Long-Term Impact of the Dutch Colorectal Cancer Screening Program on Cancer Incidence and Mortality—Model-Based Exploration of the Serrated Pathway

Marjolein J.E. Greuter1, Erhan Demirel1, Jie-Bin Lew2,3, Johannes Berkhof1, Xiang-Ming Xu2,3, Karen Canfell2,3, Evelien Dekker4, Gerrit A. Meijer3, and Veerle M.H. Coupé1

Abstract

Background: We aimed to predict the long-term colorectal cancer incidence, mortality, and colonoscopy demand of the recently implemented Dutch colorectal cancer screening program.

Methods: The Adenoma and Serrated pathway to Colorectal Cancer model was set up to simulate the Dutch screening program consisting of biennial fecal immunochemical testing (FIT) in individuals aged 55 to 75 years. The impact of screening and surveillance was evaluated under three sets of natural history assumptions differing in the contribution of the serrated pathway to colorectal cancer incidence. In sensitivity analyses, other assumptions concerning the serrated pathway were varied. Model-predicted outcomes were yearly colorectal cancer incidence, mortality, and colonoscopy demand per year.

Results: Assuming an aging population, colorectal cancer incidence under 30 years of screening is predicted to decrease by 35% and 31% for a contribution of 0% and 30% of the serrated pathway to colorectal cancer, respectively. For colorectal cancer mortality, reductions are 47% and 45%. In 2044, 110,000 colonoscopies will be required annually assuming no contribution of the serrated pathway (27 per 1,000 individuals in the screening age range). Including the serrated pathway influences predicted screening effectiveness if serrated lesions are neither detected nor treated at colonoscopy, and/or if colorectal cancers arising from serrated lesions have substantially lower survival rates than those arising from adenomas.

Conclusions: The Dutch screening program will markedly decrease colorectal cancer incidence and mortality but considerable colonoscopy resources will be required.

Impact: Predictions of long-term screening effectiveness are preferably based on both pathways to colorectal cancer to transparently describe the impact of uncertainties regarding the serrated pathway on long-term predictions. Cancer Epidemiol Biomarkers Prev; 25(1): 135–44. ©2015 AACR.

Introduction

Colorectal cancer screening significantly reduces colorectal cancer incidence and mortality, as demonstrated by large studies with a long follow-up period (1–4). The Netherlands has recently implemented a colorectal cancer screening program, consisting of biennial fecal immunochemical testing (FIT) in individuals aged 55 to 75 years. Individuals with a positive test outcome are referred for diagnostic colonoscopy during which detected colorectal cancer precursor lesions are removed. On the basis of the findings at diagnostic colonoscopy, individuals enter the surveillance program. To avoid an overload of colonoscopy services, a phased rollout is employed (5).

The expected benefits of this program, which concern the reduction in cancer cases and deaths, should be appropriately balanced against the burden of screening in terms of false-positive test results and invasive tests. This balance between benefit and burden can be estimated using mathematical models such as the Adenoma and Serrated pathway to Colorectal Cancer (ASCCA) model (6). The ASCCA model simulates the progression of adenomas to colorectal cancer by taking into account the growth architecture (7, 8). Besides the adenoma–carcinoma pathway, the model includes the serrated pathway to colorectal cancer as the malignant potential of serrated lesions is increasingly emphasized (9–14).

Although the adenoma–carcinoma pathway is reasonably well studied, the literature remains inconclusive regarding the natural history of the serrated pathway and the detection of serrated lesions by screening. It is still questioned whether hyperplastic polyps and sessile serrated adenomas (SSA) arise independently or that SSAs develop from hyperplastic polyps (14–16). Furthermore, estimates of the proportion of colorectal cancers that originate from serrated lesions range from 5% to 30%, based on genetic alterations (9–14). Regarding screening, it is hypothesized that detection of serrated lesions by FIT and colonoscopy is
hampered because these lesions are less likely to bleed compared with adenomas (17–19), have a flat appearance, and are more often located in the proximal colon (17, 20). Because the ASCCA model is the first model to include both pathways to colorectal cancer, this provides the unique opportunity to assess the impact of varying assumptions regarding the serrated pathway on long-term predictions of screening benefits and burden.

This study aims to predict the long-term colorectal cancer incidence, mortality, and colonoscopy demand of the Dutch screening program in combination with the revised surveillance guidelines as well as the impact of potentially influential but unknown model parameters on these predictions. Using the ASCCA model, we predict the impact of screening and surveillance between 2014 and 2044, comprising both the phased rollout and full implementation of the program.

Materials and Methods

ASCCA model

The structure and calibration of the ASCCA model are extensively described elsewhere (6). Figure 1 shows the model structure. In brief, the model incorporates two pathways to colorectal cancer: the adenoma–carcinoma pathway which models the progression of adenomas, and the serrated pathway which describes the development of hyperplastic polyps and SSAs. Individual health trajectories are simulated from age 20 until age 90 or death.

During their life, individuals can develop up to 10 adenomas and 10 serrated lesions. Because the relationship between hyperplastic polyps and SSAs is unclear (14, 15, 21, 22), the model includes two structural options for the serrated pathway. For the base-case model, we assume that hyperplastic polyps and SSAs arise independently. The alternative, that hyperplastic polyps are precursors of SSAs, is explored in sensitivity analyses. The growth in size for each lesion is modeled independently. For adenomas, also the development of high-grade dysplasia and villous components is taken into account. When a lesion has progressed to SSA or advanced adenoma, it can develop into colorectal cancer.

The contribution of the serrated pathway to colorectal cancer is assumed to be 15% in the base-case model (6). Four colorectal cancer stages for both asymptomatic and symptomatic tumors are included. Each year, asymptomatic tumors have the probability to progress to a more advanced stage or to become detected. Because screen-detected colorectal cancer has a better prognosis compared with symptom-detected colorectal cancer, we assigned different survival probabilities based on mode of detection, except for stage IV. The survival probabilities for symptom-detected colorectal cancer, which are based on the Dutch Cancer Registry, were adjusted based on a reported HR of 0.62 for screen-detected colorectal cancer compared with symptom-detected colorectal cancer (23).

The model is calibrated to the lower limit, mean, and upper limit of the 95% confidence intervals of the adenoma and serrated lesion prevalence as reported in the Dutch COlonoscopy or CT COlonography for Screening (COCOS) trial (24) and Dutch colorectal cancer incidence and mortality rates (25). This resulted in low, intermediate, and high prevalence parameter sets for each pathway. The intermediate prevalence parameter sets were used for the base-case analyses.

Dutch screening program and surveillance guidelines

The Dutch screening program involves biennial FIT screening combined with revised surveillance guidelines and was implemented in 2014. The rollout is phased; each year, new age groups are invited for screening until the program is fully implemented in 2019. From 2019, all individuals aged 55 to 75 years will be invited biennially. Individuals with a positive test outcome are referred for diagnostic colonoscopy during which all detected lesions are removed, with the exception of small hyperplastic polyps (<5 mm) located in the rectosigmoid. We assumed complete removal for all lesions and a small risk of dying due to the

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Figure 1.
Flowchart of the natural history model. Note that advanced adenoma is a definition and not a state in the model. The structure of the serrated pathway is flexible so both scenarios (1) hyperplastic polyps (HP) and SSAs develop independently and (2) SSAs originate from hyperplastic polyps, can be simulated.
procedure, i.e. 0.001% (26, 27). Postpolypectomy surveillance is guided by a risk score based on the number, size, and location of colorectal polyps encountered (28). This risk score determines the surveillance interval, i.e. 3 or 5 years. If the risk score equals zero, the individual returns to the screening program after 10 years. Individuals over 75 years will exit the surveillance program. It should be noted that the Dutch surveillance guideline is one of the first guidelines that explicitly recommends the removal of serrated lesions and surveillance for individuals with large serrated lesions.

Test characteristics
Table 1 summarizes key model parameters. Lesion-specific test characteristics for FIT were obtained by calibration as extensively described in a previous study (6). In short, for diminutive and serrated lesions, we assumed the positivity rate to be equal to one minus the specificity. The latter is based on results from Imperiale and colleagues showing that FIT sensitivity for serrated lesions was comparable to the false-positive rate (29). Then, we calibrated the specificity and the positivity rate for small and large adenomas against the positivity rate, detection rates, and positive predictive values as found in the Dutch pilot study (30). Because the Dutch COCOS trial reported a sensitivity of 33% for advanced adenoma (31), we used this as an indication of the positivity rate for large adenomas.

For colonoscopy, miss rates of 26%, 13%, and 2.1% for, respectively, diminutive, small, and large adenomas were applied (32). Miss rates for serrated lesions are not reported but are likely to be higher than those for adenomas due to their proximal location, pale color, and flat appearance (17, 20). We assumed that the miss rate for serrated lesions is 10% higher than the miss rate for adenomas.

Screening attendance
On the basis of the Dutch screening pilot evaluating three rounds of FIT screening (33), we set the overall participation rate of FIT screening at 63%. However, studies assessing participation over multiple rounds of stool-based testing found that screening attendance is heterogeneous as some individuals participate in (almost) every screening round, whereas others participate occasionally or only seldom (33–35). Therefore, we divided individuals into three groups: a high, low, and very low participation group (Table 1). We calibrated the percentage of individuals pertaining to each group and the participation rate within each group assuming that individuals remain in the same participation group over time. Calibration targets were derived from the screening pilot and consisted of overall participation per round, the percentage of individuals who participated in all rounds, and the percentage of individuals who participated at least once. For diagnostic and surveillance colonoscopy we assumed a participation rate of 96% (36).

Analyses
The ASCCA model was set up to simulate the Dutch screening program in combination with surveillance over a period of 30 years, independently from the presence and absence of serrated lesions. The probability of adenomas arising from serrated pathway was derived from the-incidence probabilities for colorectal caner arising from adenomas and serrated lesions arising from serrated lesions (39). The colorectal cancer survival probabilities were derived from the survival probabilities for colorectal cancer arising from serrated lesions (14, 15, 21, 22).
years; from the introduction of the program in 2014 to 2044 while accounting for the phased rollout. We adopted an open-model approach, which is suitable to assess temporal trends, by simulating multiple birth cohorts and combining the results. We accounted for population aging based on predictions of the Central Bureau of Statistics (37).

We evaluated a “no screening” scenario under the assumption that all colorectal cancers arise from adenomas. Furthermore, screening under three sets of natural history assumptions was evaluated, namely, (i) all colorectal cancers arise from adenomas, (ii) 85% of colorectal cancers arise from adenomas and 15% from serrated lesions, and (iii) 70% of colorectal cancers arise from adenomas and 30% from serrated lesions. We did not simulate a “no screening” scenario for different contributions of the serrated pathway to colorectal cancer because these were calibrated to the same natural history targets and, therefore, will lead to similar predictions. Model-predicted outcomes were colorectal cancer incidence and mortality per 100,000 individuals per year and the number of diagnostic and surveillance colonoscopies per year from 2014 until 2044.

Sensitivity analyses
To explore the impact of uncertainty regarding the serrated pathway, we varied structural and parametric assumptions. First, to gain insight into the maximally possible impact of the serrated pathway on model predictions of screening impact on colorectal cancer incidence and mortality, we assumed that serrated lesions or tumors arising from serrated lesions are not detected at all by screening. Second, we assumed that there is no co-occurrence of adenomas and serrated lesions in individuals. Third, we changed the miss rate for serrated lesions. We increased the miss rate assuming that the miss rate for serrated lesions is 25% higher than the miss rate for adenomas as well as decreased the miss rate assuming equal miss rates for all colorectal lesions (38). Fourth, the model was set up to reflect the hypothesis that hyperplastic polyps are precursor lesions of SSAs (14, 16); yearly incidence rates of SSAs were put to zero while the transition probability from hyperplastic polyps to SSA was calibrated to the age- and sex-specific prevalence of hyperplastic polyps and SSAs in the COCOS trial (24). Finally, we lowered the survival rate of colorectal cancers arising from serrated lesions by 10% per year because the existing but limited evidence suggests a worse prognosis for these colorectal cancers (39).

In addition, several sensitivity analyses were conducted. First, all base-case analyses were repeated with a low and high prevalence parameter set. Furthermore, we altered the overall participation rate of FIT screening to 40%, 80%, and 100% although maintaining the same proportion of individuals in each participation group as in the base-case scenario. Subsequently, we evaluated the impact of lowering compliance to surveillance to 80%. Finally, we evaluated the impact of changes in FIT characteristics by decreasing the specificity by 1% and increasing the sensitivity for small and large lesions by 5% and 10%, respectively.

Results
Impact on colorectal cancer incidence and mortality
Without screening, model-predicted colorectal cancer incidence in 2014 is 77 per 100,000 individuals per year and increases...
to 109 per 100,000 in 2044 due to aging of the Dutch population. Figure 2 shows for each of the four scenarios colorectal cancer incidence from 2013, which is the year before the screening program was introduced, to 2044. Screening first increases colorectal cancer incidence in all natural history scenarios compared with no screening due to the detection of prevalent yet asymptomatic tumors. In 2014, colorectal cancer incidence peaks at 104 cases per 100,000 for all three natural history scenarios. A second small peak is seen in 2017 due to the inclusion of a relatively old cohort in the program. After that, the incidence gradually decreases because of the removal of colorectal cancer precursor lesions. By 2044, colorectal cancer incidence has decreased to between 71 and 75 per 100,000 for the scenarios in which all colorectal cancers or 70% of colorectal cancers arise from adenomas, respectively. Thus, as the proportion of colorectal cancers arising from serrated lesions increases, the projected reduction in colorectal cancer mortality decreases (35%, 34%, and 31% for 0%, 15%, and 30% of colorectal cancers via the serrated pathway, respectively). However, differences are small.

Impact of screening in different birth cohorts

Because of the phased rollout, birth cohorts differ in the number of invited screening rounds leading to different screening effectiveness per cohort. To illustrate this, colorectal cancer incidence and mortality between 2014 and 2044 is shown in Fig. 3 for birth cohorts differing in number of screening invitations. As a reference, an unscreened cohort is plotted.

Colonoscopy resources

In 2009, 191,339 colonoscopies were performed in the Netherlands (40). Screening will evidently increase the colonoscopy demand; Fig. 4 shows the predicted number of diagnostic and surveillance colonoscopies performed per year due to the screening program. Thus, colonoscopies in high-risk individuals are not included, nor did we correct for a potential decrease in colonoscopy use outside the screening program because symptomatic individuals start participating in the program instead.

For diagnostic colonoscopies, the demand is comparable for all three natural history assumptions. The demand rapidly rises in the first years of the program and peaks in 2018 around 82,000. Then, the number of diagnostic colonoscopies...
gradually decreases to around 60,000 in 2044. Note that the number of diagnostic colonoscopies is directly related to the number of FIT-positive individuals. In the first 3 years of the program, around 30% and 22% of all diagnostic colonoscopies are due to a false-positive FIT when assuming that all or 70% of colorectal cancers arise from adenomas, respectively. These figures gradually increase over time to around 44% and 33% in 2044, respectively.

The first surveillance colonoscopies take place in 2017 after which the demand gradually increases. The demand peaks in 2033 around 56,000, 57,000, and 59,000 colonoscopies under the assumption that 0%, 15%, and 30% of colorectal cancers arise from serrated lesions, respectively (12.3, 12.6, and 12.9 per 1,000 individuals in the screening age range, respectively), followed by a gradual decrease.

Note that the impact of including the serrated pathway on colonoscopy demand is limited but is more apparent in the number of surveillance colonoscopies. This is due to the Dutch surveillance guidelines, which also recommend surveillance for individuals with large serrated lesions.
Table 2. Reduction in colorectal cancer incidence after 30 years of screening; base-case results and sensitivity analyses

<table>
<thead>
<tr>
<th>Parameter set</th>
<th>Reduction in colorectal cancer incidence (%)</th>
<th>Reduction in colorectal cancer mortality (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>100% of colorectal cancer via adenomas</td>
<td>85% of colorectal cancer via adenomas</td>
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<tr>
<td>No co-occurrence of A and SL</td>
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<tr>
<td>Higher miss rate SL during colonoscopy</td>
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<td>34</td>
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<td>Higher mortality for colorectal cancer arising from SL</td>
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<tr>
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Abbreviations: A, adenomas; NA, not applicable; SL, serrated lesions.

*Decreased specificity to 95% for men and 96% for women and increased sensitivity for small and large lesions by 5% and 10%, respectively.

Sensitivity analyses

Table 2 shows the results of the sensitivity analyses. As a reference, note that in the base-case analysis the predicted decrease in colorectal cancer incidence and mortality due to screening is 35% and 47%, respectively, when including only the adenoma–carcinoma pathway. The maximum impact of the serrated pathway on long-term predictions of colorectal cancer incidence and mortality is reached when colorectal cancer in fact partly arises via the serrated pathway but serrated lesions are neither detected by screening nor colonoscopy. In that situation, a substantially lower decrease in incidence and mortality is predicted: 30% and 40%, respectively, when assuming a 15% contribution of the serrated pathway, and 25% and 33%, respectively, when assuming a 30% contribution of the serrated pathway.

When serrated lesions are detected at colonoscopy, with miss rates equal to adenomas or at a 25% higher miss rate than for adenomas, the impact of the serrated pathway on predicted screening effectiveness is relatively small. The same holds for the sensitivity analyses concerning co-occurrence of serrated lesions and adenomas and the sensitivity analysis concerning the natural history of serrated lesions. In contrast, when we assumed that colorectal cancers arising via the serrated pathway have lower survival rates, this led to a significant decrease in the effectiveness of screening on colorectal cancer mortality.

We repeated all base-case analyses with a low and high prevalence parameter set but differences between predictions were negligible. Furthermore, we varied the participation rate of FIT screening. Higher participation rates lead to more effective screening; incidence reductions up to 53% are predicted with 100% participation. Note that the difference in predicted incidence and mortality between the different contributions of the serrated pathway to colorectal cancer becomes more pronounced when participation increases. Model predictions are robust to lowering compliance to surveillance. However, the number of surveillance colonoscopies decreases by 8,500 (100% via adenoma–cancer pathway). Screening effectiveness is increased when assuming lower specificity and higher sensitivity of FIT. This is accompanied by a substantial increase in colonoscopy demand.

Discussion

This study predicts that without screening, colorectal cancer incidence will increase by 42% in the next 30 years. The Dutch colorectal cancer screening program combined with surveillance guidelines will decrease colorectal cancer incidence by 35% and 31% for a contribution of 0% and 30% of the serrated pathway to colorectal cancer, respectively. For colorectal cancer mortality, reductions are 47% and 45%. Note that colorectal cancer incidence after 30 years of screening will be at a similar level as current incidence rates without screening, due to population aging. In the first years of the program, the model predicts a substantial increase in colorectal cancer incidence due to the detection of prevalent yet asymptomatic tumors. Furthermore, implementation of the program causes a rapid increase in additional diagnostic and surveillance colonoscopies.

A substantial part of these diagnostic colonoscopies, i.e. between 22% and 30% in the first 3 years of the program and between 33% and 44% in 2023, is due to false-positive FITs. This means that in 2024 between 19,700 and 26,300 individuals in the Netherlands will undergo an unnecessary invasive procedure. In addition to the potential harm caused by these procedures, overuse of colonoscopies leads to a waste of scarce health care resources. Therefore, efforts should be made to improve the specificity of FIT to reduce the number of false-positive tests.

As the malignant potential of serrated lesions is increasingly emphasized (9–14), it is important to assess the relevance of the serrated pathway for long-term predictions of screening effectiveness. Including both pathways to colorectal cancer, the ASCCA
model provides a realistic description of the development of colorectal cancer (6). However, compared with the adenoma–cancer pathway, there is substantial uncertainty regarding the natural history of the serrated pathway. That is, little is known on the contribution of the serrated pathway to colorectal cancer incidence, the relationship between hyperplastic polyps and SSAs, and the detection of serrated lesions by screening.

This study assessed the effect of these uncertainties on screening effectiveness by varying relevant parameters over ranges suggested in the literature. When assuming a contribution of 15% and 30% of the serrated pathway to colorectal cancer incidence, our base-case predictions of screening effectiveness were similar to model predictions using only the adenoma–cancer pathway. There are two reasons for this limited impact on screening effectiveness. First, about 40% of individuals with serrated lesions also have adenomas (unpublished observations from the COCOS trial, 2012) which may lead to a positive FIT and referral to colonoscopy. This co-occurrence of serrated and adenomatous lesions was included in the base-case model, but was set to zero in sensitivity analyses. Furthermore, the Dutch guidelines for polypectomy and surveillance were simulated, which means that all serrated lesions, except small hyperplastic polyps located in the rectosigmoid, are removed and individuals with large serrated lesions enter surveillance. Second, in healthy individuals attending multiple screening rounds with a FIT with 96.5% specificity (average for the two sexes), the cumulative chance of a false-positive test in the model is around 20%. As FIT was assumed to have an equal positivity rate in individuals with serrated lesions as in healthy individuals, there is thus a considerable chance that individuals with serrated lesions test positive at some point in time, after which they receive colonoscopy and polypectomy.

Additional sensitivity analyses showed that if serrated lesions cause colorectal cancer although not being detected in a screening program and not being removed during colonoscopy, predictions based on the adenoma–cancer pathway only are overly optimistic. This can lead to an overestimation of the reduction in colorectal cancer mortality of up to 14% if 30% of colorectal cancers would arise from serrated lesions. If the reality is that (the majority of) serrated lesions are detected and removed, model predictions based on the adenoma–cancer pathway only are comparable with those including both pathways. This was also true in the absence of co-occurrence of adenomatous and serrated lesions. However, it becomes important to include the serrated pathway if colorectal cancers arising from serrated lesions have a substantially worse prognosis than those arising from adenomas. Future research into survival differences between molecularly different colorectal cancer subtypes may increase our insight in this regard (41).

The long-term impact of stool-based testing on colorectal cancer mortality has also been assessed in trials. These studies showed that three to seven rounds of biennial guaiac fecal occult blood testing (gFOBT) screening reduces colorectal cancer mortality by 16% after 8 to 13 years of follow-up (2, 42, 43). The Minnesota trial, in which individuals were subjected to six rounds of biennial gFOBT screening, reported a 22% mortality reduction after 30 years of follow-up (3). These trials show that a substantial decrease in colorectal cancer mortality due to screening can be achieved. Considering that we evaluated more screening rounds and assessed a screening test that is more sensitive than gFOBT (44), it can be expected that the current study predicts an even higher reduction in colorectal cancer mortality. Moreover, the Italian FIT screening program led to a 22% reduction in colorectal cancer mortality after 10 years of screening (45), which is comparable with the 23% to 26% reduction predicted by the ASCCCA model.

Also the Microsimulation Screening Analysis (MISCAN) model has evaluated the long-term effect of FIT screening (5, 46). This model predicts an increase in colorectal cancer incidence in the first years of the screening program as well. After 30 years of screening, the MISCAN model predicts a decrease of 12% in colorectal cancer incidence and a decrease of 29% in colorectal cancer mortality, whereas the ASCCCA model predicts a decrease of 35% and 47%, respectively (100% via adenoma–cancer pathway). This difference could be explained by several factors. Most importantly, we accounted for population aging. Furthermore, the dwell time from adenoma to colorectal cancer in the MISCAN model is 11 years, which is much shorter than the 24 years in the ASCCCA model. It is demonstrated that a shorter dwell time leads to lower screening effectiveness (47). Other factors that could contribute to the discrepancy in predicted screening effectiveness is that the ASCCCA model assumed a higher detection rate for small and large adenomas with FIT, a slightly higher participation rate for FIT screening and follow-up and included the recently updated surveillance guidelines. Because these parameters in the ASCCCA model are based on recent Dutch studies, we believe the model adequately reflects the Dutch colorectal cancer screening setting.

Although the ASCCCA model is mainly based on Dutch data, we believe our model predictions can also be of interest for other Western countries. The model structure is based on the two pathways that describe the development from precursor lesions to colorectal cancer. This natural history is thought to be universal. On the other hand, model parameters, especially prevalence rates, may differ between countries. Age- and sex-specific adenoma prevalences are reported for Germany, Austria, and Israel (48–50). In general, these prevalences are lower than those in the COCOS trial. The prevalences of serrated lesions, on the other hand, are similar to those reported in an American colonoscopy study (51). For countries with other prevalence rates, recalibration of the model to country-specific prevalence rates is required to acquire more accurate estimations of screening impact for those countries. Although the results of this study are not directly transferable to all countries, they indicate that FIT screening is a highly effective method to decrease colorectal cancer incidence and mortality.

To conclude, this study predicts a substantial reduction in colorectal cancer incidence and mortality over the next 30 years due to the Dutch colorectal cancer screening program and surveillance guidelines. At the same time, considerable colonoscopy resources will be required. Consideration of the serrated pathway to colorectal cancer is important in predicting screening effectiveness if serrated lesions are not detected nor treated at colonoscopy, and/or if colorectal cancers arising from serrated lesions have a substantially worse prognosis than colorectal cancers arising from adenomas. Otherwise, predictions may be based on the adenoma–cancer pathway only.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Demirel, E. Dekker
References


