	76,947	(20.2%)	93,881	(24.6%)	78,362	(20.6%)	64,371	(16.9%)	56,093	(14.7%)	11,204	(2.9%)
2007	82,678	(19.7%)	96,401	(23.0%)	88,775	(21.2%)	70,209	(16.7%)	59,571	(14.2%)	21,890	(5.2%)
2008	124,768	(20.9%)	130,326	(21.8%)	120,431	(20.1%)	100,736	(16.8%)	81,370	(13.6%)	40,230	(6.7%)
2009	207,433	(21.4%)	203,613	(21.0%)	192,470	(19.8%)	164,107	(16.9%)	132,759	(13.7%)	70,838	(7.3%)
2010	298,073	(21.6%)	279,971	(20.3%)	279,627	(20.2%)	225,020	(16.3%)	189,222	(13.7%)	109,061	(7.9%)
2011	339,145	(21.0%)	321,494	(20.0%)	317,497	(19.7%)	267,034	(16.6%)	218,456	(13.6%)	147,739	(9.2%)

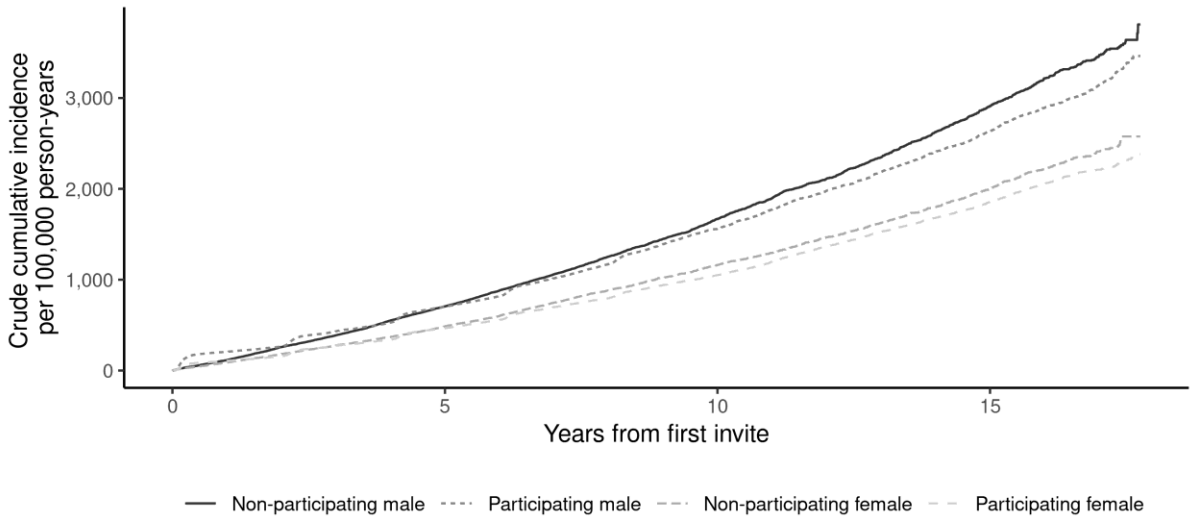
2012	357,830	(20.8%)	339,212	(19.8%)	316,700	(18.4%)	293,561	(17.1%)	225,389	(13.1%)	184,587	(10.7%)
2013	376,959	(20.7%)	357,825	(19.6%)	323,931	(17.8%)	310,399	(17.0%)	233,617	(12.8%)	221,685	(12.2%)
2014	398,197	(20.6%)	375,480	(19.5%)	332,956	(17.3%)	323,005	(16.7%)	244,065	(12.6%)	256,410	(13.3%)
2015	411,856	(20.3%)	393,919	(19.5%)	342,353	(16.9%)	337,714	(16.7%)	249,651	(12.3%)	289,123	(14.3%)
2016	425,191	(20.1%)	408,845	(19.3%)	354,588	(16.8%)	338,041	(16.0%)	267,472	(12.7%)	320,149	(15.1%)
2017	422,301	(19.3%)	423,926	(19.4%)	367,652	(16.8%)	331,431	(15.2%)	290,065	(13.3%)	352,178	(16.1%)

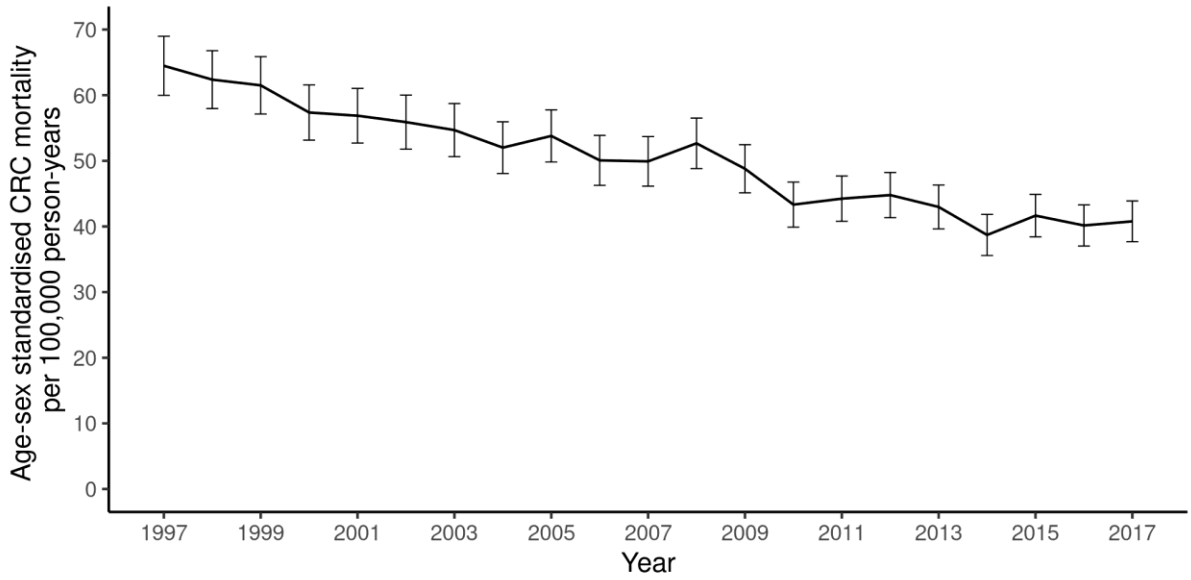
Supplementary Table 2: Age distribution of colorectal cancers, by year, in six age groups (years)

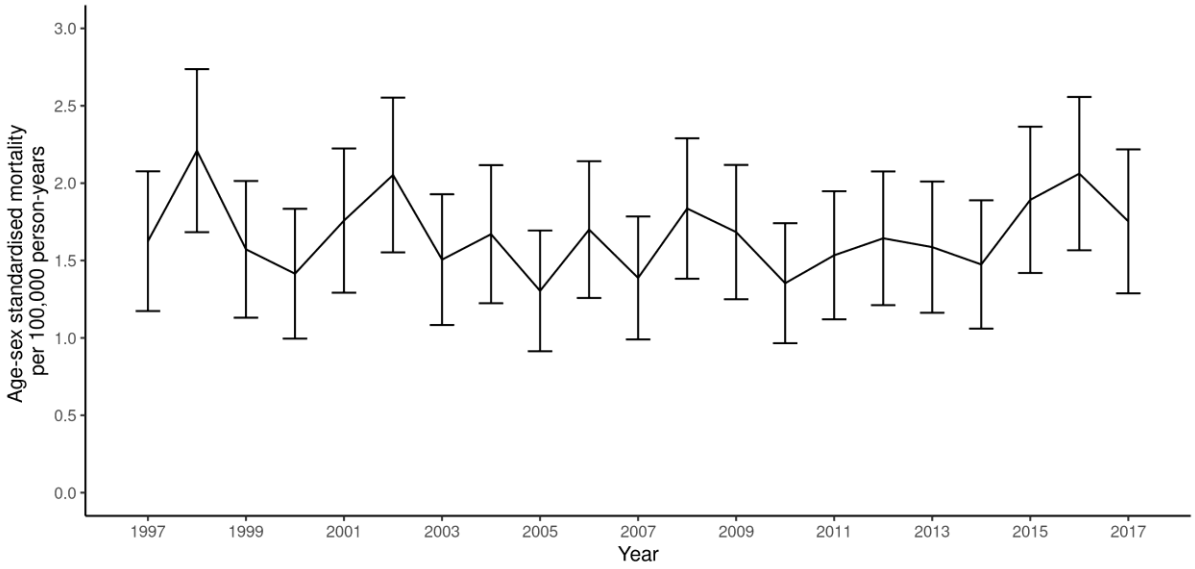
Age distribution of colorectal cancers detected in screening population, n (%)

Year	50-54		55-59		60-64		65-69		70-74		75+	
2001	18	(8.2%)	44	(20.0%)	49	(22.3%)	77	(35.0%)	32	(14.5%)	-	(0.0%)
2002	28	(8.6%)	48	(14.8%)	100	(30.9%)	102	(31.5%)	46	(14.2%)	-	(0.0%)
2003	25	(6.8%)	67	(18.3%)	80	(21.9%)	112	(30.6%)	82	(22.4%)	-	(0.0%)
2004	26	(7.0%)	60	(16.1%)	90	(24.1%)	117	(31.4%)	80	(21.4%)	-	(0.0%)
2005	21	(5.2%)	68	(16.7%)	71	(17.4%)	110	(27.0%)	126	(31.0%)	11	(2.7%)
2006	21	(5.1%)	50	(12.0%)	82	(19.8%)	117	(28.2%)	116	(28.0%)	29	(7.0%)
2007	42	(8.1%)	68	(13.1%)	101	(19.4%)	113	(21.7%)	127	(24.4%)	69	(13.3%)
2008	56	(6.8%)	84	(10.2%)	152	(18.5%)	184	(22.4%)	222	(27.1%)	122	(14.9%)
2009	93	(7.3%)	144	(11.3%)	217	(17.1%)	277	(21.8%)	318	(25.0%)	222	(17.5%)
2010	132	(6.6%)	212	(10.6%)	351	(17.6%)	423	(21.2%)	505	(25.3%)	372	(18.6%)
2011	160	(6.7%)	247	(10.3%)	394	(16.4%)	539	(22.4%)	593	(24.7%)	470	(19.6%)
2012	158	(6.5%)	243	(10.0%)	391	(16.1%)	530	(21.8%)	579	(23.9%)	525	(21.6%)

2013	160	(6.5%)	266	(10.8%)	355	(14.4%)	531	(21.6%)	556	(22.6%)	594	(24.1%)
2014	152	(6.0%)	248	(9.9%)	319	(12.7%)	532	(21.1%)	523	(20.8%)	743	(29.5%)
2015	172	(6.6%)	212	(8.1%)	361	(13.8%)	468	(17.9%)	502	(19.2%)	899	(34.4%)
2016	183	(6.6%)	270	(9.8%)	350	(12.7%)	490	(17.8%)	574	(20.8%)	887	(32.2%)
2017	165	(5.7%)	267	(9.2%)	375	(13.0%)	492	(17.0%)	596	(20.6%)	993	(34.4%)







STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9-10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9 -10
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	12-14
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12-14
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.