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How should individuals with a false-positive fecal occult blood test for colorectal cancer be managed? A decision analysis

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Abstract

Several industrialized nations recommend fecal occult blood testing (FOBT) to screen for colorectal cancer (CRC), but corresponding screening guidelines do not specify how individuals with a prior false positive FOBT result (fpFOBT) should be managed in terms of subsequent CRC screening. Accordingly, we conducted a decision analysis to compare different strategies for managing such individuals.

We used a previously-developed CRC microsimulation model, SimCRC, to calculate life-years and the lifetime number of colonoscopies (as a measure of required resources) for a cohort of 50-year-olds to whom FOBT-based CRC screening is offered annually from age 50 to 75. We compared three management strategies for individuals with a prior fpFOBT: 1) resume screening in 10 years with 10-yearly colonoscopy (SwitchCol_long); 2) resume screening in 1 year with annual FOBT (ContinueFOBT_Short); and 3) resume screening in 10 years (i.e., the recommended interval following a negative colonscopy) with annual FOBT (ContinueFOBT_long). We performed sensitivity analyses on various parameters and assumptions.

When using different management strategies for individuals with a prior fpFOBT the variation in the number of life-years gained relative to no screening was less than 2%, while the variation in the lifetime number of colonoscopies was 23% (percentages are calculated as the maximum difference across strategies divided by the lowest number across strategies). The ContinueFOBT_long strategy showed the lowest lifetime number of colonoscopies per life-year gained even when key assumptions were varied.

In conclusion, the ContinueFOBT_long strategy was advantageous regarding both clinical benefit and required resources. Specifying an appropriate management strategy for individuals with a

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prior fpFOBT may substantially reduce required resources within a FOBT-based CRC screening program without limiting its effectiveness.

Keywords

colorectal cancer; screening; fecal occult blood

INTRODUCTION

An increasing number of industrialized nations recommend the use of fecal occult blood testing (FOBT) to screen for colorectal cancer (CRC) (1,2), which has been shown to reduce both incidence and mortality of the disease (3–6). Corresponding screening guidelines typically specify both the target age range for screening and the screening interval and recommend colonoscopy for diagnostic follow-up of positive FOBT results. If a positive FOBT result is found to be a "*true* positive", i.e., colorectal neoplasia is detected on follow-up colonoscopy, there are detailed recommendations that specify the colonoscopic surveillance of such individuals (7–9).

However, if a positive FOBT result is found to be a "*false* positive" (for example caused by hemorrhoids or the use of non-steroidal anti-inflammatory drugs), i.e., no adenomas or CRC are detected at the follow-up colonoscopy, it is less clear how to manage such individuals regarding further CRC screening. Guidelines in the US and Germany do not specify whether individuals with a prior false positive FOBT result (fpFOBT) should switch to screening colonoscopy or whether they should continue with FOBT screening and if so, when the next FOBT should be performed (7–9). The bowel cancer screening programme in the UK recommends that individuals with a prior fpFOBT re-enter the programme, i.e., they should continue with FOBT screening after 2 years (10), while the Dutch advisory report on CRC screening recommends continuing with FOBT screening after 10 years (11).

If continuing screening with FOBT is recommended, it is important to question the assumption of conditional independence of sequential testing, because individuals with a prior fpFOBT result might be more likely to have a second positive result at repeated testing as a result of a persistent source of gastrointestinal bleeding. To address these issues, we performed a decision analysis to compare different strategies for managing individuals with a prior fpFOBT, considering potential deviations from the assumption of conditional independence of sequential testing.

METHODS

We performed a decision analysis of population-based FOBT screening for CRC to compare different management strategies for individuals with a fpFOBT result. We used a previously developed CRC microsimulation model, SimCRC (Simulation Model of Colorectal Cancer) (12–14) to calculate the life-years as well as the lifetime number of colonoscopies (as an indicator for required resources and risk for complications) for each strategy. The lifetime number of colonoscopies considers all colonoscopies that are related to the screening

program, including those for follow-up of positive FOBTs and those for lifelong surveillance of individuals in whom adenomas have been detected and removed.

Model description

Appendix I describes the SimCRC model and a standardized model profile is available at http://cisnet.cancer.gov/colorectal/profiles.html. In brief, the model simulates the life histories of a large population of individuals from birth to death. The model has a natural history component and a screening component.

Natural history component—The model's natural history component simulates the adenoma-carcinoma pathway in the absence of screening. Simulated individuals are at risk of developing one or more colorectal adenomas during their life, some of which may further progress to preclinical CRC. Preclinical cancer may progress from stage I through stage IV and has the chance of being diagnosed by symptoms at any stage. Survival from CRC depends on the stage at diagnosis and is based on data from the Surveillance, Epidemiology, and End Results (SEER) program (15). Individuals are at risk of dying from causes other than CRC based on all-cause mortality estimates from US life tables (16). The natural history component of the model was calibrated to data on adenoma prevalence, size, and location from autopsy studies (17–26) and to SEER program data on CRC incidence for 1975–1979, which was before the introduction of CRC screening (15).

Screening component—Different CRC screening strategies can be superimposed on the natural history component to estimate the effectiveness of screening in terms of life-years gained relative to no screening, and to estimate the resources required for screening. A simulated individual *with* an adenoma or CRC has a chance of having it detected through screening. All individuals with an adenoma detected were assumed to undergo colonoscopy surveillance according to the guidelines of the U.S. Multi-Society Task Force (7,8), which recommend a surveillance interval of 3 or 5 years depending on the number and size of adenomas detected at the most recent colonoscopy. We assumed that colonoscopy surveillance continues until a diagnosis of colorectal cancer or death. Non-adenomatous polyps are not modeled explicitly, but their detection is reflected in the false-positive rate of the test. The model incorporates the risk for fatal complications associated with perforation during colonoscopy (Table 1). The model also considers that some colonoscopies may be incomplete and need to be repeated to ensure visualization of the entire colon, which was assumed to affect 5% of colonoscopies (2 colonoscopies were counted in this case). The model has been validated against the long-term reductions in incidence and mortality of CRC with annual FOBT in the Minnesota Colon Cancer Control Study (3,4,27) and showed good concordance with the trial results.

Screening strategy and management strategies for individuals with a false positive FOBT

For the present analysis, we simulated a cohort of individuals to whom FOBT-based CRC screening is offered annually from ages 50 to 75. We considered three commonly used FOBTs - Hemoccult II, Hemoccult SENSA and immunochemical FOBT (FIT) – that differ in terms of test characteristics. We used established estimates for test characteristics of these FOBTs (28) and of colonoscopy (29), as well as for mortality rate of colonoscopy (Table 1).

In the base-case analysis we assumed 100% adherence with FOBT and with the recommended follow-up and surveillance colonoscopies, which was subjected to sensitivity analysis as described below.

A simulated individual *with* an adenoma or CRC has a chance of having it detected through a (true) positive FOBT result followed by colonoscopy, depending on the sensitivity of FOBT and of follow-up colonoscopy. Follow-up colonoscopy may also fail to detect the lesion causing the positive FOBT, depending on the sensitivity of colonoscopy for adenomas and CRC. Screened individuals *without* an adenoma or CRC may have a (false) positive FOBT followed by (unnecessary) colonoscopy, depending on the specificity of FOBT. The comparison of strategies for managing individuals with a fpFOBT is the focus of this analysis and is described in detail below.

We compared annual FOBT screening starting at age 50 with three different alternatives for managing individuals who experience a fpFOBT during the program (Figure 1):

A. Switching to screening colonoscopy with a 10-year interval, starting 10 years after the fpFOBT (SwitchCol_long)

B. Continuing FOBT screening with the next test being offered according to the FOBT screening interval, i.e., one year after the fpFOBT in the base-case analysis (ContinueFOBT_short)

C. Continuing FOBT screening with the next test being offered 10 years after the fpFOBT (i.e., the recommended interval following a negative colonoscopy) (ContinueFOBT_long).

In the base-case analysis of the strategies ContinueFOBT_short (B) and ContinueFOBT_long (C) we assumed conditional independence of sequential testing, i.e., the false positive rate (100%-specificity) was assumed to be the same among individuals with and without a prior fpFOBT.

Sensitivity analyses

The main focus of our sensitivity analyses was to consider potential deviations from the assumption of conditional independence of sequential testing for individuals with a prior fpFOBT, which is relevant for strategies that continue FOBT screening, i.e., ContinueFOBT_short (B) and ContinueFOBT_long (C). We considered different scenarios in which individuals with a prior fpFOBT are more likely to get a positive FOBT result than individuals without a prior fpFOBT. We assumed that the false-positive rate in individuals with a prior fpFOBT is increased by 5%, 10% and 15%, respectively, compared to individuals without a prior fpFOBT (Figure 1). Individuals with a prior fpFOBT who do not develop adenomas afterwards – the majority – are thus assumed to be more likely to get a false positive test at repeated testing, i.e., specificity in those individuals is reduced. Likewise, individuals with a prior fpFOBT who develop one or more adenomas afterwards or who bear lesions that were missed at follow-up colonoscopy – the minority – are assumed to be more likely to get a positive test result at repeated testing due to unspecific bleeding, leading to chance detection of the lesion.

Furthermore, we performed sensitivity analyses in which we considered no upper age limit for screening (compared to an upper age limit of 75 in the base-case analysis) and in which screening was offered biennially (instead of annually as in the base-case analysis). We also varied the sensitivity of colonoscopy according to a meta-analysis by van Rijn et al. (29) (Table 1). Since we compared the management strategies for three FOBTs with different performance characteristics, we did not conduct further sensitivity analyses on performance characteristics of each of the three FOBTs. In additional sensitivity analyses, we assumed the mortality rate of colonoscopy to be zero in order to assess the impact of this parameter on the effectiveness of the different strategies for managing individuals with a prior fpFOBT (Table 1). To consider scenarios of imperfect adherence, we explored the impact of overall adherence rates of 50% and 80%. For these analyses, we assumed that the population consists of 4 groups with different screening behavior: those who are never screened and those with low, moderate, and high adherence; 10% of the population was in the never-screened group and 30% were in each of the other groups. The proportion of the population who was adherent at each screening round was randomly composed of individuals from the three groups with low, moderate and high adherence, to come up with a final overall adherence of 50% and 80%, respectively. We assumed that adherence with follow-up and surveillance was 75%, 85%, and 95% for those with low, moderate, and high adherence, respectively, and that individuals remain in their screening behavior group.

RESULTS

Figure 2 illustrates the results of the base-case analyses for annual screening with Hemoccult II, Hemoccult SENSA and FIT, respectively, comparing annual FOBT screening with three different alternatives for managing individuals with a prior fpFOBT. As expected based on the tests' sensitivity, Hemoccult SENSA and FIT were equally effective, both saving more life-years than Hemoccult II. The lifetime number of colonoscopies (as a measure of required resources) was generally highest for the FOBT with the lowest specificity (that is, Hemoccult SENSA) and lowest for the FOBT with the highest specificity (that is, Hemoccult II).

Within each type of FOBT, the number of life years gained (LYG) relative to no screening was highest for the ContinueFOBT_short strategy and lowest for the ContinueFOBT_long strategy, with differences of 1.7, 5.1, and 3.9 LYG (expressed per 1000 50-year-old individuals) for screening with Hemoccult II, Hemoccult SENSA, and FIT, respectively. Using different management strategies for individuals with a prior fpFOBT thus resulted in a variation of less than 2% in the number of LYG relative to no screening (percentages are calculated as the maximum difference in LYG across strategies divided by the lowest number of LYG across strategies).

The lifetime number of colonoscopies was highest for the SwitchCol_long strategy and lowest for the ContinueFOBT_long strategy. The difference in the number of colonoscopies between these strategies was 272, 522, and 455 (expressed per 1000 50-year-old individuals) for screening with Hemoccult II, Hemoccult SENSA, and FIT, respectively. Using different management strategies for individuals with a prior fpFOBT thus resulted in a variation of up to 23% in the lifetime number of colonoscopies related to the screening program

(percentages are calculated as the maximum difference in the number of colonoscopies across strategies divided by the lowest number of colonoscopies across strategies) (Figure 2, Appendix II).

For all three tests, the SwitchCol_long strategy resulted in more colonoscopies over a lifetime but was less effective (i.e., saved fewer life-years) than the ContinueFOBT_short strategy. The ContinueFOBT_short strategy saved 0.7%, 2.0%, and 1.5% more life-years compared to the ContinueFOBT_long strategy, but also required 5%, 22%, and 14% more colonoscopies for screening with Hemoccult II, Hemoccult SENSA and FIT, respectively.

Sensitivity analyses

The ContinueFOBT_short strategy was most influenced by deviations from the assumption of conditional independence of sequential testing. The lifetime number of colonoscopies required for this strategy strongly increased when we assumed slight deviations from the assumption of conditional independence of sequential FOBT testing and exceeded the lifetime number of colonoscopies required for the SwitchCol_long strategy (Figure 3, Appendix II). When individuals with a prior fpFOBT were assumed to be 5% more likely to get a positive FOBT result compared to individuals without a prior fpFOBT (corresponding to a decrease in specificity by 5%), the lifetime number of colonoscopies increased for all three tests by 15% compared to the base-case analyses, which assumed conditional independence of sequential testing. The lifetime number of colonoscopies further increased when we assumed individuals with a prior fpFOBT to be 10% and 15% more likely to get a positive FOBT result compared to individuals without a prior fpFOBT. By contrast, the difference in effectiveness between the various scenarios and strategies remained small.

The lifetime number of colonoscopies required for the ContinueFOBT_long strategy was less affected when we assumed deviations from the assumption of conditional independence. Even when we assumed individuals with a prior fpFOBT to be 15% more likely to get a positive FOBT result compared to individuals without a prior fpFOBT, the strategy still required 8–10% fewer colonoscopies compared to the SwitchCol_long strategy for all three FOBTs. Again, the difference in terms of effectiveness between the various scenarios was small relative to the difference in terms of colonoscopy use (Figure 3, Appendix II).

The above-described patterns were similar when we varied the target age range for screening, the screening interval, the sensitivity of colonoscopy, the mortality rate of colonoscopy and the adherence with screening in sensitivity analyses (Appendix II).

DISCUSSION

Our decision analysis suggests that the management of individuals with a prior fpFOBT affects the resources that are required for FOBT-based CRC screening to a greater degree than it affects the effectiveness of the program. The lifetime number of colonoscopies related to the screening program varied by about 20% when different management strategies for individuals with a prior fpFOBT were used, while the life-years gained varied by less than 2%. Our findings indicate the importance of an appropriate strategy for the

management of individuals with a prior fpFOBT. This contrasts to the fact that several CRC screening guidelines do not devote any attention to this issue.

In the absence of guidelines, clinicians are left on their own regarding the management of individuals with a fpFOBT. To our knowledge, there are no reports on corresponding practice patterns. Decision analyses on CRC screening conducted for the US Preventive Services Task Force assumed that individuals with a fpFOBT switch to screening colonoscopy with a 10-year interval (13,14), corresponding to the SwitchCol_long strategy. Our results, however, showed that this strategy required the most resources without being more effective than the other strategies under the assumption of conditional independence of sequential FOBT testing. The bowel cancer screening programme in the UK recommends that individuals with a prior fpFOBT re-enter the programme (10), i.e., they are re-invited to the next FOBT screening round, corresponding to the ContinueFOBT_short strategy. The resources required for the ContinueFOBT_short strategy markedly increased when individuals with a prior fpFOBT were assumed to be slightly more likely to test positive compared to individuals without a prior fpFOBT. By contrast, the ContinueFOBT_long strategy, which assumes that individuals with a prior fpFOBT continue with FOBT screening10 years after the fpFOBT, was rather robust in this regard and required fewer colonoscopies than the other strategies. It thus appeared to be a reasonable strategy for managing individuals with a prior fpFOBT when considering required resources, effectiveness as well as the uncertainty regarding the assumption of conditional independence of sequential testing.

We systematically explored the relevance of potential deviations from this assumption - which typically underlies models that simulate FOBT-based CRC screening programs -in the context of our research question as there are arguments supporting that individuals with a prior fpFOBT may have an increased likelihood of testing positive again. For example, some diagnostic studies suggested that the positivity rate of FOBTs is slightly higher among users than among non-users of aspirin (including low-dose aspirin) and other non-steroidal anti-inflammatory drugs (30–32). The use of low-dose aspirin for prevention of cardiovascular disease is common in the elderly, a group that is in the target age range for CRC screening. A certain proportion of individuals may thus have a positive FOBT due to this drug use, and if they are tested again their likelihood of getting another positive result may be increased since the use of low-dose aspirin is typically long-lasting. Apart from that, hemorrhoids are a common condition in the target age range for CRC screening (33). Positivity rates of FOBT among individuals with hemorrhoids have been reported to be 10% and higher (34,35). Since this health condition is often persistent, individuals with hemorrhoids who once tested positive at FOBT may also have a higher likelihood of getting another positive result if they continue with FOBT.

We found that the management strategy for individuals with a prior fpFOBT matters in terms of required resources, which appears plausible given that the group of individuals who are at risk of getting a false positive test result, i.e., those who do not have CRC or adenomas, represent the majority of the screening population. Also, our finding that the management strategy for individuals with a prior fpFOBT has a negligible impact in terms of health effects appears plausible in view of epidemiological evidence suggesting that the

risk of CRC among individuals with a prior negative sigmoidoscopy or colonoscopy (the latter applies to individuals with a prior fpFOBT) is very low for up to 20 years or longer (36–40). This was also observed in settings where the prior negative endoscopy has not been performed for screening, but mainly for diagnostic purposes (36,37,40), including the follow-up of positive fecal occult blood tests or gastrointestinal symptoms. Even the prevalence of advanced adenomas has been reported to be very low for several years after a negative colonoscopy (39,40). These findings from epidemiological observational studies raised the debate whether individuals with a prior negative colonoscopy need further CRC screening at all, but this is a separate research question that needs careful consideration, which was beyond the scope of our analysis.

We have addressed the question of how to manage individuals with a prior false positive FOBT with respect to further CRC screening. Whether or not a false positive FOBT may lead to further diagnostic work-up, e.g. esophagogastroduodenoscopy, was thus not within the scope of our analysis. According to a recent review article, the current body of evidence is insufficient to recommend for or against routine esophagogastro-duodenoscopy as a means of detecting gastric or esophageal cancers for patients with a positive FOBT but a negative follow-up colonoscopy in a population-based CRC screening program. The authors of this review article suggested that the decision regarding further diagnostic work-up beyond the colorectum should be individualized and based on clinical judgement (41).

Our analysis has several limitations that need to be considered. First, we used the number of colonoscopies as a surrogate outcome for required resources, although this does not exactly reflect all resources that are required for screening. However, we aimed at expressing the outcomes of our analyses in as general terms as possible since our findings could be relevant to several countries that use FOBT as a tool for CRC screening. The costs of colonoscopy, which are a multiple of the costs of the FOBT, strongly vary across countries and account for the majority of the costs related to the screening program.

Second, it might be of concern that some individuals with a prior fpFOBT have been misclassified by follow-up colonoscopy and bear colorectal neoplasia that has not been detected. To consider this potential misclassification we based our base-case estimates on test characteristics of colonoscopy on a meta-analysis of polyp miss rate determined by tandem colonoscopy (29) and subjected them to sensitivity analyses. Furthermore, we considered that some colonoscopies may be incomplete and need to be repeated to ensure visualization of the entire colon. Nevertheless, the validity and quality of colonoscopy may differ between settings, but given that epidemiological studies across different settings confirm the low risk of colorectal neoplasia after a negative colonoscopy, we feel that our analysis took this potential misclassification sufficiently into account.

Third, in the context of our research question it was important to consider potential scenarios in which individuals with a prior fpFOBT have an increased chance of getting another positive test result if they continue screening with FOBT. In the lack of direct evidence from longitudinal studies we considered these scenarios in sensitivity analyses supported by indirect evidence from diagnostic cross-sectional studies as mentioned above.

Fourth, we have not conducted probabilistic sensitivity analysis to consider the uncertainty in parameter estimates, but we assessed the robustness of our conclusions by systematically varying relevant model parameters and assumptions in a discrete manner.

Fifth, we did not consider potential differences in adherence levels between the three alternatives for managing individuals with a prior fpFOBT, since there are no observational data we could refer to. On the one hand patient preferences could play a role in this regard. On the other hand, the availability of organizational structures allowing for medical record linkage and tracking may be important to ensure that individuals continue with screening only after a certain time interval has passed.

As described above we aimed at expressing the outcomes of our analyses in as general terms as possible since our findings could be relevant to several - typically industrialized - countries that offer CRC screening. The fact that we used US life tables and US data on CRC incidence and mortality is not expected to limit generalizability of our findings to other industrialized countries given that demographic patterns and trends in CRC incidence and mortality have been reported to be comparable in industrialized countries (42,43).

In conclusion, our decision analysis suggests that the choice of management strategy for individuals with a prior fpFOBT substantially affects the resources that are required for FOBT-based CRC screening, while it hardly affects the effectiveness of the program. Continuing with FOBT screening 10 years after the false positive test showed to be an advantageous strategy, and this finding was robust even when key assumptions were varied. Specifying an appropriate strategy to manage individuals with a prior fpFOBT may – on the one hand - save resources, that could – on the other hand – be redistributed to increase the effectiveness of FOBT-based CRC screening, e.g., by offering up-to-date FOBTs that have improved in terms of analytical robustness and diagnostic performance or by implementing an invitation system to increase adherence with screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and impact statement

- We conducted, for the first time, a decision analysis on the question of how to manage individuals with a prior false positive fecal occult blood test (FOBT) with respect to further colorectal cancer (CRC) screening. Continuing with FOBT screening 10 years after the false positive test showed to be the most advantageous strategy regarding both clinical benefit and required resources.
- Specifying an appropriate management strategy for individuals with a prior false positive FOBT result may substantially reduce required resources within a FOBT-based CRC screening program (by about 20%) without limiting its effectiveness. This finding may have implications on the further optimization of CRC screening programs and has relevance for scientists, clinicians and decision makers involved in CRC screening.

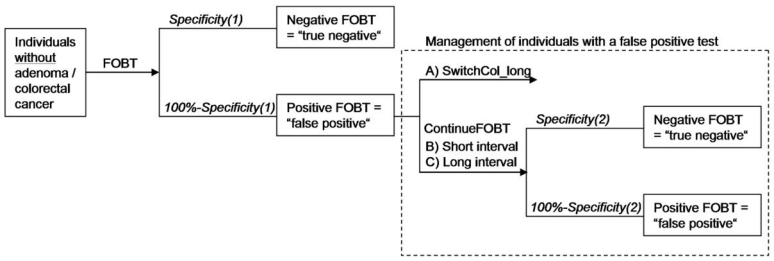

Figure 1.

Illustration of the model structure regarding different strategies for managing individuals with a false positive fecal occult blood test results with respect to further colorectal cancer screening.[1,2]

Abbreviations:

FOBT: fecal occult blood test; ContinueFOBT: continuing with FOBT screening 1 year (base-case analyses) or 2 years (sensitivity analyses) after the false positive FOBT result (short interval) or 10 years after the false-positive FOBT result (long interval); SwitchCol_long: Switching to screening colonoscopy with a 10-year interval, starting 10 years after the false positive FOBT result.

Footnotes:

[1]A minority of individuals may develop adenomas after the false positive test result or bear adenomas that have not been detected at follow-up colonoscopy, which is considered in the model as described in the methods section, but which is not depicted here.

[2]In the base-case analyses, specificity(1) and specificity(2) were assumed to be the same (corresponding to the assumption of conditional independence of sequential testing). In sensitivity analyses, specificity(2) was assumed to be lower than specificity(1) as described in the methods section.

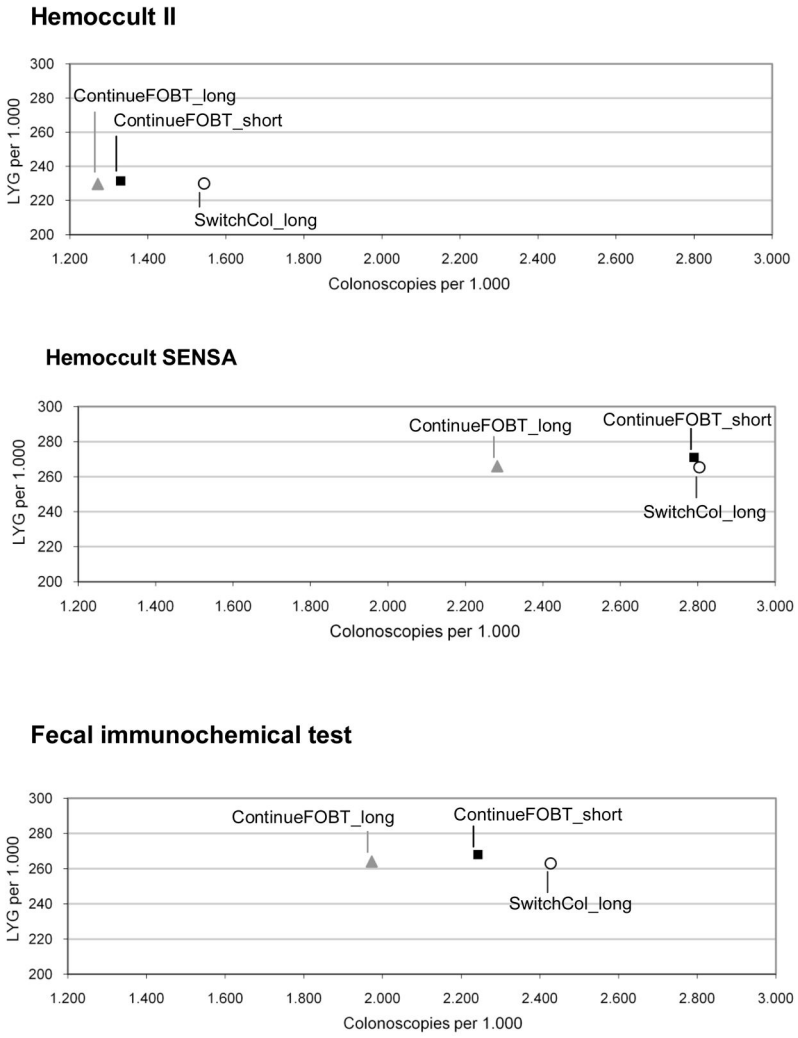

Figure 2.

Results of the base-case analyses regarding the comparison of different management strategies for individuals with a prior false positive result at screening with Hemoccult II, Hemoccult SENSA and a fecal immunochemical test, respectively (ContinueFOBT_long: gray triangle; ContinueFOBT_short: black square; SwitchCol_long: open circle). The outcomes are expressed per 1000 50-year old individuals.

Abbreviations:

LYG: life-years gained relative to no screening; ContinueFOBT_long: continuing with FOBT screening 10 years after the false-positive FOBT result; ContinueFOBT_short: continuing with FOBT screening 1 year after the false positive FOBT result; SwitchCol_long: switching to screening colonoscopy with a 10-year interval, starting 10 years after the false positive FOBT result.

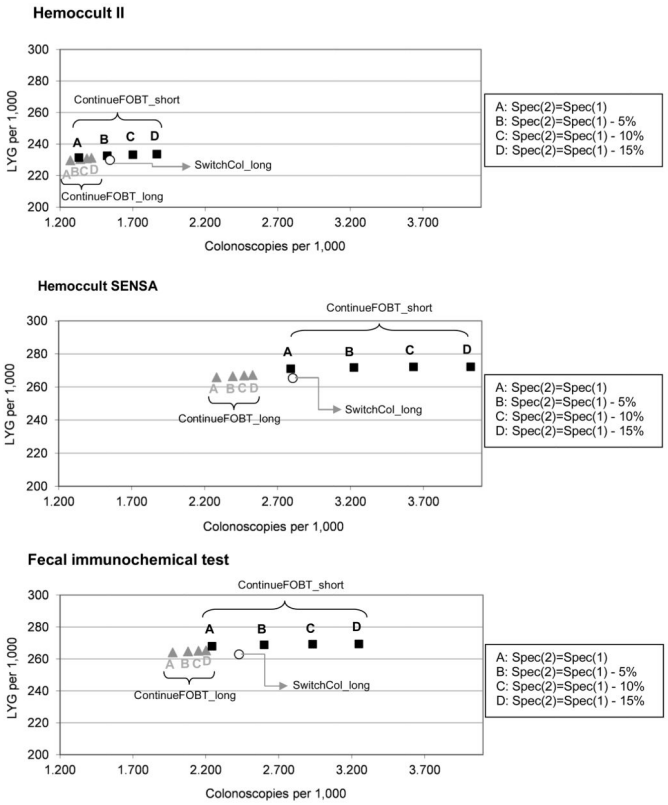

Figure 3.

Sensitivity analyses regarding the impact of potential deviations from the assumption of conditional independence of sequential testing among individuals with a prior false positive FOBT result for different management strategies (ContinueFOBT_long: gray triangle; ContinueFOBT_short: black square; SwitchCol_long: open circle). The outcomes are expressed per 1000 50-year old individuals. (abbreviations see next page)

Abbreviations:

LYG: life-years gained relative to no screening; Spec(1): specificity of the FOBT among individuals *without* a prior false positive FOBT result; Spec(2): specificity of the FOBT among individuals *with* a prior false positive FOBT result; ContinueFOBT_long: continuing with FOBT screening 10 years after the false positive FOBT result; ContinueFOBT_short: continuing with FOBT screening 1 year after the false positive FOBT result; SwitchCol_long: switching to screening colonoscopy with a 10-year interval, starting 10 years after the false positive FOBT result.

Table 1

Test characteristics used in the analyses

	Test characteristics, %	
Hemoccult II		
Sensitivity for adenomas ≤ 5 mm[1]	2.0	
Sensitivity for adenomas 6–9 mm	5.0	
Sensitivity for adenomas ≥ 10 mm	12.0	
Sensitivity for cancer	40.0	
Specificity[2]	98.0	
Hemoccult SENSA		
Sensitivity for adenomas ≤ 5 mm[1]	7.5	
Sensitivity for adenomas 6–9 mm	12.4	
Sensitivity for adenomas ≥ 10 mm	23.9	
Sensitivity for cancer	70.0	
Specificity[2]	92.5	
Fecal immunochemical test (FIT)		
Sensitivity for adenomas ≤ 5 mm[1]	5.0	
Sensitivity for adenomas 6–9 mm	10.1	
Sensitivity for adenomas ≥ 10 mm	22.0	
Sensitivity for cancer	70.0	
Specificity[2]	95.0	
Colonoscopy		
I) Base-case analyses		
Sensitivity for adenomas ≤ 5 mm	75.0	
Sensitivity for adenomas 6–9 mm	85.0	
Sensitivity for adenomas ≥ 10 mm	95.0	
Sensitivity for cancer	95.0	
Specificity	90.0	
Mortality rate	1 per 10,000	
II) Sensitivity analyses	**Best-case value**	**Worst-case value**
Sensitivity for adenomas ≤ 5 mm	79.0	70.0
Sensitivity for adenomas 6–9 mm	92.0	80.0
Sensitivity for adenomas ≥ 10 mm	99.0	90.0
Sensitivity for cancer	99.0	90.0
Specificity	Not varied	
Mortality rate	0	

[1]We assumed that small adenomas do not bleed and cannot be detected by fecal occult blood testing. The sensitivity for adenomas ≤ 5 mm is based on the false-positive rate (that is, 1-specificity)

[2]In sensitivity analyses, specificity of fecal occult blood testing among individuals with a prior false positive fecal occult blood test result was varied as described in the methods section.