Colorectal cancer screening for average- and high-risk individuals: beyond one-size-fits-all

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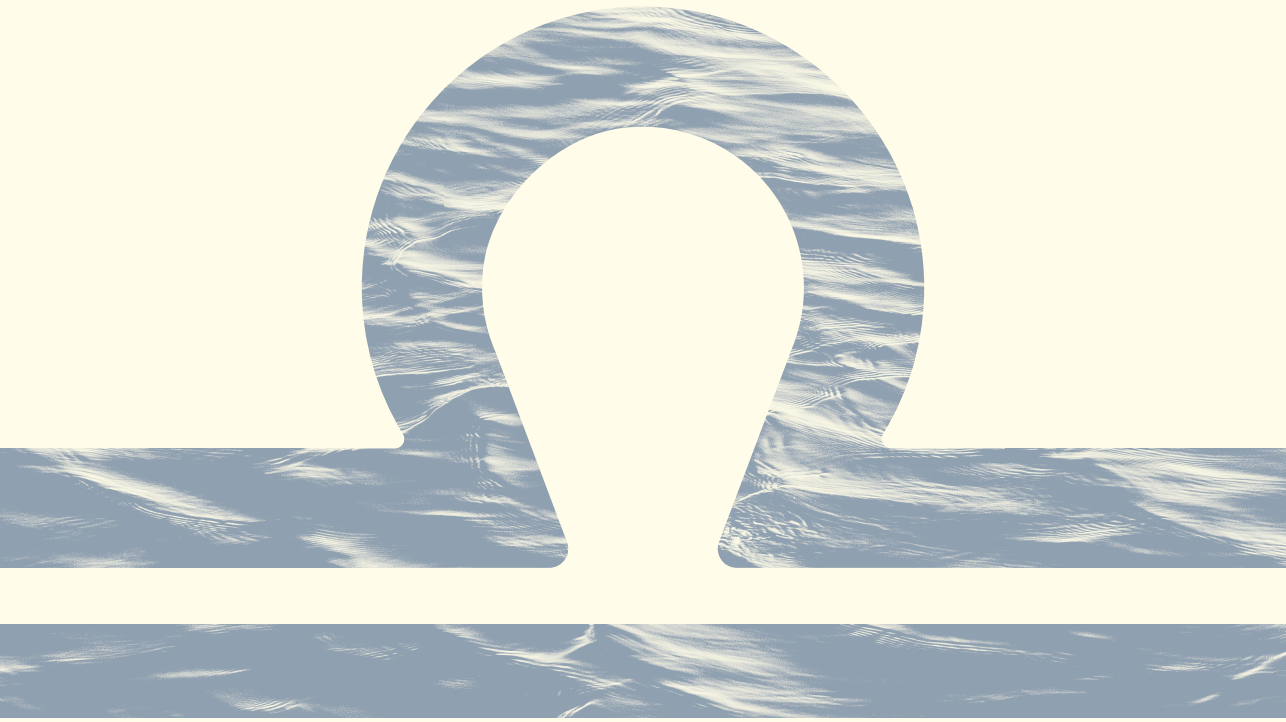

Chapter 5

Advanced serrated polyps as a target of screening: detection rate and positive predictive value within a fecal immunochemical test-based colorectal cancer screening population

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ABSTRACT

Background

Advanced serrated polyps (ASPs) have a comparable risk to advanced adenomas for progression to colorectal cancer (CRC). The yield of most CRC screening programs, however, is based on advanced adenomas and CRC only. We assessed the ASP detection rate, and positive predictive value (PPV) including ASPs in a fecal immunochemical test (FIT)-based screening program.

Methods

We analyzed the findings of follow-up colonoscopies of FIT-positive screenees in the Dutch CRC screening program from 2014 until 2020. Data were retrieved from the national screening and pathology database. An ASP was defined as any serrated polyp of ≥ 10 mm, sessile serrated lesion with dysplasia, or traditional serrated adenoma. The ASP detection rate was defined as the proportion of colonoscopies with ≥ 1 ASP. PPV was originally defined as the proportion of individuals with a CRC or advanced adenoma. The updated PPV definition included CRCs, advanced adenomas, and/or ASPs.

Results

322,882 colonoscopies were included in the analyses. The overall detection rate of ASPs was 5.9%. ASPs were detected more often in women than men (6.3% vs. 5.6%; $P < 0.001$). ASP detection rates in individuals aged 55–59, 60–64, 65–69, and 70 + were 5.2%, 6.1%, 6.1%, and 5.9%, respectively ($P < 0.001$). The PPV for CRCs and advanced adenomas was 41.1% and increased to 43.8% when including ASPs. The PPV increase was larger in women than in men (3.2 vs. 2.4 percentage points).

Conclusions

5.9% of FIT-positive screenees had ASPs, but half of these were detected in combination with a CRC or advanced adenoma. Therefore, including ASPs results in a small increase in the yield of FIT-based screening.

INTRODUCTION

Colorectal cancer (CRC) is the third most diagnosed cancer worldwide and causes substantial mortality and morbidity (1). CRC arises from polyps over the course of years. Until two decades ago, it was generally believed that adenomas were the sole precursors of CRC. In recent years, serrated polyps have also been identified as precursors and 15%–30% of all CRCs seem to arise from serrated polyps (2).

Advanced serrated polyps (ASPs) are serrated polyps that have a high risk of developing into CRC. Data on the prevalence of ASPs are sparse, partly owing to inconsistent terminology (3–5). In the most recent literature, ASPs are defined as either a serrated polyp ≥10mm in size, or one of the two serrated polyp subtypes, namely sessile serrated lesions (SSLs) with dysplasia, or traditional serrated adenomas (TSAs). This definition is based on large retrospective population studies that have reported an increased risk of metachronous CRC after the resection of these serrated polyp subtypes when compared with individuals without any significant lesions on baseline colonoscopy (6–8).

Despite the proven relevance of ASPs, they are usually not considered as a target lesion and are not accounted for in the yield of fecal immunochemical test (FIT) screening programs. Historically, the fact that serrated polyps were a relatively new concept, without a generally accepted and matured definition, has hampered their implementation into established performance indicators for screening.

Studies have shown the inferior diagnostic accuracy of FIT for the detection of large serrated polyps (≥10mm in size), with sensitivity varying between 5.1% and 18.4% (9–11). This may be explained by the low tendency of serrated polyps to bleed and the preferred proximal location of serrated polyps. Correct registration and classification of ASPs may help to set detection standards for future new screening tests. Timely detection of ASPs is especially relevant because these polyps follow a rapid transition to CRC once dysplasia develops.

The aim of this study was to determine the detection rate of ASPs in the Dutch FIT-based CRC screening program and to evaluate the additional yield of screening, taking into account ASPs, along with CRCs and advanced adenomas.

METHODS

Study design and population

We performed a cross-sectional analysis on colonoscopy and pathology data within the Dutch national CRC screening program (12). In this program, Dutch residents aged between 55 and 75 are biennially invited to perform a FIT. Screenees are referred for colonoscopy if they had a fecal hemoglobin (f-Hb) concentration above the set cutoff value for positivity. The FIT cutoff was 15 µg Hb/g feces at the introduction of the CRC screening program in 2014, and was increased to 47 µg Hb/g feces after 6 months (mid-2014).

All endoscopists performing screening colonoscopies within the national CRC screening program are required to perform high quality colonoscopies assessed by an upfront examination for accreditation, and regular monitoring and auditing (13). In short, all included endoscopists performed ≥200 colonoscopies per year, ≥50 polypectomies per year, achieved cecal intubation rates of ≥95%, adenoma detection rates of ≥30%, and removal rates of ≥90% of detected polyps. Reporting pathologists also require accreditation and regular monitoring, and were obligated to pass a validated e-learning on the histopathologic diagnosis of serrated polyps (14).

All colonoscopies that were performed in FIT-positive screenees between January 2014 and December 2020 were eligible for inclusion in our study. To ensure high quality data, colonoscopies were excluded from the analysis when the cecum was not reached and/or bowel preparation was insufficient (Boston Bowel Preparation Score <6) (15,16). Colonoscopies in which CRC was found were not excluded.

Data sources

Colonoscopy and pathology data were collected from the national screening information system (ScreenIT). As it was recognized that not all lesions were removed directly at the index colonoscopy, we considered all pathology findings until a period of 6 months after the index colonoscopy as screen-detected findings. Additional data on follow-up colonoscopies were retrieved from the Dutch nationwide pathology databank, PALGA (17).

Outcome definitions

Our main outcome parameter was the ASP detection rate, calculated as the proportion of colonoscopies in which at least one ASP was detected. The second

main outcome parameter was the incremental positive predictive value (PPV) when including ASPs as a relevant finding (i.e. advanced neoplasia). An updated definition of the PPV of FIT was calculated as the proportion of individuals diagnosed with advanced neoplasia (ASP, advanced adenoma, or CRC) within all screenees who underwent colonoscopy, and this was compared to the original definition of advanced neoplasia (advanced adenoma and CRC). CRCs were regarded as the most advanced lesions, followed by advanced adenomas, and then ASPs.

All CRCs were histologically confirmed as either adenocarcinoma, signet-cell carcinoma, or mucinous adenocarcinoma. Appendiceal cancers were excluded from analysis. Advanced adenoma was defined as any conventional adenoma of ≥10mm in diameter or adenoma with advanced histology (tubulovillous/ villous histological features or high grade dysplasia) (18). ASPs were defined as at least one serrated polyp of ≥10mm in diameter or an SSL with (low/high grade) dysplasia or a TSA (Figure 1) (19,20). Polyps with intramucosal carcinoma or carcinoma in situ were classified as high grade dysplasia in adenomas and as dysplasia in SSLs or TSAs. Non-relevant findings were categorized as "other findings," including nonadvanced serrated polyps and nonadvanced adenomas, and "no CRC and no polyp."

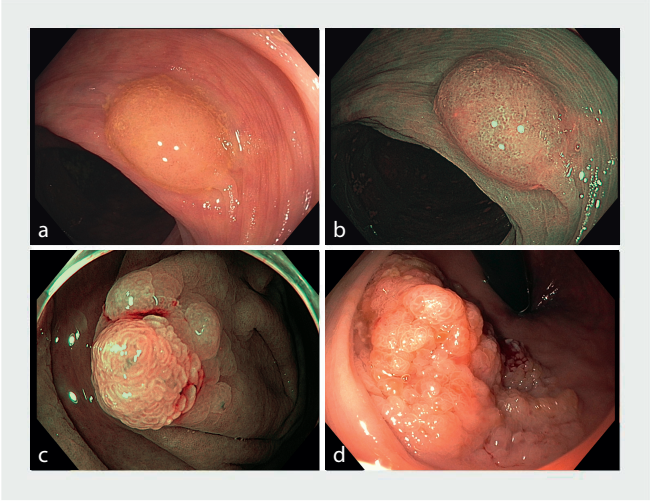

Figure 1 - Endoscopic images of three different types of advanced serrated polyps showing: a,b a sessile serrated lesion larger than 10mm in size on: a white-light endoscopy, with the typical mucus cap visible covering the polyp; **b** narrow-band imaging, with wide crypts recognizable as "black spots"; **c** a sessile serrated lesion with a focus of dysplasia seen as a villous pattern on top of the lesion; **d** a traditional serrated adenoma with typical polypoid and villous features.

Statistical analyses

Descriptive analyses for the ASP detection rate (and subgroups) are presented as counts and proportion of all colonoscopies, and median and interquartile range (IQR). Detection rates were stratified by sex, age (55–59, 60–64, 65–69, 70+ years), and invitation round (first/consecutive round). Differences between ASP subgroups were evaluated by using chi-squared testing for categorical variables and Mann-Whitney U testing for continuous variables.

The number needed to scope (NNS) for ASPs was defined as the total number of colonoscopies that would need to be performed in order to detect at least one ASP and was calculated by the inverse of the detection rate of ASPs. Furthermore, detection rates of each subgroup of ASP were evaluated, as well as the detection rate of ASPs stratified for polyp location and polyp size. The proximal colon was defined as being located proximal to the descending colon, including the splenic flexure. Analyses for polyp location and size were performed per polyp and therefore separately determined for index colonoscopies from the ScreenIT database and for colonoscopies within 6 months after the index colonoscopy from the PALGA database.

To identify risk predictors for the detection of ASPs, we performed univariate and multivariate logistic regression analysis including sex, age (55–59, 60–64, 65–69, 70+years) and invitation round (first/consecutive). Collinearity of the predictors were evaluated and considered absent with a tolerance level of >0.1. P values were two-sided and were considered statistically significant when <0.05. The PPV was stratified by sex and invitation round.

To evaluate whether the lower FIT cutoff influenced the PPV, we performed a sensitivity analysis calculating the PPV of individuals who were referred for colonoscopy using a FIT cutoff of 15 µg Hb/g feces. All analyses were performed in IBM SPSS Statistics 26.

Ethical approval

This study was conducted in accordance with the Dutch population screening act. Returning the FIT is considered as consent for the use of pseudonymized data of all screening colonoscopy and pathology reports, following the population screening act (WBO). All individuals had the right to object to the use of their data.

RESULTS

A total of 334,615 colonoscopies were performed during the study period, of which 11,733 (3.5%) were excluded, because of insufficient bowel preparation (2.8%; n=9,484) and/or no cecal intubation (2.0%; n=6,777). Of 322,882 included screenees who underwent a colonoscopy, the median (IQR) age was 66 (61–71) years and 133,552 (41.4%) were women (Table 1). In total 180,038 screenees (55.8%) were referred for colonoscopy after a positive FIT in the first invitation round, 142,844 (44.2%) were referred for colonoscopy after a positive FIT in consecutive rounds. In 310,387 cases (96.1%), screenees were tested with a FIT cutoff of 47 µg Hb/g feces and 11,896 screenees (3.7%) were tested with a FIT cutoff of 15 µg Hb/g feces.

Advanced neoplasia detection

The percentage of screenees with at least one CRC was 6.6% and this was 36.4% for advanced adenomas. In 19,014 screenees (5.9%), at least one ASP was detected (Table 1). ASPs were more often detected in women than in men (6.3% vs. 5.6%; P<0.001). The ASP detection rate differed by age, with lower detection rates for age group 55–59 years than the older age groups of 60–64, 65–69, and 70+ years (5.2% vs. 6.1% vs. 6.1% vs. 5.9 %; P<0.001). The proportion of screenees with at least one serrated polyp ≥10mm, SSL with dysplasia, or TSA were 4.1%, 1.3 %, and 0.9 %, respectively. Serrated polyps ≥10mm were more often diagnosed in women than in men (4.4% vs. 3.8%; P<0.001). The NNS to detect at least one ASP was lower for women than for men in age groups above 60 years (Figure 2). The opposite was true for advanced adenoma: the NNS to detect at least one advanced adenoma was lower for men than for women in these age groups. The NNS for CRC declined substantially with increases in the age groups for women and men.

Table 1 - Characteristics of the fecal immunochemical test (FIT)-positive screenees with advanced serrated polyps. Total FIT-positive colonoscopies

	Total FIT-positive colonoscopies	**≥1 ASP**	**p-value†**	**≥1 SP ≥10mm***	**p-value†**	**≥1 SSL with dysplasia***	**p-value†**	**≥1 TSA***	**p-value†**
	n= 322,882	n=19,014 (5.9%)		n=13,162 (4.1%)		n=4,214 (1.3%)		n=2,994 (0.9%)	
Sex, n (%)			p<0.001		p<0.001		p=0.20		p=0.02
Male	189,330 (59)	10,646 (5.6)		7,242 (3.8)		2,430 (1.3)		1,820 (1.0)	
Female	133,552 (41)	8,368 (6.3)		5,920 (4.4)		1,784 (1.3)		1,174 (0.9)	
Age, median (IQR)	66 (61-71)	66 (61-71)	-	65 (61-71)	-	67 (63-71)	-	67 (63-71)	-
Age groups, n (%)			p<0.001		p<0.001		p<0.001		p<0.001
55-59	59,891 (19)	3,128 (5.2)		2,262 (3.8)		559 (0.9)		406 (0.7)	
60-64	71,031 (22)	4,305 (6.1)		3,065 (4.3)		824 (1.2)		645 (0.9)	
65-69	102,607 (32)	6,279 (6.1)		4,314 (4.2)		1,458 (1.4)		944 (0.9)	
70+	89,353 (28)	5,302 (5.9)		3,521 (3.9)		1,373 (1.5)		999 (1.1)	
FIT-round, n (%)			p=0.79		p=0.94		p=0.06		p<0.001
first	180,038 (56)	10,620 (5.9)		7,335 (4.1)		2,289 (1.3)		1,773 (1.0)	
successive	142,844 (44)	8,394 (5.9)		5,827 (4.1)		1,925 (1.3)		1,221 (0.9)	
F-Hb (µg Hb/g feces), median (IQR)‡			-		-		-		-
15 µg/g	65 (28-171)	80 (31-186)		77 (30-185)		82 (32-186)		106 (31-193)	
47 µg/g	128 (72-208)	135 (75-213)		134 (74-213)		136 (75-212)		155 (80-221)	

ASP, advanced serrated polyp; SSL, sessile serrated lesion; TSA, traditional serrated adenoma; IQR, interquartile range; Hb, hemoglobin. F-Hb: fecal hemoglobin concentration.

* Screenees could be included in more than one column if they had more than one different subtype of ASP.

† Chi-squared test for categorical variables.

‡ Missing data for 599 screenees.

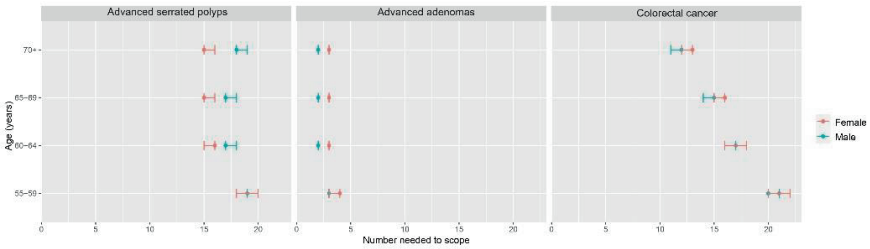

Figure 2 - Number needed to scope in order to detect at least one advanced serrated polyp, advanced adenoma, and colorectal cancer, according to age group and sex.

Predictors for advanced serrated polyp detection

Multivariate logistic regression analysis showed that individuals in older age groups were more likely to have an ASP diagnosis than individuals of 55–59 years (60–64 years, odds ratio [OR] 1.17, 95%CI 1.12–1.23; 65–69 years, OR 1.19, 95%CI 1.14– 1.24; and 70+years, OR 1.15, 95%CI 0.09–1.20). Men were less likely to have an ASP diagnosis than women (OR 0.89, 95% CI 0.87–0.92) (Table 2). Invitation round was not significantly associated with the detection of an ASP (OR 1.00, 95%CI 0.98– 1.03).

Table 2 - Association between the presence of an advanced serrated polyp and patient characteristics.

	Univariate OR (95%CI)	Multivariate OR (95%CI)
Sex, male	0.89 (0.87–0.92)	0.89 (0.87–0.92)
Age groups, years		
55-59	reference	reference
60-64	1.17 (1.12–1.23)	1.17 (1.12–1.23)
65-69	1.19 (1.13–1.24)	1.19 (1.14–1.24)
70+	1.15 (1.09–1.20)	1.15 (0.09–1.20)
FIT round, first	1.00 (0.97–1.03)	*NA*

OR: odds ratio; FIT, fecal immunochemical test; NA, not applicable.

Location and size of advanced serrated polyps

ASPs were more often detected in the proximal colon than in the distal colon, both at the index colonoscopy (63.4% vs. 36.6%) and in colonoscopies in the following 6 months (57.8% vs. 42.2%) (Table 3). Serrated polyps ≥10mm were more often located in the proximal colon (65.3% at the index colonoscopy;

56.0% in the following 6 months), which was also true for SSLs with dysplasia (69.9% and 75.2%, respectively). TSAs however were more common in the distal colon (73.8% and 67.1%, respectively), as were advanced adenomas (69.5% and 55.0%). At the index colonoscopy, the median size of serrated polyps ≥10mm was 12 mm, the median size of SSLs with dysplasia was 7 mm, and that of TSAs was 10 mm. The median size of advanced adenomas was in line with the size of ASPs at 11 mm.

Table 3 - Location and size of the serrated polyps identified by subtype.

	Advanced Serrated Polyps	**SP ≥10mm**	**SSL with dysplasia**	**TSA**
No. polyps, n (%)*				
Index colonoscopy (n=695,571)	23,905 (3.4)	19,353 (2.8)	4,772 (0.7)	3,089 (0.4)
6 months (n=45,803)	2,198 (4.8)	1,393 (3.0)	614 (1.3)	394 (0.1)
Index colonoscopy†, n(%)				
Proximal	13,866 (63.4)	11,641 (65.3)	3,058 (69.9)	671 (26.2)
Distal	7,990 (36.6)	6,187 (34.7)	1,319 (30.1)	1,893 (73.8)
6 months†				
Proximal	1,088 (57.8)	654 (56.0)	407 (75.2)	108 (32.9)
Distal	795 (42.2)	513 (44.0)	134 (24.8)	220 (67.1)
Size in mm, median (IQR) ‡				
Index colonoscopy	10 (10-15)	12 (10-15)	7 (4-10)	10 (5-15)
6 months	12 (10-15)	12 (10-15)	10 (6-14)	13 (7.5-22)

SSL, sessile serrated lesion; TSA, traditional serrated adenoma; IQR, interquartile range.

* Polyps could be included in more than one column if a serrated polyp ≥10mm also had dysplasia.
† For index colonoscopies, the location was missing for advanced serrated polyps, serrated polyps ≥10mm, SSLs with dysplasia, and TSAs in 2049, 1525, 395, and 525 cases, respectively, and for procedures within 6 months after the index colonoscopy in 315, 226, 73, and 66 cases, respectively.

‡ Polyp size for the index colonoscopy was based on the colonoscopy report, whereas for colonoscopies within 6 months, it was based on the pathology report.

Positive predictive value including advanced serrated polyps

Based on the most advanced lesion, the PPVs for CRC, advanced adenoma, and ASP were 6.6%, 34.5%, and 2.7%, respectively (Figure 3), meaning, in 2.7% of all FIT-positive screenees, at least one ASP was present in the absence of a CRC or advanced adenoma. As such, the PPV for relevant findings was 41.1% using the current definition of the national CRC screening program, which increased to 43.8% using our suggested updated definition including ASP. This PPV did not significantly change after exclusion of those colonoscopies performed in screenees using the lower FIT cutoff of 15 µg Hb/g feces. For the remaining 11,896 colonoscopies the PPV for CRC was 5.9%, for advanced adenoma 37.5%, and for ASP 2.2%. The PPV using the current definition was 36.3% for women and 44.5% for men and increased to 39.5% and 46.9%, respectively, when including ASPs. This increase of 3.2 percentage points for women and 2.4 percentage points for men was significantly different ($P<0.001$). The increase in PPV owing to the inclusion of ASPs was lower in the first invitation round (from 47.5% to 49.9%) than in consecutive rounds (from 32.9% to 36.0%; $P<0.001$).

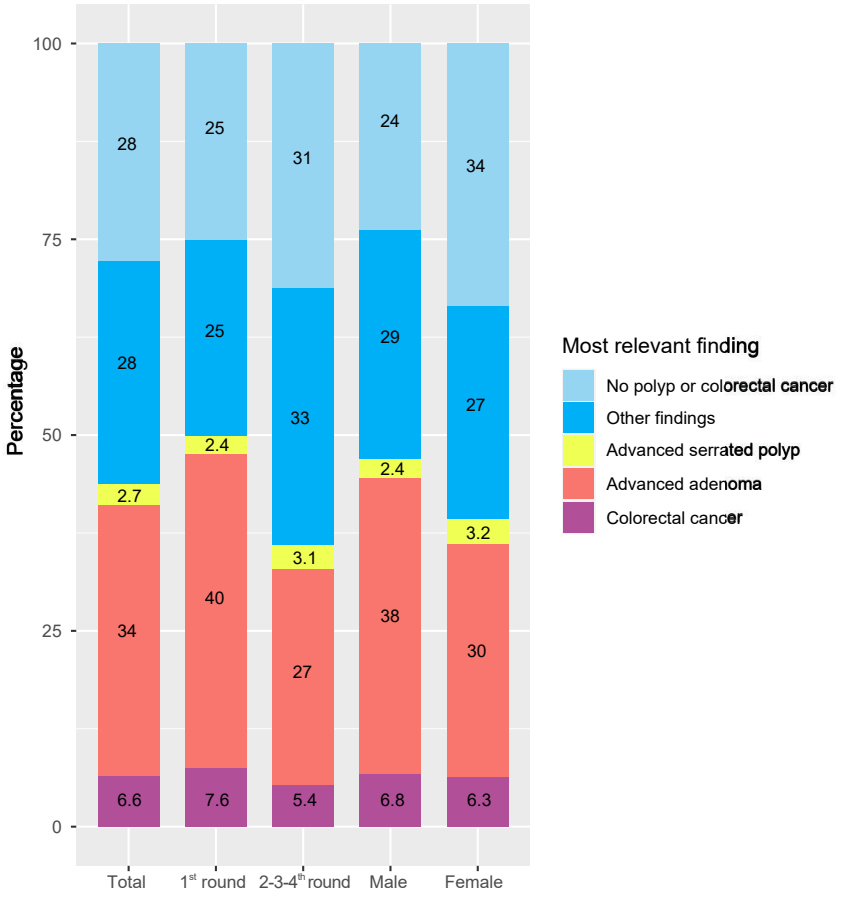

Figure 3 - Positive predictive value of the screening program based on the updated definition for advanced neoplasia including advanced serrated polyps.

Note: proportions have been rounded so they do not completely align with the numbers in the text.

DISCUSSION

In this study within the Dutch FIT-based CRC screening program, a considerable proportion of FIT-positive screenees who underwent follow-up colonoscopy had at least one ASP (5.9%). These lesions were more frequently detected in women and individuals in the older age groups (>60 years). Including ASPs in the yield of FIT-screening increased the PPV for advanced neoplasia from 41.1% to 43.8%.

Results from this study demonstrate that in a FIT-based CRC screening program, the additional yield of ASPs is modest at best. Definitions for yield and detection rates should be distinguished here because half of the screenees who had an ASP had a concurrent CRC or advanced adenoma so, following the original definition, were already considered as having a relevant finding (a positive finding when evaluating yield).

No previous studies have reported the additional yield of screening when including ASPs in terms of the PPV for advanced neoplasia, nor have they reported on the PPV for ASPs using our definition (i.e. any serrated polyp ≥10mm, SSL with dysplasia, or TSA). One study reported on the PPV for advanced neoplasia including CRC, advanced adenomas, and SSLs ≥10mm in a colonoscopy cohort, showing a PPV of 41%, which was comparable with our result (43.8%) (11). The estimated individual PPVs were 9% for CRC, 27% for advanced adenoma, and 3% for ASP, which are also consistent with our findings (6.6%, 34.5%, and 5.9%, respectively). However, this study by Redwood et al. was based on only 661 screenees who were scheduled for an average-risk screening or surveillance colonoscopy, making comparison with our setting of organized FIT-based screening difficult.

Our observation that FIT has a higher PPV for ASP in consecutive rounds, while detection rates were comparable, might be a result of the poor sensitivity of FIT for ASPs. In contrast, a higher bleeding risk associated with CRCs and advanced adenomas most likely explains these lesions being detected more often in the first screening round. This hypothesis is also supported by the fact that the PPV was not significantly higher when individuals who received a colonoscopy after testing positive at a lower FIT cutoff of 15 µg Hb/g feces were evaluated separately. Of note, when evaluating the current literature regarding the yield of CRC population

screening, one should take into consideration that a small proportion of serrated polyps might have been classified among advanced neoplasia owing to the limited reproducibility of the optical and pathological diagnosis of serrated polyps.

Some studies have reported detection rates of the different categories of ASPs in FIT-based or primary colonoscopy screening; however, none of these studies have used our definition of ASP and assessed it within an organized FIT-based CRC screening program. A study comparing three FIT-based national CRC screening programs showed comparable detection rates with our study, with detection rates for serrated polyps ≥10mm of 1.2%–2.5%, for SSLs with dysplasia of 0.2%–0.6%, and for TSAs of 0.1% (21). Studies reporting on primary colonoscopy screening demonstrated detection rates for serrated polyps ≥10mm of 1.1%–2.6%, for SSLs with dysplasia of 0.2%–1.5%, and for TSAs of 0.1%–0.8% (21–23).

Interestingly, when we compare these different screening settings, the ASP detection rates seem highly similar and in line with our results. Possibly this is also a result of the low sensitivity of FIT for ASPs, meaning that the detection of ASPs is a coincidental finding, rather than their being detected by FIT.

Therefore, the detection rate of ASPs likely corresponds to the ASP prevalence in the general population, instead of a preselected high risk population. Hence, here lies a great potential for a screening test that also targets screenees with ASPs. The ColoGuard (Exact Sciences; Madison, Wisconsin, USA) for instance, a multitarget stool DNA test including methylation markers, seems to have a promising higher sensitivity for ASPs, because SSLs with dysplasia are characterized by high DNA methylation levels (9,11). Screening with such tests could result in higher overall detection rates of ASPs, and therefore timely detection and resection of ASPs. The main restriction for the worldwide implementation of the ColoGuard are its complex logistics owing to the required large stool samples, lower specificity, and higher costs compared with FIT (24,25).

In this FIT-screening setting, ASPs were more often detected in women and older screenees. This finding is in line with previous studies, in which female sex has already been described as a risk factor for SSLs with

dysplasia and serrated polyp-derived CRCs (26–29). The differences between women and men were small however and were considered clinically less relevant. Nevertheless, it is important to note that this higher detection of ASPs in women is contrary to the known higher performance of FIT in men to detect advanced adenoma and CRC that our results have confirmed (30–32). These major sex differences in the performance of FIT testing might be relevant in the near future when a more personalized strategy based on risk factors, such as previous hemoglobin concentration, age, and sex could be used. If ASPs are not taken into consideration, women might be invited for CRC screening at an older age than men. As a consequence, relatively large numbers of ASPs would be missed and could develop into CRC.

Despite the modest increase in PPV when including ASPs as target lesions, this study substantially contributes to our under- standing of ASPs for the following reasons. First, the extensive organization of FIT-based screening programs depends completely on the cutoff value for positivity, and is led by multiple factors, including: colonoscopy capacity, the proportion of false positives and false negatives that is deemed acceptable, cost-effectiveness, and public health policies. Decision-making regarding false positives and false negatives should be based on the yield and expected CRC-related mortality reduction of a program, thereby taking into account all relevant lesions. Although modest, the increase in PPV by 2.7 percentage points is of importance, and reflects screenees who are currently incorrectly classified as false positives. Second, estimation of the detection rates of ASPs within a FIT-based screening program are necessary to enable any comparison with other screening tests, for example the multitarget stool tests. Third, accurate registration of (advanced) serrated polyps is essential to monitor and optimize the quality of (proximal) serrated polyp detection among endoscopists, which is highly relevant in clinical practice because higher serrated polyp detection rates are associated with a lower risk of interval postcolonoscopy CRC (33).

For the interpretation of our results, some limitations must be taken in consideration. First, colonoscopy reports were not linked automatically per polyp to pathology reports in the standardized database, impeding proper evaluation of polyp size, as this requires pathological polyp diagnosis and estimated polyp size by the endoscopist. We estimated an incorrect linkage of polyp type and polyp size in about 2% of all polyps. This included half of the

group of polyps within a FIT-positive screenees that had the same pathological diagnosis (serrated polyp or adenoma) and also shared the same location. This proportion, however, was too low to have influenced our outcomes significantly. Second, relevant findings like CRC and advanced adenoma were more often detected at the start of the screening program, owing to the fact that relatively older individuals were invited in the first years. The results we are currently presenting might therefore evolve over time. Third, the relative high cutoff value in our screening program might have influenced our outcomes; however, given the low sensitivity of FIT for ASPs, this might not have significantly affected the detection rates or PPVs for ASPs (34).

A strength of this study derives from the nationwide, prospective, and comprehensive data collection within our CRC screening program, which allowed for the analysis of a large sample of FIT-positive screenees referred for colonoscopy. Colonoscopies were performed across the Netherlands and the data is of high quality because of the thorough training and quality monitoring of endoscopists and pathologists in the screening program. Essential for this study was the quality of histopathological diagnosis, especially the subclassification of serrated polyps, which was assured by an obligatory e-learning module for all participating pathologists. This e-learning was shown to be effective (14).

In conclusion, we demonstrated a considerable detection rate of ASPs within colonoscopies performed after a positive FIT, while the additional yield of screening was 2.7 percentage points. We believe that, although this is a rather modest increase in the yield of screening, it nevertheless has some important clinical implications. As ASPs are high risk premalignant lesions, and reference standards for FIT and other new screening tests are needed, our results support taking these lesions into account when determining the yield of screening in a FIT-based population. Routinely monitoring the detection rate and PPV of relevant colorectal lesions including ASPs should be standard practice in organized CRC screening programs.

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