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Authors

Goede, Simon Lucas
Rabeneck, Linda
Lansdorp-Vogelaar, Iris
et al.

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The Impact of Stratifying by Family History in Colorectal Cancer Screening Programs

S. Lucas Goede[1], **Linda Rabeneck**[2,3,4], **Iris Lansdorp-Vogelaar**[1], **Ann G. Zauber**[5], **Lawrence F. Paszat**[3], **Jeffrey S. Hoch**[3,6], **Jean H.E. Yong**[6], **Frank van Hees**[1], **Jill Tinmouth**[3,7], and **Marjolein van Ballegooijen**[1]

[1]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands [2]Prevention and Cancer Control, Cancer Care Ontario, Toronto, Canada [3]Institute for Clinical Evaluative Sciences, Toronto, Canada [4]Department of Medicine, University of Toronto, Toronto, Canada [5]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY [6]Centre for Excellence in Economic Analysis Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada [7]Department of Medicine, Division of Gastroenterology, Sunnybrook Health Sciences Centre, Toronto, Canada

Abstract

In the province-wide colorectal cancer (CRC) screening program in Ontario, Canada, individuals with a family history of CRC are offered colonoscopy screening and those without are offered guaiac fecal occult blood testing (gFOBT, Hemoccult II). We used microsimulation modeling to estimate the cumulative number of CRC deaths prevented and colonoscopies performed between 2008 and 2038 with this family history-based screening program, compared to a regular gFOBT program. In both programs, we assumed screening uptake increased from 30% (participation level in 2008 before the program was launched) to 60%. We assumed that 11% of the population had a family history, defined as having at least one first-degree relative diagnosed with CRC. The programs offered screening between age 50-74 years, every two years for gFOBT, and every ten years for colonoscopy. Compared to opportunistic screening (2008 participation level kept constant at 30%), the gFOBT program cumulatively prevented 6,700 more CRC deaths and required 570,000 additional colonoscopies by 2038. The family history-based screening program increased these numbers to 9,300 and 1,100,000, a 40% and 93% increase, respectively. If biennial gFOBT was replaced with biennial fecal immunochemical test (FIT), annual Hemoccult Sensa or five-yearly sigmoidoscopy screening, both the added benefits and colonoscopies required would

Corresponding author. S. Lucas Goede, Department of Public Health, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands; Phone: +31-10-7038459; Fax: +31-10-7038474; s.goede@erasmusmc.nl.

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decrease. A biennial gFOBT screening program that identifies individuals with a family history of CRC and recommends them to undergo colonoscopy screening would prevent 40% (range in sensitivity analyses: 20-51%) additional deaths while requiring 93% (range: 43-116%) additional colonoscopies, compared to a regular gFOBT screening program.

Keywords

Colorectal cancer; screening; computer simulation; prevention and control

Introduction

Colorectal cancer (CRC) is the second most diagnosed malignancy in Western Countries,[1] and its incidence is likely to increase because most cases are diagnosed later in life and life expectancy is increasing in many countries. Screening for CRC and its precursor lesions, adenomas, can prevent the disease or detect it at an earlier and more curable stage. Several trials have proven that screening reduces CRC incidence and mortality,[2, 3] and that screening is cost-effective.[4]

Based on recommendations from the Canadian Task Force on Preventive Health Care and Health Canada's National Committee on Colorectal Cancer Screening in 2008 the ColonCancerCheck screening program was launched in Ontario, Canada.[5] ColonCancerCheck is a population-based screening program, which includes individuals aged 50-74 years old. At launch, the program relied on family physicians to identify eligible patients in their practices and to recommend screening, and on a public awareness campaign encouraging eligible individuals to discuss CRC screening with their family physicians. Several components including mailed invitations (newly eligible individuals), recall letters (previous screening participants), and annually recurring public awareness campaigns are being planned and introduced in a phased implementation.[5, 6]

At the family physician visit, individuals are risk stratified based on their family history of CRC. Individuals with a positive family history, defined as having at least one first-degree relative with a diagnosis of CRC, are recommended to undergo ten-yearly colonoscopy screening. Individuals without family history are offered biennial screening with the Hemoccult II guaiac fecal occult blood test (gFOBT).

To our knowledge the ColonCancerCheck is the first population-based screening program which actively identifies individuals with a family history in order to provide them with a more sensitive test. We aimed to estimate the effects of this family history-based screening approach on the cumulative number of CRC deaths prevented and colonoscopies performed, compared to a screening program where only gFOBT is recommended.

Methods

The MISCAN-colon microsimulation model was used to model two program screening scenarios in Ontario: a program in which everyone was offered gFOBT screening and a program in which those with a family history of CRC were offered colonoscopy screening.

The program outcomes were compared to a scenario that reflects the opportunistic screening participation observed in Ontario in 2008, prior to the launch of the ColonCancerCheck program (i.e. the "opportunistic screening" scenario).

MISCAN-Colon Microsimulation Model

The MISCAN-colon microsimulation model has been described in detail in Appendix 1 and in previous publications.[7-9] In brief, the model simulates the life histories of individuals from birth to death. CRC arises in the population according to the adenoma-carcinoma sequence.[10] More than one adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas can progress in size from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm), and some may eventually become malignant. A preclinical (i.e., not detected) cancer has a chance of progressing through stages I-IV and may be detected by symptoms at any stage. After clinical diagnosis of CRC, survival depends on the stage at diagnosis. At any time during his/her life an individual may die of other causes. With screening, an individual with a positive test will be referred for diagnostic colonoscopy for possible removal of adenomas and detection of cancers. This way CRC mortality can be reduced.

For this analysis the age-specific CRC incidence and stage distribution of the total population (i.e. average risk and family history populations combined) were calibrated to 2001 incidence data from the Canadian Cancer Registry, which was before the introduction of screening.[11] In the runs for the analysis we assumed that the CRC stage distribution in the absence of screening was similar between both risk groups, only the CRC incidence in each risk group was adjusted based on their relative risk for CRC (see section "study population"). The model used all-cause mortality estimates from the 2000-2002 Ontario life tables.[11] Because age- and stage-specific data on CRC relative survival were not available for Canada, we assumed the same age- and stage-specific survival as observed in the Surveillance, Epidemiology, and End-Results (SEER) database in the US, in the period 2000-2003.[12] We assumed that survival did not differ between individuals with and without family history. We did not include historical changes in risk factor prevalence or CRC relative survival, therefore any simulated changes in CRC incidence and mortality are attributable solely to changes in screening behavior.

Study population

Table 1 provides an overview of the main estimates and assumptions in the model. We simulated the Ontario population aged 50 years and older. The population was followed from 2008-2038, with new 50-year-olds entering the population each year. The age distribution was based on the observed age distribution in Ontario in 2008.[11] We modeled two subpopulations; individuals with and without a family history, defined as having at least one first-degree relative with a diagnosis of CRC. We assumed that 11% of the total population had a family history[13] and that their relative risk (RR) for developing adenomas and CRC was on average 2.24 times higher than that of the general population.[14] The model allowed for individual variability of CRC risk within each subpopulation. As the general population includes those with and without a family history of CRC, the persons without a

family history would have slightly lower than average risk for developing CRC. The model adjusts risk downward modestly for these “average risk” individuals (average RR=0.85).

The screening history prior to the start of the program was based on observed screening rates in Ontario.[5] It was assumed that in the average risk population individuals between 50-74 years old would be able to participate in CRC screening with biennial gFOBT, and would only get a colonoscopy after a positive gFOBT result. After age 74 individuals would stop screening, and new individuals turning age 50 would potentially start screening. The screening participation was assumed to increase steadily over time. In 2003, 15% of the 50-74 year old average risk individuals had a gFOBT within the past two years, this increased to 20% in 2005, and 30% in 2008. For the increased risk population we assumed individuals between age 50-74 years would be able to participate in ten-yearly colonoscopy screening. The proportion of increased risk individuals who had a colonoscopy within the past ten years was assumed to increase over time similarly to the gFOBT participation in the average risk population, i.e. 15% in 2003, 20% in 2005, and 30% in 2008. We assumed no significant screening in either risk group prior to 1995.

Base case analysis

In both program scenarios we assumed that participants were screened between age 50-74, and that the screening uptake in the average risk and increased risk populations would increase, over approximately 10 years, from 30% (observed 2008 participation level[5]) to 60% (comparable to current mammography screening in Ontario[17]):

1. *gFOBT program*: A screening program that offers biennial gFOBT screening to all participants and does not actively identify increased risk individuals. We assumed that 30% of the increased risk population would receive colonoscopy screening, consistent with the colonoscopy uptake prior to the start of the program.
2. *Family history-based program*: screening program that identifies individuals with a family history of CRC (i.e. because of a CRC diagnosis in at least one first degree relative) and invites them to undergo ten-yearly colonoscopy screening. Although colonoscopy is more invasive than gFOBT, which could negatively affect screening uptake, for the base case analysis we assumed the increased risk individuals would obtain similar uptake as the average risk individuals, because they were identified as being at increased risk for CRC.[18, 19] As in the gFOBT program, average risk individuals were recommended to undergo biennial gFOBT screening.

The two program screening scenarios were compared to a scenario that reflects the opportunistic screening participation observed in Ontario in 2008, prior to the launch of the ColonCancerCheck program (opportunistic screening scenario), that is, 30% gFOBT screening in the average risk population and 30% colonoscopy screening in the increased risk population.

In all scenarios, approximately 10% of the average risk gFOBT participants ever had a positive gFOBT result and received colonoscopy screening as part of the surveillance program (i.e. with 30% gFOBT screening participation approximately 3% of the average risk population would be in colonoscopy surveillance). Among increased risk gFOBT

participants (only applicable to the gFOBT program scenario) approximately 13% ever had a positive gFOBT result and received colonoscopy screening as part of the surveillance program.

Adenomas could be detected and removed during diagnostic colonoscopy after a positive gFOBT or during colonoscopy screening (increased risk individuals only). Depending on the number and size of adenomas detected, the individual would be recommended for surveillance colonoscopy after three or five years. If no adenomas were detected the individuals would be recommended to undergo colonoscopy after ten years.[20] We assumed that once individuals entered surveillance they would remain in surveillance for the rest of their lives (i.e. they would not stop screening at age 74). Adherence to diagnostic colonoscopy after a positive gFOBT, and to surveillance colonoscopy after detection and removal of adenomas were assumed to be 71% and 80% respectively.[5] These rates were assumed to be equal for average and increased risk individuals, and to remain constant over time. Individuals who did not adhere to the recommendation to undergo diagnostic colonoscopy, would return to screening. Individuals who did not adhere to the recommendation for surveillance colonoscopy would receive another recommendation for surveillance colonoscopy after three or five years (depending on the findings at the previous colonoscopy).

Sensitivity analyses

In order to investigate the robustness of our results to model assumptions, we evaluated several sensitivity analyses (Table 1). The following assumptions had an effect during the screening program (2008-2038), as well as the screening history: 1) the proportion of individuals at increased risk was varied by 30% (low value: 8%; high value: 14%); 2) the RR of CRC in the increased risk population compared to the general population was varied by 50% (low value: RR=1.62; high value: RR=2.86); 3) the uptake rate for both diagnostic and surveillance colonoscopies was increased to 85% (base case value: 71% and 80% respectively); 4) age- and stage-specific CRC relative survival in individuals with a family history was increased by 10%; 5) 15% of the population (in the average risk as well as the increased risk population) who did not participate in CRC screening before the program, but who would start screening during the program, would get a colonoscopy unrelated to CRC screening 5-10 years before the start of the screening program; 6) dependency of FOBT results in sequential screening rounds were assumed for 74% of the large adenomas (≥10mm), because individuals with a false negative test result are likely to have a higher than average probability to have another false negative test result at a successive screening round.[16]

The following assumptions only had an effect during the screening programs (2008-2038): 7) the family history assessment was only able to identify 50% if the increased risk individuals (those individuals with a false negative family history assessment were assumed to receive gFOBT instead of colonoscopy screening) 8) biennial gFOBT screening was replaced by either annual gFOBT, biennial fecal immunochemical test (FIT) at a cut-off level of 50 or 100 ng Hb/ml, five-yearly sigmoidoscopy, or annual Hemoccult Sensa; 9) all screening participants, including those at average risk, were screened with ten-yearly

colonoscopy; 10) screening uptake in the average risk and increased risk populations during the screening programs was varied independently from 30% to 100% at ten percent increments.

Outcomes

The main outcomes of the analysis are the cumulative number of CRC deaths prevented and colonoscopies performed in the population aged 50 years and older, in the program screening scenarios between 2008 and 2038, compared to opportunistic screening. In addition, we provide age adjusted annual CRC incidence and mortality rates as intermediate outcomes.

All simulation runs were performed using common random seeds, and a large sample size (600 million) in order to minimize the impact of stochastic variations on model outcomes.

Results

In all scenarios screening participation was increasing slowly in the years before 2008, reaching 30% uptake with ten-yearly colonoscopy in the increased risk population and 30% uptake with biennial gFOBT in the average risk population. In the opportunistic screening scenario screening participation was assumed to level off from 2008 onwards. As a result, the age-adjusted CRC incidence rate in this scenario was first decreasing following 2008, and with a lag time leveled off at 185.5 cases per 100,000 individuals per year in 2038 (Figure 1). Assuming that the gFOBT and family history-based screening programs increased screening uptake from 30% to 60% resulted in an increase in CRC incidence in the first years of the programs, reflecting the detection of prevalent cancers in screened individuals. After approximately ten years the CRC incidence rate dropped below that of the opportunistic screening scenario, resulting in 180.5 and 174.5 cases per 100,000 per year in 2038, in the gFOBT and family history-based programs respectively. In the opportunistic screening scenario the CRC mortality rate declined from 71.0 to 66.7 deaths per 100,000 individuals per year in 2038. With the gFOBT and family history-based screening programs the mortality rate declined to 60.3 and 57.9 deaths per 100,000 per year, in 2038 (Figure 2).

The cumulative number of CRC deaths prevented reached 6,700 by 2038 in the gFOBT program, compared to opportunistic screening (Figure 3). The family history-based program resulted in 9,300 deaths prevented by 2038, a 40% increase compared to the gFOBT program. In order to achieve this effect the cumulative number of colonoscopies performed compared to opportunistic screening increased by 93% from 570,000 in the gFOBT program, to 1,100,000 in the family history-based program (Figure 4).

Sensitivity Analyses

The results were robust to varying model assumptions. In most sensitivity analyses the family history-based program provided 20-51% more deaths prevented than the gFOBT program, compared to opportunistic screening, while requiring 43-116% more colonoscopies (Table 2). However, the results were sensitive to gFOBT screening interval and main screening modality. Annual gFOBT screening or replacing Hemoccult II by FIT, Hemoccult Sensa, or sigmoidoscopy reduced both the additional benefit and colonoscopies

required of family history-based compared to non-family history-based screening: 3-16% additional deaths prevented (base case: 40%) and 11-55% additional colonoscopies required (base case: 93%).

In the base case analysis, we assumed 60% screening uptake with colonoscopy in individuals with a family history (the same uptake rate as gFOBT screening in average risk individuals). If colonoscopy uptake in the family history-based program was 40% or less, this program became less effective than the gFOBT program (6,400 versus 6,700 deaths prevented compared to opportunistic screening, Appendix 2).

Discussion

Our results suggest that a family-history based CRC screening approach where individuals at increased risk are offered colonoscopy screening, could prevent approximately 40% (range: 20-51%) more deaths within 30 years, than a program that only recommends biennial gFOBT (Hemoccult II) screening. In order to achieve this effect, 93% (range: 43-116%) more colonoscopies would be required. In a screening program that performs gFOBT annually, or uses FIT, Hemoccult Sensa, or sigmoidoscopy instead of Hemoccullt II, a family history-based screening approach would still be more effective but the added benefits and added colonoscopy demand are reduced.

In the opportunistic screening scenario there is a lag time between the leveling off of the screening uptake rate and the leveling off of the CRC incidence and mortality. This lag time results from the increasing trend in screening participation before 2008 and the time it takes for the removal of adenomas and early detection of CRC to have an effect on CRC incidence and mortality.

The benefits of the CRC screening programs are directly related to the additional number of colonoscopies performed. Implementing a family history-based screening program, and similarly, reducing the gFOBT screening interval or replacing gFOBT by FIT or sigmoidoscopy will increase the number of colonoscopies required. In many health care systems colonoscopy capacity is limited and in order to prevent unacceptably long waiting lists, the introduction of a large scale screening program requires careful planning up front and a phased rollout in the target population.

Although this study focused on the added benefits of family history-based screening, compared to a regular gFOBT program, one could argue that increasing gFOBT uptake in the general population has a larger potential for health benefits than providing a more sensitive test in the family history population (which is only about 11% of the general population). Based on the data from Appendix 2 we estimated that compared to 60% screening uptake in the gFOBT program (6,700 additional deaths prevented compared to opportunistic screening), providing colonoscopy to increased risk individuals (also with 60% uptake) was approximately as effective as increasing the gFOBT screening participation in the general population to 70% (9,300 versus 8,900 additional deaths prevented respectively).

To our knowledge only one published study had estimated the added benefits of family history-based screening within a population-based screening program.[21] Ramsey et al.

modeled several scenarios where individuals with a family history were screened with colonoscopy from younger ages and/or with shorter screening intervals than the average risk population. The study estimated fewer additional CRC deaths prevented with family history screening than our current analysis. The difference is mainly explained by the screening test used; in the study of Ramsey et al. all individuals in usual care (including average risk) were screened with colonoscopy between age 50 and 80 years. Colonoscopy is a more sensitive test than gFOBT, leaving less room for additional health benefits from family history screening. Furthermore, Ramsey et al. used a narrower definition of a positive family history; one first degree relative diagnosed with CRC before age 60 or two or more affected first degree relatives of any age. Using this definition, only two percent of the population had a positive family history, compared to 11% in our analysis.

We have focused on family history, because this was the strategy used in the province-wide screening program in Ontario. However, several other risk factors, in addition to family history, are also associated with an increased risk for CRC.[22] Researchers have proposed risk prediction models to help customize screening recommendations.[23-28] Although most of these models look promising, none has been implemented in population-based screening. Inclusion of one or more risk factors into a risk stratified screening program, or considering different levels of risk within the family history population (e.g. individuals with more than one first degree relative with CRC), might provide greater health benefits compared to the findings in our analysis. However, such strategy would make the program more complicated and if more individuals will be identified as being at increased risk the colonoscopy demand will also increase.

Several limitations need to be acknowledged. First, there are no randomized controlled trial data available yet for the effect of colonoscopy screening on CRC incidence and mortality, but there is data available for sigmoidoscopy [29] We assumed that the effectiveness of sigmoidoscopy in the distal colon and rectum could be extrapolated to the proximal colon when using colonoscopy. However, it has been suggested that colonoscopy effectiveness might be lower in the proximal colon, because proximal lesions are more often flat and might have a higher probability to progress into CRC.[30] This would mean we might have overestimated the mortality reduction from screening increased risk individuals with colonoscopy instead of gFOBT.

Second, we assumed that the increased risk in individuals with a family history is solely the result of an increased adenoma incidence. In reality, reduced adenoma dwell time and/or a greater proportion of adenomas that progress to cancer may also play a role. If this were the case, the added benefits of colonoscopy screening in increased risk individuals might be reduced.

Third, we only modeled CRC screening between age 50-74. However, for people at increased risk of colorectal cancer due to a family history, the ColonCancerCheck program recommends screening with colonoscopy beginning at age 50 or 10 years earlier than the age at which their relative was diagnosed, whichever occurs first.[5] Since we did not take into account the effects of the family-history based program in individuals who will participate in screening before age 50, we have underestimated both the number of colonoscopies

performed and number of deaths prevented of the family history-based program compared to the gFOBT program.

Fourth, we assumed that the family physician was able to identify all individuals with a family history of CRC in clinical assessment. Using this approach we are able to demonstrate the potential added health benefits of a stratified screening approach. However, family history assessments by the physician do not identify all individuals at increased risk in the general population.[31] If the family history assessment would only manage to identify 50% of the individuals at increased risk, both the number of CRC deaths prevented and number of colonoscopies performed would decreased by a similar proportion (see sensitivity analyses). In addition, most population-based screening programs will identify individuals at increased risk at least to some degree. For instance, on the patient information website about the national FIT screening program in The Netherlands it is recommended to seek medical advice if there is a family history of cancer.[32] This might reduce the added effects of family history-based screening within gFOBT programs.

Finally, we did not include costs in our analysis. Screening with both gFOBT and colonoscopy have been demonstrated to be very cost-effective in the general population.[4] Unless the process of family history assessment is very costly, we anticipate that colonoscopy screening of individuals with a family history would be cost-effective. However, for healthcare systems considering implementing a screening program a cost-effectiveness analysis would still be necessary before family history risk assessment would be incorporated. In addition, even if a family history-based screening program is cost-effective it would require a considerable upfront financial investment which may become a barrier given the currently available health care budget.

In Ontario the family history assessment is performed during one consultation with the family physician (approximately 10 minutes) and the reimbursement rate for a consultation is approximately 32 Canadian dollars.[33] There is currently no data available about the acceptance rate to colonoscopy screening after an individual has been identified to have an increased risk for CRC.

In conclusion, a biennial gFOBT screening program that identifies individuals with a family history of CRC (approximately 11% of the general population) and recommends them to undergo colonoscopy screening would prevent 40% (range: 20-51%) additional deaths while requiring 93% (range: 43-116%) additional colonoscopies, compared to a regular gFOBT program. In order to increase the health benefits of a gFOBT screening program, a strategy incorporating family history risk assessment comparable to the Ontario province-wide CRC screening program should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; 61:69–90. [PubMed: 21296855]
2. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2012; 9:e1001352. [PubMed: 23226108]
3. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol. 2008; 103:1541–9. [PubMed: 18479499]
4. Cruzado J, Sanchez FI, Abellan JM, Perez-Riquelme F, Carballo F. Economic evaluation of colorectal cancer (CRC) screening. Best Pract Res Clin Gastroenterol. 2013; 27:867–80. [PubMed: 24182607]
5. Rabeneck L, Tinmouth JM, Paszat LF, Baxter NN, Marrett LD, Ruco A, Lewis N, Gao J. Ontario's ColonCancerCheck: Results from Canada's first province-wide colorectal cancer screening program. Cancer Epidemiol Biomarkers Prev. 2014; 23:508–15. [PubMed: 24443406]
6. Cancer Quality Council of Ontario. [accessed December 22, 2014] Colorectal Cancer Screening Participation. http://www.csqi.on.ca/cms/One.aspx?portalId=289784&pageId=296144
7. Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res. 1999; 32:13–33. [PubMed: 10066353]
8. Loeve, F.; Boer, R.; van Ballegooijen, M.; van Oortmarssen, GJ.; Habbema, JDF. Final Report MISCAN-COLON Microsimulation Model for Colorectal Cancer: Report to the National Cancer Institute Project No NO1-CN55186. Rotterdam, The Netherlands: Department of Public Health, Erasmus University; 1998.
9. Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, Zauber A, Habbema JD. A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials. Cancer. 2009; 115:2410–9. [PubMed: 19288570]
10. Morson B. President's address. The polyp-cancer sequence in the large bowel. Proc R Soc Med. 1974; 67:451–7. [PubMed: 4853754]
11. Statistics Canada. [accessed May 26, 2014] CANSIM (database). http://www5.statcan.gc.ca/cansim/home-accueil?lang=eng
12. Surveillance Epidemiology and End Results (SEER) Program. Bethesda, MD: National Cancer Institute; SEER*Stat Database: Incidence - SEER 9 Regs Public Use. Nov 2003 Sub (1973-2001), DCCPS, Surveillance Research Program, Cancer Statistics Branch. Based on the November 2003 submission. http://www.seer.cancer.gov [accessed May 26, 2014]
13. Cotterchio M, Manno M, Klar N, McLaughlin J, Gallinger S. Colorectal screening is associated with reduced colorectal cancer risk: a case-control study within the population-based Ontario Familial Colorectal Cancer Registry. Cancer Causes Control. 2005; 16:865–75. [PubMed: 16132797]
14. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer. 2006; 42:216–27. [PubMed: 16338133]

15. Birgisson H, Ghanipour A, Smedh K, Pahlman L, Glimelius B. The correlation between a family history of colorectal cancer and survival of patients with colorectal cancer. Fam Cancer. 2009; 8:555–61. [PubMed: 19714489]

16. Zorzi M, Barca A, Falcini F, Grazzini G, Pizzuti R, Ravaioli A, Sassoli de Bianchi P, Senore C, Sigillito A, Vettorazzi M, Visioli C. Screening for colorectal cancer in Italy: 2005 survey. Epidemiol Prev. 2007; 31:49–60. [PubMed: 17824362]

17. Cancer Quality Counsil of Ontario. [accessed May 26, 2014] Breast Cancer Screening: Participation. http://www.csqi.on.ca/cms/one.aspx?portalId=258922&pageId=273161#.UjV2rRYyl8P

18. Perencevich M, Ojha RP, Steyerberg EW, Syngal S. Racial and ethnic variations in the effects of family history of colorectal cancer on screening compliance. Gastroenterology. 2013; 145:775–81 e2. [PubMed: 23796457]

19. Martinez-Ochoa E, Gomez-Acebo I, Beunza JJ, Rodriguez-Cundin P, Dierssen-Sotos T, Llorca J. Investigators SUNP. Influence of family history of colorectal cancer on health behavior and performance of early detection procedures: the SUN Project. Ann Epidemiol. 2012; 22:511–9. [PubMed: 22571992]

20. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008; 149:627–37. [PubMed: 18838716]

21. Ramsey SD, Wilschut J, Boer R, van Ballegooijen M. A decision-analytic evaluation of the cost-effectiveness of family history-based colorectal cancer screening programs. Am J Gastroenterol. 2010; 105:1861–9. [PubMed: 20461066]

22. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010; 138:2029–43 e10. [PubMed: 20420944]

23. Stegeman I, Bossuyt PM. Cancer risk models and preselection for screening. Cancer Epidemiol. 2012; 36:461–9. [PubMed: 22841151]

24. Park HW, Han S, Lee JS, Chang HS, Lee D, Choe JW, Myung SJ, Yang SK, Kim JH, Byeon JS. Risk stratification for advanced proximal colon neoplasm and individualized endoscopic screening for colorectal cancer by a risk-scoring model. Gastrointest Endosc. 2012; 76:818–28. [PubMed: 22884098]

25. Stein B, Anderson JC, Rajapakse R, Alpern ZA, Messina CR, Walker G. Body mass index as a predictor of colorectal neoplasia in ethnically diverse screening population. Dig Dis Sci. 2010; 55:2945–52. [PubMed: 20112063]

26. Rubinstein WS, Acheson LS, O'Neill SM, Ruffin MTt, Wang C, Beaumont JL, Rothrock N. Clinical utility of family history for cancer screening and referral in primary care: a report from the Family Healthware Impact Trial. Genet Med. 2011; 13:956–65. [PubMed: 22075527]

27. Schroy PC 3rd, Coe AM, Mylvaganam SR, Ahn LB, Lydotes MA, Robinson PA, Davis JT, Chen CA, Ashba J, Atkinson ML, Colditz GA, Heeren TC. The your disease risk index for colorectal cancer is an inaccurate risk stratification tool for advanced colorectal neoplasia at screening colonoscopy. Cancer Prev Res (Phila). 2012; 5:1044–52. [PubMed: 22689913]

28. Driver JA, Gaziano JM, Gelber RP, Lee IM, Buring JE, Kurth T. Development of a risk score for colorectal cancer in men. Am J Med. 2007; 120:257–63. [PubMed: 17349449]

29. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, Parkin DM, Wardle J, Duffy SW, Cuzick J. Investigators UKFST. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010; 375:1624–33. [PubMed: 20430429]

30. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med. 2009; 150:1–8. [PubMed: 19075198]

31. Mai PL, Garceau AO, Graubard BI, Dunn M, McNeel TS, Gonsalves L, Gail MH, Greene MH, Willis GB, Wideroff L. Confirmation of family cancer history reported in a population-based survey. J Natl Cancer Inst. 2011; 103:788–97. [PubMed: 21562245]

32. Ministry of Health, Welfare Sport - National Institute for Public Health and the Environment. [accessed December 22, 2014] Voor wie is het bevolkingsonderzoek darmkanker?. [article in

Dutch]. http://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_darmkanker/Voor_wie_is_het_bevolkingsonderzoek_darmkanker

33. Ontario Ministry of Health and Long-Term Care. [accessed December 22, 2014] Schedule of Benefits for Physician Services under the Health Insurance Act. http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html

Abbreviations

CRC	colorectal cancer
gFOBT	guaiac fecal occult blood test
FIT	fecal immunochemical test
FH	family history

What's new?

The Canadian ColonCancerCheck screening program offers individuals with and without family history of CRC ten-yearly colonoscopy and biennial gFOBT screening, respectively. Using microsimulation modeling we quantified the additional CRC deaths prevented and colonoscopies performed in this program, compared to a gFOBT-only program. The family history-based program prevented substantially more deaths than the gFOBT program, with an acceptable increase in colonoscopy demand, and therefore seems a good strategy to increase the effectiveness of gFOBT screening programs.

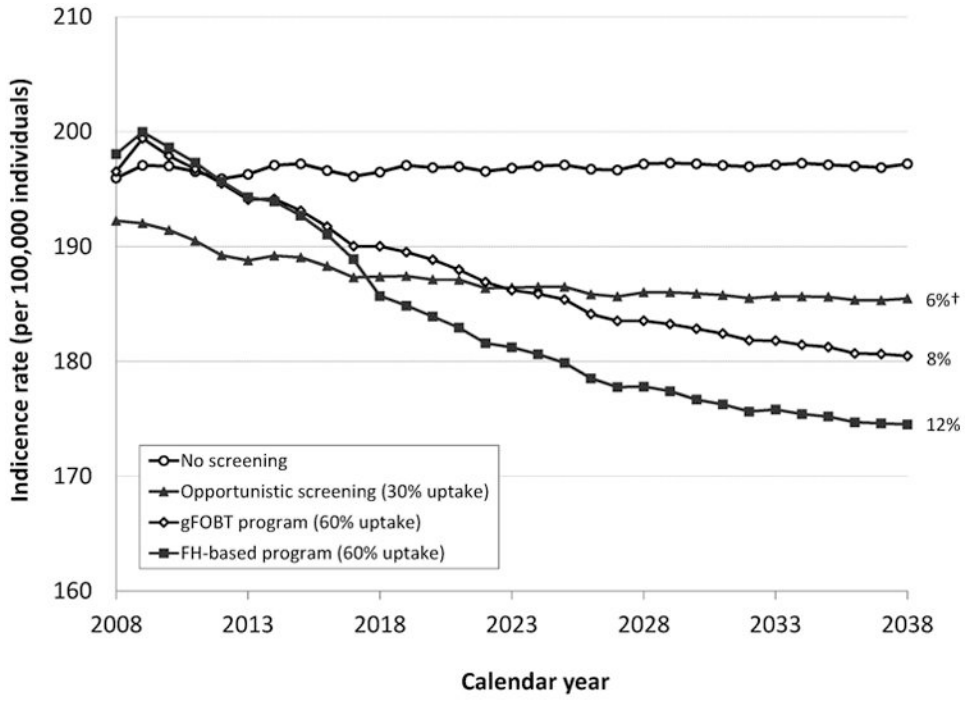

Figure 1.

Age adjusted* CRC incidence rate per 100,000 individuals aged 50 years and older, after implementing screening programs with and without family history-based screening in Ontario.

CRC: colorectal cancer; gFOBT: guaiac fecal occult blood test; FH: family history.

*The data are age adjusted to the 1991 Canadian Standard Population aged 50 years and older.

In the model we did not take into account historical changes in risk factor prevalence or CRC relative survival, therefore any simulated changes in CRC incidence and mortality are attributable solely to changes in screening behavior. The no screening scenario provides an estimate of background CRC risk in the absence of screening.

†Numbers behind the curves indicate the CRC incidence reduction of the screening scenarios compared the no screening in the year 2038.

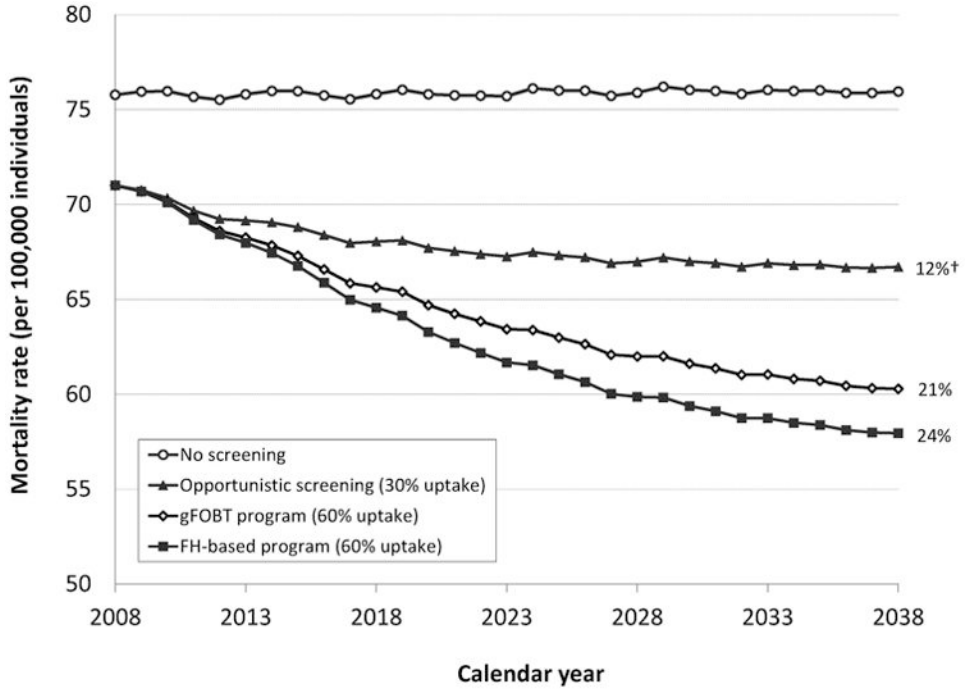

Figure 2.

Age adjusted* CRC mortality rate per 100,000 individuals aged 50 years and older, after implementing screening programs with and without family history-based screening in Ontario.

CRC: colorectal cancer; gFOBT: guaiac fecal occult blood test; FH: family history.

*The data are age adjusted to the 1991 Canadian Standard Population aged 50 years and older.

In the model we did not take into account historical changes in risk factor prevalence or CRC relative survival, therefore any simulated changes in CRC incidence and mortality are attributable solely to changes in screening behavior. The no screening scenario provides an estimate of background CRC risk in the absence of screening.

†Numbers behind the curves indicate the CRC mortality reduction of the screening scenarios compared the no screening in the year 2038.

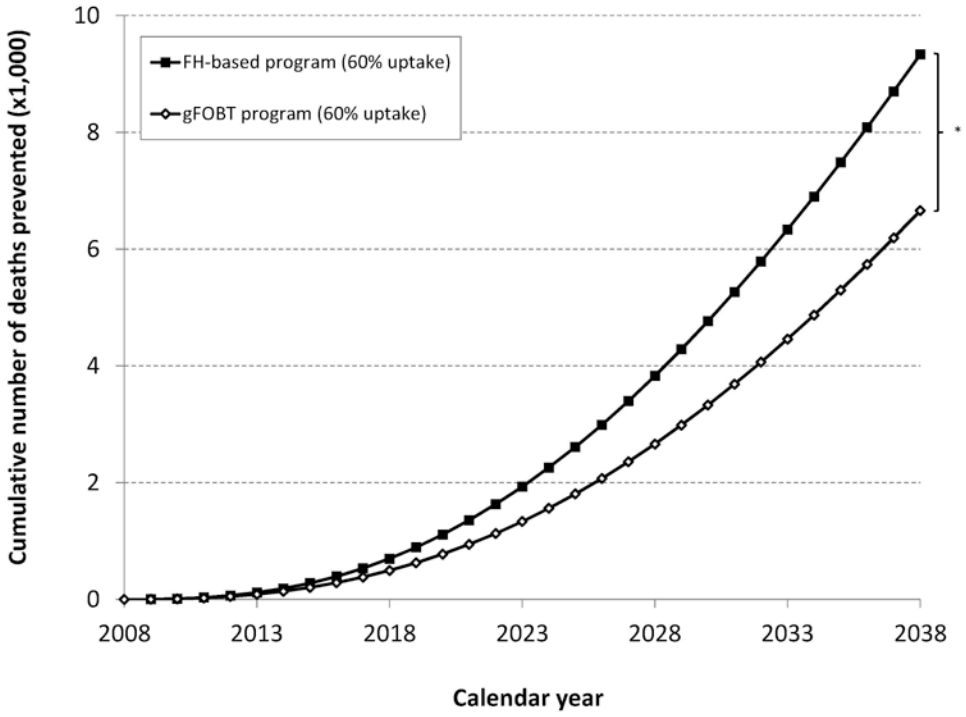

Figure 3.

Cumulative number of CRC deaths prevented in the population aged 50 years and older, after implementing screening programs with and without family history-based screening in Ontario, compared to opportunistic screening.

CRC: colorectal cancer; gFOBT: guaiac fecal occult blood test; FH: family history.

*Added effect the family history-based program, compared to the gFOBT program: 2,700 additional CRC deaths were prevented by 2038.

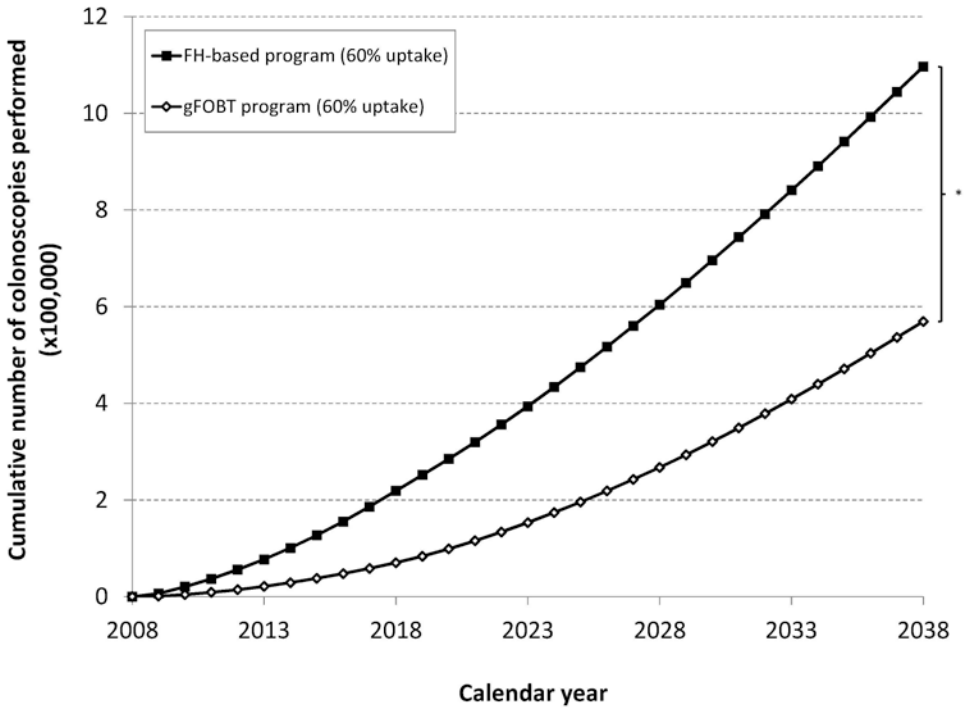

Figure 4.

Cumulative number of colonoscopies performed in the population aged 50 years and older, after implementing screening programs with and without family history-based screening in Ontario, compared to opportunistic screening.

CRC: colorectal cancer; gFOBT: guaiac fecal occult blood test; FH: family history.

*Added effect the family history-based program, compared to the gFOBT program: 530,000 additional colonoscopies were performed by 2038.

Table 1

Overview of the main assumptions in the base case and sensitivity analyses.

Variable	Base case analysis	Sensitivity analyses
Proportion of population with a family history of CRC	11%[13]	8% (low value), and 14% (high value)
RR of those with a family history of CRC compared to general population	Average RR = 2.24[14]	1.62 (low value), and 2.86 (high value)
CRC relative survival	Based on data from SEER[12], assumed to be similar for average and increased risk individuals	10% improved survival for increased risk individuals[15]
Adherence to diagnostic and surveillance colonoscopies	71%[5] and 80% (assumption) respectively	85% uptake for both diagnostic and surveillance colonoscopies
Dependency of gFOBT results in sequential screening rounds	None	74% of the large adenomas (≥10 mm) that are not detected, will not be detected in the next screening round [16]
Screening history (1990-2008)	Screening uptake gradually increased to 30% in 2008. We assumed individuals with a family history received ten-yearly colonoscopy, and average risk individuals received biennial gFOBT.[5]	15% of the population (both average and increased risk) who did not participate in CRC screening before the program, get a colonoscopy unrelated to CRC screening 5-10 years before the start of the screening program
Screening uptake during program (2008-2038)	- Average risk population: Increasing gradually from 30% to 60% over approximately 10 years. - Increased risk population: Increasing gradually from 30% to 60% over approximately 10 years.	Varying for both populations independently from 30% to 100%, at 10% increments.
Average risk screening during program (between age 50-74 years)	Biennial gFOBT (Hemoccult II)	**1** annual gFOBT **2** biennial FIT50 **3** biennial FIT100 **4** 5-yearly sigmoidoscopy **5** annual Hemoccult Sensa **6** 10-yearly colonoscopy
Increased risk screening during program (between age 50-74 years)	10-yearly colonoscopy	-

RR: relative risk; CRC: colorectal cancer; SEER: Surveillance, Epidemiology, and End-Results database; gFOBT: guaiac fecal occult blood test; FIT50: fecal immunochemical test, 50 ng Hb/ml cut-off value; FIT100: fecal immunochemical test, 100 ng Hb/ml cut-off value.

Table 2

Overview of the sensitivity analyses. Cumulative number of CRC deaths prevented and colonoscopies performed by 2038 in the screening programs with and without family history-based screening in Ontario, compared to opportunistic screening.*

Scenario	Additional CRC deaths prevented (×1,000)			Additional colonoscopies performed (×100,000)		
	gFOBT program (A)	FH-based program (B)	Difference (B-A)	gFOBT program (A)	FH-based program (B)	Difference (B-A)
Base case	6.7	9.3	2.7 (40%)	5.7	11.0	5.3 (93%)
RR for CRC among those with a family history: 2.24 → 1.62	6.6	8.6	1.9 (29%)	5.7	10.8	5.1 (90%)
RR for CRC among those with a family history: 2.24 → 2.86*	6.7	10.1	3.4 (50%)	5.7	11.0	5.4 (95%)
Proportion at increased risk: 11% → 8%†	6.4	8.3	1.9 (31%)	5.6	9.4	3.8 (68%)
Proportion at increased risk: 11% → 14%†	6.9	10.3	3.4 (49%)	5.8	12.5	6.7 (116%)
Uptake rate diagnostic and surveillance colonoscopies: 71%/80% → 85%/85%	7.7	10.2	2.5 (32%)	6.6	11.9	5.3 (80%)
10% increased CRC survival for all increased risk individuals	6.5	8.9	2.4 (37%)	5.7	11.0	5.3 (93%)
15% of the population get a colonoscopy unrelated to CRC screening before the start of the screening program	5.1	7.4	2.3 (44%)	5.1	10.0	5.0 (98%)
Sensitivity of FH assessment: 100% → 50%	6.7	8.0	1.3 (20%)	5.7	8.3	2.6 (46%)
Dependency of gFOBT test results between screening rounds	5.7	8.6	2.9 (51%)	4.9	10.4	5.5 (111%)
Biennial gFOBT replaced by:						
•Annual gFOBT	10.5	12.2	1.7 (16%)	10.5	15.0	4.6 (44%)
•Biennial FIT50	12.7	13.9	1.1 (9%)	12.5	16.6	4.1 (33%)
•Biennial FIT100	11.0	12.6	1.6 (14%)	8.4	13.1	4.7 (55%)
•5-yearly sigmoidoscopy	10.7	12.3	1.6 (15%)	8.4	12.5	4.1 (48%)
•Annual Hemoccult Sensa	15.6	16.0	0.4 (3%)	24.9	27.7	2.8 (11%)
10-yearly colonoscopy screening for all (including average risk individuals)	-	17.3	-	-	50.6	-

CRC: colorectal cancer; gFOBT: guaiac fecal occult blood test; FH: family history; FIT50: fecal immunochemical test, 50 ng Hb/ml cut-off value; FIT100: fecal immunochemical test, 100 ng Hb/ml cut-off value

Base case: base case scenario; RR for CRC among those with a family history: 2.24 → 1.62, relative risk of individuals with a family history of CRC is assumed 1.62 compared to the general population (base case value: 2.24); RR for CRC among those with a family history: 2.24 → 2.86, the relative risk of individuals with a family history of CRC is assumed 2.86 compared to the general population (base case value: 2.24); Proportion at increased risk: 11% → 8%, 8% of the population is considered to be at increased risk because of a family history of CRC (base case value: 11%); Proportion at increased

risk: 11% → 14%, 14% of the population is considered to be at increased risk because of a family history of CRC (base case value: 11%); Uptake rate diagnostic and surveillance colonoscopies: 71%/80% → 85%/85%, the uptake rate of both diagnostic and surveillance colonoscopies was increased to 85% (base case value: 71% and 80% respectively); 10% increased CRC survival for all increased risk individuals, age- and stage-specific CRC relative survival in individuals with a family history is improved by 10%; 15% of the population get a colonoscopy unrelated to CRC screening before the start of the screening program, 15% of the population who did not participate in CRC screening prior to the program (but who would start screening during the program) get a colonoscopy unrelated to CRC screening 5-10 years before the start of the screening program; Sensitivity of FH assessment: 100% → 50%, the family history assessment was only able to identify 50% if the increased risk individuals (those individuals with a false negative family history assessment were assumed to receive gFOBT instead of colonoscopy screening); Dependency of gFOBT test results between screening rounds, 74% of all large adenomas (≥10 mm) that are not detected by gFOBT, will not be detected in the next screening round[16]; Biennial gFOBT replaced by: annual gFOBT/biennial FIT50/biennial FIT100/5-yearly sigmoidoscopy/annual Hemocccult Sensa, biennial gFOBT screening was replaced by either annual gFOBT, biennial fecal immunochemical test (FIT) at a cut-off level of 50 ng Hb/ml, biennial FIT at a cut-off level of 100 ng Hb/ml, five-yearly sigmoidoscopy, or annual Hemoccult Sensa; 10-yearly colonoscopy screening for all (including average risk individuals); all screening participants are screened with 10-yearly colonoscopy screening.

*Results include events in the population aged 50 years and older.

†[x]→[y]: [x] represents the base case value, and [y] represents the alternative value assumed in the sensitivity analysis.