Impact of differences in adenoma and proximal serrated polyp detection rate on the long-term effectiveness of FIT-based colorectal cancer screening

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Abstract
Background: Both the adenoma detection rate (ADR) and proximal serrated polyp detection rate (PSPDR) vary among endoscopists. It is unclear how these variations influence colorectal cancer (CRC) screening effectiveness. We evaluated the effect of variation in these detection rates on the long-term impact of fecal immunochemical test (FIT) based screening.

Methods: The Adenoma and Serrated pathway to Colorectal CAnce (ASCCA) model was set up to simulate the Dutch national biennial FIT-based CRC screening program between 2014 and 2044. Adherence to FIT and colonoscopy was 73 and 92%. Besides a ‘no screening scenario’, several screening scenarios varying in ADR and PSPDR were evaluated. Using the available literature on colonoscopy miss rates led to a base-case ADR of 59% and PSPDR of 11%, which were varied with intervals of 3 and 2%.

Results: Compared to no screening, FIT-screening in the base-case scenario reduced long-term mortality with 51.8%. At a fixed PSPDR of 11%, an increase in ADR from 44 to 62% would result in a 10.7% difference in mortality reduction. Using a fixed ADR of 59%, changing the PSPDR from 3 to 15% did not substantially influence long-term mortality (51.0 to 52.3%).

Conclusions: An increase in ADR gradually reduces CRC burden in a FIT-based screening program, whereas an increase in PSPDR only minimally influences long-term outcomes at a population-level. The limited effect of the PSPDR can be explained by the limited sensitivity of FIT for serrated polyps (SPs). Other triage modalities aiming to detect relevant SPs should be explored.

Keywords: Colorectal cancer, Screening, Health economic modeling, Adenoma detection rate, Proximal serrated polyp detection rate

Background
Colorectal cancer (CRC) is one of the most prevalent causes of cancer-related morbidity and mortality in Western countries [1]. Both can be reduced by the detection of cancers at early, curable stages and by the detection and removal of colorectal adenomas, the most important CRC precursor lesions [2, 3]. Colonoscopy is the reference standard for the detection and removal of adenomas and its associated CRC mortality reduction is why CRC screening is implemented in many Western countries [2–4]. CRC screening programs can be divided in primary colonoscopy screening programs in which all participants undergo a screening colonoscopy, and screening programs in which the screening colonoscopy is preceded by a triage modality, such as non-invasive stool tests [4]. Only test-positives will undergo colonoscopy. The effectiveness of all CRC screening programs therefore relies on the quality of the colonoscopy, of which the adenoma
detection rate (ADR) is the most established quality indicator [5–8]. In primary screening colonoscopy cohorts lower ADRs were associated with higher post-colonoscopy CRC and CRC mortality risks [5, 6].

An increasing body of evidence suggests that serrated polyps (SPs) also contribute to CRC oncogenesis [9–11]. Of all post-colonoscopy CRCs, a significant proportion seems to arise from proximal located SPs, presumably because of high lesion miss rates [12, 13]. As such, the detection of proximal SPs is of importance and the proximal serrated polyp detection rate (PSDPR) has been proposed as a screening colonoscopy quality indicator as well [14–17]. However, the PSDPR is not an established quality indicator, as the association between the PSDPR and the occurrence of post-colonoscopy CRCs has not been established yet [14, 17].

Both the ADR and the PSDPR are known to vary among endoscopists [5, 6, 14, 17–23]. Nonetheless, little is known about the effect of these variations in ADR and PSDPR on the effectiveness of a screening program using biennial fecal immunochemical testing (FIT) as a triage modality. Therefore, this study aimed to evaluate the effect of variation in ADR and PSDPR on the long-term impact of a biennial FIT-based CRC screening program using the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model.

Methods

ASCCA model

The ASCCA model, which is extensively described elsewhere, was used for all analyses [24]. In brief, the natural history model incorporates two pathways to CRC: the adenoma-carcinoma pathway and the serrated pathway. The serrated pathway is assumed to contribute to 15% of CRC cases [25]. Individual health trajectories are simulated from age 20 to age 90 or death, whichever comes first. During their life, individuals can develop up to 10 adenomas and 10 SPs. In the model only hyperplastic polyps (HPs) and sessile serrated lesions (SSLs) were included as traditional serrated adenomas are very rare [26]. The development of each lesion in terms of growth in size is modelled independently. For adenomas, also the development of high-grade dysplasia and villousity is taken into account. Only advanced adenomas and SSLs can progress to CRC. Once an asymptomatic tumor has developed, there is an annual chance that the tumor becomes detected by symptoms or progresses to a more advanced stage. Table 3 in Appendix provides an overview of the natural history parameters. The model satisfactorily replicates Dutch colorectal lesion prevalence, CRC incidence and CRC mortality in the absence of screening [27, 28]. The natural history model is supplemented with a flexible screening and surveillance component, which can be set up to evaluate a range of screening and surveillance strategies. Parameters of the screening and surveillance component are updated regularly using the results of the national monitor of the Dutch CRC screening program [29].

**Dutch screening program and surveillance guidelines**

The ASCCA model was set up to simulate the Dutch national CRC screening program; model parameters are shown in Table 1. The Dutch screening program was implemented in 2014 and involves biennial FIT-screening [30]. The implementation is phased; each year new birth cohorts are invited until the program is fully implemented in 2019. From 2019 onwards, all

| Table 1 Overview of important model parameters |
|-----------------------------------------------|
| Variable                                      | Base-case analysis | Sensitivity analysis | Reference |
| FIT-screening                                 |                  |                     | National monitor of the Dutch CRC screening program [29, 34] |
| Participation FIT                             | 0.73              |                     | [27, 29]  |
| Adherence to FIT-positive colonoscopy         | 0.92              |                     |          |
| Adherence to surveillance colonoscopy         | 0.92              |                     |          |
| Primary colonoscopy screening                 |                  |                     |          |
| Adherence to screening colonoscopy            | 0.22              |                     |          |
| Adherence to surveillance colonoscopy         | 0.92              |                     |          |
| FIT positivity rate per lesion                |                   |                     | [31]     |
| Healthy                                      | 0.96a             | 0.97a               |          |
| Diminutive adenoma                           | 0.004             | 0.003               |          |
| Small adenoma                                | 0.12              | 0.10                |          |
| Large adenoma                                | 0.30              | 0.28                |          |
| Small SP                                     | 0.004             | 0.003               | 0.06     |
| Large SP                                     | 0.004             | 0.003               | 0.30     |
| Early stage CRC                              | 0.50              | 0.50                |          |
| Late stage CRC                               | 0.85              | 0.85                |          |
| Contribution of serrated pathway to CRC incidence | 15%               | 30%                 | [12]     |
| Complications after colonoscopy              | 0.0028            |                     | [35–37]  |
| Fatal complications after colonoscopy        | 0.0001            |                     | [35–37]  |

FIT, fecal immunochemical test

*aSpecificity per individual*
individuals aged 55 to 75 will be invited biennially. Individuals with a positive test outcome (cut-off 75 ng/ml) are referred for colonoscopy. FIT characteristics for detecting adenomas were obtained following a previously described calibration procedure [24]. We calibrated against the positivity rate, detection rates and positive predictive values of a Dutch screening pilot study [31]. For SPs, the positivity rate was assumed to be equal to one minus the specificity [32]. We assumed that during colonoscopy, all detected lesions are completely removed, with the exception of small HPs (< 5 mm) located in the rectosigmoid [33]. Adherence rates to FIT and FIT-positive colonoscopy were set at 73 and 92% based on the national monitor of the Dutch CRC screening program [29, 34].

Colonoscopy surveillance is modelled in accordance with Dutch guidelines, which is guided by a risk score based on the number, size and location of the encountered colorectal polyps [33]. This risk score determines the surveillance interval, i.e. 3 or 5 years. If during FIT-positive colonoscopy no adenomas or only one small (≤ 1 cm) tubular adenoma is detected, the individual returns to screening after 10 years. Adherence to surveillance colonoscopy was assumed to be equal to that of FIT-positive colonoscopy, i.e. 92%, and surveillance ends at age 75.

Detection settings
Besides the no screening comparator, we considered FIT-screening with different detection settings (varying both ADR and PSPDR). To estimate the ADR and PSPDR, the model was set up to simulate one round of FIT-screening (cut-off 75 ng/ml) in previously unscreened, asymptomatic individuals aged 55–75 years. First, we assumed size-specific detection rates per adenoma during FIT-positive colonoscopy as reported in a systematic review on adenoma miss rates to calculate the base-case ADR [7]. For SPs, lesion miss rates are not described in the literature. Since the flat appearance, proximal location and pale color of SPs hampers detection, a 10% lower detection rate per SP than per adenoma was assumed to calculate the base-case PSPDR [35]. Subsequently, the detection rate per adenoma was calibrated, such that the ADR increased and decreased with steps of 3% with a minimal ADR of 44%. As the prevalence of proximal SPs is lower than the adenoma prevalence, the PSPDR was increased and decreased with steps of 2% when calibrating the SP detection rate. A minimal PSPDR of 3% was assumed. The maximum ADR and PSPDR were reached under the assumption that all adenomas or SPs were detected. To achieve a specific ADR or PSPDR, the detection rates for the different size categories per lesion were varied jointly rather than individually. More specifically, we assumed that the absolute difference in detection rates between the different size categories per lesion type remained equal to those reported by Van Rijn et al. [7].

Analyses and study outcomes
Screening was modelled from the introduction of the program in 2014 to 2044, while accounting for the phased rollout. We started with a population based on the 2013 Dutch population age-composition and assumed that this population will age in accordance with the predictions of the Dutch Central Bureau of Statistics [36]. For each FIT-screening scenario with different detection settings, yearly CRC incidence and mortality rates per 100,000 individuals and colonoscopy demand were evaluated. The FIT-screening scenario assuming the base-case ADR and PSPDR was compared to no screening. Subsequently, we assessed the impact of increasing the PSPDR with the ADR fixed at the base-case value as well as the impact of increasing the ADR with the PSPDR fixed at the base-case value.

Sensitivity analyses
To assess the robustness of our results, we conducted one-way sensitivity analyses, i.e. varying only one parameter at the time. As there is much debate regarding the contribution of the serrated pathway to the CRC incidence [9–11], all FIT-screening scenarios with different detection settings were repeated assuming that 30% of CRCs arise from SPs instead of 15% used in the base-case analyses. Furthermore, we assumed that FIT detects adenomas and SPs equally well (Table 1).

In order to evaluate the impact of surveillance colonoscopy on the study outcomes, we repeated all analyses assuming an alternative strategy of FIT screening without surveillance, in which individuals considered at intermediate or high risk for metachronous lesions at FIT-positive colonoscopy return to FIT-screening after 2 years. Those at low risk return to the screening program after 10 years [37]. To allow for comparability of model results with other studies on ADR variances, all analyses were repeated assuming a fully implemented primary colonoscopy screening program. In this program, individuals aged 55 to 75 are invited every 10 years to undergo screening colonoscopy and dependent on the findings, may enter colonoscopy surveillance. Adherence rates for screening and surveillance colonoscopy were set at 22 and 92% [27, 29]. To
evaluate the maximal impact of changes in ADR and PSPDR, also primary colonoscopy screening assuming perfect compliance was simulated.

**Results**

**Adenoma and proximal SP detection rates**

Table 2 shows the results of calibrating the ADR and PSPDR in one round of FIT-screening in previously unscreened individuals. Assuming detection rates per adenoma based on Van Rijn et al. led to an ADR of 59% [7]. This was considered the base-case ADR. The maximal ADR of 62% was reached when assuming that all adenomas were detected during FIT-positive colonoscopy. A minimal ADR of 44% was assumed for which the detection rates of diminutive, small and large adenomas were 36, 49 and 60%. Thus, the plausible ADR range is between 44 and 62%.

For SPs, 10% lower detection rates per SP compared to the detection rates per adenoma were assumed, leading to a base-case PSPDR of 11% [7]. Assuming that all SPs are detected during FIT-positive colonoscopy led to a maximal PSPDR of 15%. We assumed a minimal PSPDR of 3% for which the detection rates were 15 and 33% for small and large SPs. Therefore, the plausible range for the PSPDR is between 3 and 15%. Table 2 also reports ADRs and PSPDRs for one round of primary colonoscopy screening.

**CRC burden and colonoscopy demand**

In 2013, CRC incidence and mortality rates were 74.0 cases and 29.3 deaths per 100,000 individuals. In the absence of screening, CRC incidence and mortality are predicted to increase to 104.3 and 42.3 per 100,000 individuals in 2044 due to aging of the population. In the base-case detection setting, 30 years of FIT-screening led to a 36.7% reduction in CRC incidence and a 51.8% reduction in CRC mortality compared to no screening. When the ADR was fixed at 59% and a PSPDR of 3% was assumed, CRC mortality reduction was 51.0% compared to no screening (Fig. 1). This reduction increased with 1.3 to 52.3% when the PSPDR was increased to 15%. At a fixed PSPDR of 11% and when an ADR of 44% was assumed, CRC mortality reduction was

| Calibrated detection rate per adenoma | ADR in previously unscreened individuals aged 55–75 years undergoing one round of FIT-screening | Calibrated detection rate per SP | PSPDR in previously unscreened individuals aged 55–75 years undergoing one round of Primary colonoscopy screening |
|--------------------------------------|--------------------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------|
| < 6 mm:                              | 36%                                              | < 10 mm: 15%                    | 3%                                                                                                               |
| 6–9 mm:                              | 49%                                              | ≥ 10 mm: 33%                    | 3%                                                                                                               |
| ≥ 10 mm:                             | 60%                                              | ≥ 10 mm: 45%                    | 5%                                                                                                               |
| < 6 mm:                              | 42%                                              | < 10 mm: 40%                    | 7%                                                                                                               |
| 6–9 mm:                              | 55%                                              | ≥ 10 mm: 58%                    | 8%                                                                                                               |
| ≥ 10 mm:                             | 66%                                              | ≥ 10 mm: 62%                    | 10%                                                                                                              |
| < 6 mm:                              | 49%                                              | < 10 mm: 54%                    | 9%                                                                                                               |
| 6–9 mm:                              | 62%                                              | ≥ 10 mm: 68%                    | 11%^[8]                                                             |
| ≥ 10 mm:                             | 73%                                              | < 10 mm: 68%                    | 12%                                                                                                              |
| < 6 mm:                              | 56%                                              | ≥ 10 mm: 86%                    | 13%                                                                                                              |
| 6–9 mm:                              | 69%                                              | < 6 mm: 74%                     | 14%                                                                                                              |
| ≥ 10 mm:                             | 80%                                              | 6–9 mm: 87%                     | 15%                                                                                                              |
| < 6 mm:                              | 65%                                              | ≥ 10 mm: 100%                   | 15%                                                                                                              |
| 6–9 mm:                              | 78%                                              | < 6 mm: 100%                    | 15%                                                                                                              |
| ≥ 10 mm:                             | 89%                                              | 6–9 mm: 100%                    | 15%                                                                                                              |
| < 6 mm:                              | 74%                                              | ≥ 10 mm: 100%                   | 15%                                                                                                              |
| 6–9 mm:                              | 87%                                              | ≥ 10 mm: 100%                   | 15%                                                                                                              |

^27% of individuals aged 55–59, 25% of individuals aged 60–64, 24% of individuals aged 65–69 and 25% of individuals aged 70–75

^[8] an ADR of 59% and a PSPDR of 11% were considered as the base-case detection setting
42.4% compared to no screening. Increasing the ADR to 62% led to a model-predicted mortality reduction of 53.1%, i.e. an increase of 10.7%. Similar patterns were observed for the CRC incidence reduction as shown in Fig. 3 in Appendix.

In the base-case detection setting 120,862 colonoscopies are required in 2044. Changes in the PSPDR at a fixed ADR of 59% did not influence colonoscopy demand. On the other hand, when the ADR was increased from 44 to 62% at a fixed PSPDR of 11%, colonoscopy demand was predicted to differ with 21,726 colonoscopies per year in 2044.

Sensitivity analyses
Under the assumption that 30% of all CRCs develop according to the serrated pathway, the difference in mortality reduction when increasing the PSPDR over its plausible range (from 3 to 15%) at a fixed ADR of 59% was slightly larger than in the base-case analysis, with an increase of 2.1% from 48.5 to 50.6% (Fig. 2). The impact of increasing the PSPDR became more pronounced under the assumption that FIT has comparable sensitivity for adenomas and SPs; the difference in mortality reduction when increasing the PSPDR over its plausible range was 3.
9% (from 53.2 to 57.2%). When considering a fixed PSPDR and variable ADR (plausible range from 44 to 62%), changes in contribution of the serrated pathway and detection of SPs by FIT led to a slightly smaller and a slightly greater difference in mortality reduction compared to the base-case analysis.

Evaluating the alternative strategy of FIT screening without surveillance, in which all individuals who were considered at intermediate or high risk at FIT-positive colonoscopy returned to screening after 2 years, we found comparable patterns with the base-case analysis. The difference in mortality reduction was 1.4% (increased from 49.1 to 50.5%) when
the PSPDR was increased over its plausible range at a fixed ADR of 59%. When the PSPDR was fixed and the ADR was increased over its plausible range, the difference in mortality reduction increased with 10.8% (from 41.0 to 51.8%).

Also when the analyses were repeated assuming a fully implemented primary colonoscopy screening program with 22% colonoscopy adherence, similar patterns were observed [27]. An increase in the PSPDR over the plausible range only slightly increased the mortality reduction (from 28.2 to 31.2%), whereas an increase in ADR over its plausible range led to a considerable higher mortality reduction (from 22.2 to 32.5%). The maximal impact of an increase in detection rates was evaluated by assuming colonoscopy screening with perfect compliance. When the ADR was fixed, the difference in mortality reduction when increasing the PSPDR over its plausible range was 4.6% (from 79.7 to 84.3%). When the PSPDR was fixed, an increase in ADR over the plausible range led to a 15% difference in mortality reduction (from 70.4 to 85.4%). Results for CRC incidence were similar as shown in Fig. 4 in Appendix.

Discussion

Based on the ASCCA model, an increase in ADR will gradually reduce CRC incidence and mortality in a biennial FIT-based CRC screening program, whereas an increase of the PSPDR does only minimally impact CRC burden at a population-level. Similar results were found when an alternative strategy of FIT screening without surveillance was evaluated. The impact of an increased PSPDR on long term-outcomes only slightly increased when assuming a 30% instead of 15% contribution of the serrated pathway and under the assumption that FIT would have a comparable sensitivity for adenomas and SPs. The maximum impact of changing either the PSPDR (from 3 to 15%) or ADR (from 44 to 62%) on mortality reduction due to screening was observed when a colonoscopy screening programme with perfect compliance was modelled. In that case, mortality reductions varied with 4.6 and 15% when varying the PSPDR and ADR over its plausible range.

There are two explanations for the limited influence of an increased PSPDR on the model-predicted effectiveness of FIT-based screening. Firstly, only 15–30% of all CRCs originate from the serrated pathway [11]. When assuming a 30% contribution of the serrated pathway to CRC incidence, CRC mortality reduction due to screening varied with 3.8% when increasing the PSPDR over its plausible range compared to 1.3% in the base-case scenario wherein a 15% contribution was assumed. Secondly, under the assumption that FIT has a comparable sensitivity for both adenomas and SPs, a 4.0% difference in mortality reduction by increasing the PSPDR over its plausible range was found. FIT is known to be ineffective to detect clinically relevant SPs, such as larger and/or proximally located HPs and SSLs, since these lesions seldom bleed [9, 11, 38, 39]. This is also supported by our calibration analysis in which equal detection rates per SP led to similar PSPDRs for FIT-screening and colonoscopy screening. In other words, FIT-screening does not lead to a subgroup of individuals referred for colonoscopy that has an increased SP prevalence. Contrastingly, the ADR was considerably higher after preselection with FIT compared to colonoscopy screening when assuming equal detection rates per adenoma. Positivity of FIT in individuals having relevant SPs is most likely due to the frequent co-occurrence of synchronous advanced adenomas or CRC [40].

The majority of individuals harbouring relevant SPs without concurrent adenomas will therefore not benefit from FIT-based screening. Particularly these individuals are at risk of developing a FIT interval cancer, as it is suggested that SPs, once dysplastic may evolve relatively quickly into malignancy [41]. Improved detection of proximal SPs during colonoscopy is only effective for improving the effectiveness of a CRC screening program, if colonoscopy is used as a primary screening modality or when a triage test would preselect individuals at increased risk for relevant SPs as well as for advanced adenomas and CRC. Molecular stool testing has shown promising results. However, costs, test specificity, and ease to perform should improve to become a realistic alternative to FIT [32]. Currently, whole stool samples are needed to enable molecular testing. This could be burdensome for screenees and will influence adherence rates, which is crucial for population-based screening programs [32].

Irrespective of the used triage modality, colonoscopy will remain the reference standard to detect and resect adenomas, SPs and cancer. To ensure the effectiveness of a screening program, quality assurance and monitoring the quality of colonoscopy is of paramount importance. To obtain and assure high quality within the Dutch national CRC screening program, national requirements were set for professionals performing screening colonoscopies. Only endoscopists satisfying pre-defined quality requirements are accredited to perform screening colonoscopies. During the accreditation process, the knowledge and skills of endoscopists are tested by an e-learning, by measuring evidence-based quality
indicators and by evaluating the practical skills during colonoscopy [42].

The ADR is endorsed as the most important (screening) colonoscopy quality indicator, since it is inversely correlated with the occurrence of post-colonoscopy CRCs cancers and CRC mortality in large primary screening colonoscopy cohorts [5, 6]. However, ADR is criticized as being slightly imprecise, as it does not provide information about incremental adenomas detected besides the first, resulting in the ‘one and done phenomenon’ [43]. Ideally, reporting of the ADR would be combined with a quality indicator reporting on the total number of detected adenomas [43]. In contrast to these data on ADR, no prospective studies evaluating the association between the PSPDR and the risk of interval cancers have been performed and recommendations for PSPDR thresholds are yet to be determined [14, 17]. As a consequence it can be hypothesized that the ‘one and done phenomenon’ currently does not apply to the PSPDR. Furthermore, both ADR and PSPDR do not select for neoplastic lesions having a higher neoplastic potential. The histopathological subtyping of SPs tends to be difficult, resulting in a broad diagnostic variability between pathologists [44]. However, by choosing the total group of SP located in the proximal colon, this interobserver variability among pathologists should not influence the results.

Both ADR and PSPDR vary widely, suggesting important lesion miss rates in low detecting endoscopists [5, 6, 14, 17–23]. Up to date, no studies have assessed interventions to improve the PSPDR. In contrast, several strategies aimed to improve ADR, including simple feedback, involvement of endoscopy nurses and mandating longer colonoscope withdrawal times, as well as multifaceted strategies involving education, audit and feedback. However, all methods had limited effect on ADR [45–49]. The minor impact and poor performance of most interventions may be caused by the paucity of evidence on appropriate factors to target for modification [50].

The interpretation of detection rates is difficult. This is due to the fact that besides endoscopy skills, detection rates are also influenced by the primary screening test and by the characteristics of the screening population, such as age, gender, screening history and prevalence of neoplastic lesions [18]. Thus, detection rates can only be interpreted in the context of the same screening setting. The calibrated detection rates in this study are based on one round of FIT-screening in previously unscreened, asymptomatic individuals aged 55–75 years. It should be noted that this differs from the Dutch CRC screening program which includes a phased implementation. During the implementation phase, selective cohorts are invited for screening starting with primarily older cohorts.

To the best of our knowledge this is the first microsimulation study investigating the influence of both the ADR and the PSPDR on the effectiveness of a biennially FIT-based as well as a primary colonoscopy screening program. Three other microsimulation studies estimated the effectiveness of primary colonoscopy screening at different levels of adenoma detection, also showing that higher ADRs were associated with important CRC incidence and mortality reductions [51–53]. The study by Meester et al. also investigated the effectiveness of annual FIT-based screening, showing a higher CRC related mortality in lower ADR settings [53]. An important difference between these models and the ASCCA model is the fact that both the adenoma-carcinoma pathway and the serrated pathway are included in the ASCCA model, whereas the other models only incorporate the adenoma-carcinoma pathway. This enabled us to also evaluate the impact of improvements in the PSPDR on CRC incidence and mortality reductions.

However, important limitations have to be acknowledged as well. First, we assumed a 10% lower detection rates rated for SPs than for adenomas to estimate the base-case PSPDR. Currently, the exact miss rates of SPs remain to be determined. However it is possible that the actual miss rates of SPs are higher than assumed in our base-case analysis, caused by the flat appearance, proximal location and pale color of SPs hampering detection [35]. On the other hand, the adenoma miss rates of colonoscopies performed nowadays may potentially be lower than miss rates reported by Van Rijn et al [7]. Since the publication of this study, the awareness of high quality colonoscopy has increased, accompanied by important improvements in the colonoscopy equipment, such as the application of high-definition colonoscopes and advanced imaging techniques. However, recently no new back-to-back studies have been published. To account for the uncertainty regarding this parameter however, we have evaluated a range of miss rates for both adenomas and SPs.

**Conclusions**

In conclusion, an increase in ADR gradually will reduce CRC incidence and mortality in a biennial FIT-based screening program after 30-years of follow-up, whereas an increase of the PSPDR does only minimally influence long-term outcomes on a population-level. This limited effect of the PSPDR is partly explained by our assumption of a 15% contribution of the serrated pathway to the development of CRC, but more importantly by the limited diagnostic accuracy of FIT for SPs. Other triage modalities aiming to detect advanced SPs should be further explored.
## Appendix

### Table 3 Natural history parameters of the ASCCA model

| Natural history parameters | One-year transition probabilities | References |
|----------------------------|-----------------------------------|------------|
| **Adenoma-carcinoma pathway** |                                   |            |
| Adenoma incidence men (No adenoma to diminutive adenoma) | (A1-A3) | |
| Age 20–39                  | 0.003                             |            |
| Age 40–49                  | 0.007                             |            |
| Age 50–54                  | 0.019                             |            |
| Age 55–59                  | 0.022                             |            |
| Age 60–64                  | 0.024                             |            |
| Age 65–69                  | 0.028                             |            |
| Age 70–74                  | 0.033                             |            |
| Age 75–90                  | 0.035                             |            |
| Adenoma incidence women | (A1-A3) | |
| Incidence factor           | 0.6<sup>a</sup>                   |            |
| **Personal risk index adenoma-carcinoma pathway** | (A2,A3) | |
| Standard deviation         | 1.6<sup>a</sup>                   |            |
| **Progression in size**    | (A1,A3-A5) | |
| Diminutive to small adenoma| 0.07                              |            |
| Small to large adenoma     | 0.10                              |            |
| **Regression in size**     | (A1,A3) | |
| Small to diminutive adenoma| 0.25                              |            |
| Large to small adenoma     | 0.15                              |            |
| **Dysplasia (Low grade to high grade)** | (A1,A3) | |
| Diminutive adenoma         | 0.004                             |            |
| Small adenoma              | 0.009                             |            |
| Large adenoma              | 0.010                             |            |
| **Villosity (Tubular to tubulovillous/villous)** | (A1,A3) | |
| Diminutive adenoma         | 0.004                             |            |
| Small adenoma              | 0.025                             |            |
| Large adenoma              | 0.085                             |            |
| **Progression from AA to CRC<sup>b</sup>** | Shape | Scale (A6) |
| Men                        | 2<sup>a</sup>                     | 29<sup>a</sup> |
| Women                      | 2<sup>a</sup>                     | 27<sup>a</sup> |
| **Serrated pathway**       |                                   |            |
| Serrated lesion incidence men (No serrated lesion to small serrated lesion) | SSA | HP (A1,A3) |
| Age 20–25                  | 0.0001                            | 0.001      |
| Age 25–29                  | 0.0001                            | 0.001      |
| Age 30–34                  | 0.0001                            | 0.002      |
| Age 35–39                  | 0.0001                            | 0.004      |
| Age 40–44                  | 0.0006                            | 0.007      |
| Age 45–49                  | 0.0015                            | 0.010      |
| Age 50–54                  | 0.0016                            | 0.010      |
| Age 55–59                  | 0.0014                            | 0.006      |

<sup>a</sup> Bronzwaer et al. BMC Cancer (2018) 18:465
Table 3  Natural history parameters of the ASCCA model (Continued)

| Natural history parameters                        | One-year transition probabilities | References |
|--------------------------------------------------|-----------------------------------|------------|
| Age 60–64                                        | 0.0008                            | 0.004      |
| Age 65–69                                        | 0.0008                            | 0.004      |
| Age 70–74                                        | 0.0007                            | 0.002      |
| Age 75–79                                        | 0.0006                            | 0.002      |
| Age 80–84                                        | 0.0005                            | 0.002      |
| Age 85–90                                        | 0.0004                            | 0.002      |

Serrated lesion incidence women

- Incidence factor SSA: 0.7<sup>a</sup> (A1,A3)
- Incidence factor HP: 0.7<sup>a</sup>

Personal risk index serrated pathway

- Standard deviation: 1.7<sup>a</sup>

Progression in size

- Small to large serrated lesion: 0.028

Regression in size

- Small HP to no serrated lesion: 0.0
- Large HP to small HP: 0.4

Progression to CRC

- 0.006 (A6)

CRC

- Dwell time in years
  - Stage 1: 2.5<sup>a</sup>
  - Stage 2: 2.0<sup>a</sup>
  - Stage 3: 1.5<sup>a</sup>
  - Stage 4: 1.0<sup>a</sup>

- Stage distribution detected CRC
  - Stage 1: 0.19<sup>a</sup>
  - Stage 2: 0.31<sup>a</sup>
  - Stage 3: 0.49<sup>a</sup>
  - Stage 4: 0.01<sup>a</sup>

<sup>a</sup>Parameter value instead of yearly transition probability

<sup>b</sup>Weibull distribution
Fig. 3 Long-term reduction in CRC incidence due to FIT-screening for different PSPDRs at a fixed ADR of 59% (a) and different ADRs at a fixed PSPDR of 11% (b).
Fig. 4 CRC incidence reduction compared to no screening for the base-case analysis and sensitivity analyses with the PSPDR varying between 3 and 15% at a fixed ADR of 59% (a) and with the ADR varying between 44 and 62% at a fixed PSPDR of 11% (b).
Abbreviations
A DR: Adenoma detection rate; ASSCA: Adenoma and Serrated pathway to Colorectal Cancer; CR C: Colorectal cancers; FIT: Fecal immunochemical test; HP: Hyperplastic polyp; PSFDR: Proximal serrated polyp detection rate; SP: Serrated polyp; SSL: Sessile serrated lesion

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Availability of data and materials
All data analyses were performed with the Adenoma and Serrated pathway to Colorectal Cancer (ASCCA) model, which is described in more detail elsewhere [24]. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors’ contributions
Study conception and design ED, MB extracted and analyzed the data and wrote the manuscript. MG performed all analyses and wrote the manuscript. AB, JI, ED and VC contributed to the design and critically revised the manuscript. All authors approved the final version.

Ethics approval and consent to participate
As this is a microsimulation study no human subjects were involved in this study and therefore no ethical approval and consent to participate were required.

Competing interests
The authors declare that they have no competing interests.

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