Serrated polyp detection and risk of interval post-colonoscopy colorectal cancer: a population-based study

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Summary

Background Adenoma detection rate (ADR) is a well-established quality indicator for colonoscopy and is inversely associated with the incidence of interval post-colonoscopy colorectal cancer. However, interval post-colonoscopy colorectal cancers frequently develop from serrated polyps, which are not included in the ADR. Therefore, the proximal serrated polyp detection rate (PSPDR) has been proposed as a quality indicator, but its association with interval post-colonoscopy colorectal cancer has not been studied. We aimed to evaluate this potential association based on data collected in the Dutch colorectal cancer screening programme.

Methods In this population-based study, using colonoscopy data from the Dutch faecal immunochemical test-based colorectal cancer screening programme and cancer data from the Netherlands Cancer Registry, we evaluated the association between endoscopists' individual PSPDR and their patients' risk of interval post-colonoscopy colorectal cancer with a shared frailty Cox proportional-hazard regression analysis. Participants in the screening programme who were eligible for inclusion were aged 55–76 years, had a positive faecal immunochemical test (cutoff 15 µg Hb/g faeces at start and changed mid-2014 to 47 µg Hb/g faeces), were asymptomatic, and underwent a colonoscopy between Jan 1, 2014, and Dec 31, 2020. The PSPDR was defined as the proportion of colonoscopies in which at least one serrated polyp proximal to the descending colon was detected, confirmed by histopathology. The ADR was defined as the proportion of all colonoscopies in which at least one conventional adenoma was detected, confirmed by histopathology. Detection rates were determined for each endoscopist individually. We additionally evaluated the risk of interval post-colonoscopy colorectal cancer for endoscopists with a PSPDR and ADR above the median versus endoscopists with either one or both parameters below the median. This study is registered with the Netherlands Trial Registry, NL8350.

Findings During the study period, 329 104 colonoscopies were done, of which 277 555, done by 441 endoscopists, were included in the PSPDR calculations. The median PSPDR was 11·9% (IQR 8·3–15·8) and median ADR was 66·3% (61·4–69·9). The correlation between the PSDPR and ADR was moderate (r=0·59; p<0·0001). During a median follow-up of 33 months (IQR 21–42), 305 interval post-colonoscopy colorectal cancers were detected. For each percentage point increase in PSPDR, the adjusted interval post-colonoscopy colorectal cancer hazard was 7% lower (hazard ratio [HR] 0·93, 95% CI 0·90–0·95; p<0·0001). Compared with endoscopists with a PSPDR greater than 11·9% and ADR greater than 66·3%, the HR of interval post-colonoscopy colorectal cancer for endoscopists with a low PSPDR and high ADR was 1·79 (95% CI 1·22–2·63), for endoscopists with a high PSPDR and low ADR was 1·97 (1·19–3·24), and for endoscopists with a low PSPDR and low ADR was 2·55 (1·89–3·45).

Interpretation The PSPDR of an endoscopist is inversely associated with the incidence of interval post-colonoscopy colorectal cancer. Implementation of PSPDR monitoring, in addition to ADR monitoring, could optimise colorectal cancer prevention.

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Introduction

Colonoscopy with resection of adenomatous polyps reduces the incidence and mortality of colorectal cancer.[1] Nevertheless, up to 9% of all colorectal cancer cases diagnosed in daily practice occur in patients who had a previous colonoscopy in which no cancer was detected.[2] These so-called post-colonoscopy colorectal cancers, particularly interval post-colonoscopy colorectal cancers, could be preventable by high-quality colonoscopy with resection of all premalignant lesions. Interval post-colonoscopy colorectal cancers are those that occur after colonoscopy and before the recommended screening or surveillance interval.[3,4]

The adenoma detection rate (ADR), defined as the proportion of colonoscopies in which an endoscopist detects at least one adenoma, is inversely associated with the incidence of interval post-colonoscopy colorectal cancer.[5] As the incidence rate of interval post-colonoscopy colorectal cancer is usually too low to be used as colonoscopy quality indicator for the individual endoscopist, ADR of endoscopists is advised as a proxy. The ADR is currently the main instrument used to

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Research in context

Evidence before this study

We searched PubMed, Cochrane Library, and MEDLINE for prospective and retrospective studies published between Jan 1, 2004, and Dec 31, 2021, using the terms "post-colonoscopy colorectal cancer", "polyp detection", "adenoma detection rate", and "serrated polyp detection", with no language restrictions. Interval post-colonoscopy colorectal cancer—ie, colorectal cancer occurring after a complete colonoscopy and before surveillance is due—represents up to 9% of all colorectal cancer cases and causes substantial mortality and morbidity. Such colorectal cancer cases often result from missed or incompletely resected polyps. Indeed, patients examined by endoscopists with high adenoma detection rate (ADR) have much lower risk of future interval post-colonoscopy colorectal cancer than those examined by endoscopists with low ADR. Therefore, ADR is the most important performance indicator for endoscopists in colonoscopy worldwide and has been a major target for colonoscopy quality improvement. Serrated polyps, which have recently come into focus as a precursor to 15–30% of all colorectal cancer cases, are not incorporated in the ADR, which is particularly troublesome since these flat, subtle lesions are easily overlooked during colonoscopy. Interval post-colonoscopy colorectal cancer disproportionately often results from missed serrated polyps rather than missed adenomas. However, unlike the ADR, serrated polyp detection rates have never been studied as predictor for interval post-colonoscopy colorectal cancer incidence. Consequently, serrated polyps are not incorporated in current quality indicators for endoscopists.

Added value of this study

We showed that serrated polyp detection is strongly related to interval post-colonoscopy colorectal cancer incidence, an effect that is independent of the ADR. Patients examined by endoscopists in the lowest quintile (in terms of serrated polyp detection) had a tripled risk for future interval post-colonoscopy colorectal cancer compared with those examined by an endoscopist in the highest quintile. Each percentage point increase in proximal serrated polyp detection rate (PSPDR) resulted in a 7% lower risk of interval post-colonoscopy colorectal cancer. The highest protective effect was found in endoscopists with an ADR and a PSPDR above the overall median.

Implications of all the available evidence

At present, the ADR is the only evidence-based polyp detection parameter. Based on our results, monitoring of serrated polyp detection could be a valuable addition to optimise colonoscopy quality and reduce interval post-colonoscopy colorectal cancer incidence.

measure and benchmark the performance of endoscopists in detecting premalignant lesions and preventing interval post-colonoscopy colorectal cancers. However, this quality indicator has one major caveat: it does not include serrated polyps, even though these lesions appear to cause a considerable proportion of interval post-colonoscopy colorectal cancers.

Serrated polyps progress to colorectal cancer via the serrated neoplasia pathway, and account for around 15–30% of sporadic colorectal cancers.[6] Serrated polyps are subdivided into sessile serrated lesions (SSLs), traditional serrated adenomas (TSAs), and hyperplastic polyps (HPs). Because of their indistinct colour, vague borders, and flat or sessile shape, the endoscopic detection and resection of serrated polyps is challenging.[7] As a result, serrated polyps are easily missed and often incompletely resected, which are both important contributors to interval post-colonoscopy colorectal cancers.[3,7] Evidenced by clinical and molecular similarities, interval post-colonoscopy colorectal cancers indeed seem more likely to originate from serrated polyps than from adenomas.[8] Both interval post-colonoscopy colorectal cancers and serrated polyps are predominantly located in the proximal colon, are frequently microsatellite instable or mismatch repair deficient, and are often CpG island methylator phenotype-high, all hallmarks of the serrated neoplasia pathway.[8,9] Thus, improved serrated polyp detection would theoretically reduce interval post-colonoscopy colorectal cancer incidence.

Over the past few years, several parameters for serrated polyp detection have been proposed, all aimed at evaluating the detection of relevant serrated polyps by individual endoscopists. These include the proximal serrated polyp detection rate (PSPDR), SSL detection rate (SSLDR), and serrated polyp detection rate (SPDR).[10,11] The PSPDR is defined as the proportion of colonoscopies in which at least one serrated polyp proximal to the descending colon is detected and its use as a parameter in daily practice has two advantages. First, the differentiation of HPs and SSLs is rather tricky for pathologists, even among experts; interobserver agreement is only moderate.[12] The PSPDR leaves out the histopathological subtyping of HPs and SSLs and could be regarded as an easy to measure proxy for the detection of all clinically relevant serrated polyps by an individual endoscopist.[12,13] Second, the PSPDR varies widely among endoscopists, thereby enabling differences between individual physicians to be identified more easily than for parameters with lower ranges.[13] However, to our knowledge, a potential association between endoscopists' PSPDR and their patients' risk of interval post-colonoscopy colorectal cancer has never been studied, and this evidence is needed to show the added value of PSPDR as a colonoscopy quality indicator. We aimed to evaluate this potential association based on data collected in the Dutch colorectal cancer screening programme.

Methods

Study design

In this population-based study, we analysed prospectively collected data in the Dutch colorectal cancer screening programme. All individuals who were eligible for inclusion had a positive faecal immunochemical test (cutoff 15 µg Hb/g faeces at start and changed mid-2014 to 47 µg Hb/g faeces) and underwent a colonoscopy between Jan 1, 2014, and Dec 31, 2020.[14] As such, all individuals included were asymptomatic and aged 55–76 years. Each endoscopist performing screening colonoscopies in the Netherlands is strictly monitored and audited and is obliged to gain specific accreditation, as described in detail previously.[15] The need to meet these standards implies that all endoscopists included in this study do at least 200 colonoscopies per year and at least 50 polypectomies per year, and achieve a caecal intubation rate of at least 95%, withdrawal time of at least 6 min in 90% or more of colonoscopies, ADR of at least 30%, removal rate of at least 90% of detected polyps, and retrieval rate of resected polyps of at least 90% in screening colonoscopies. To standardise the quality of histopathological assessment of colonic lesions within our national screening programme, pathologists performing histopathological analyses were obliged to complete an e-learning module. This e-learning covered several topics, including subclassification of serrated polyps, and was proven to increase the homogeneity among pathologists in differentiating serrated polyps.[16]

For the calculation of the PSPDR per endoscopist, only complete colonoscopies with caecal intubation were included, with adequate bowel preparation and written statement that all detected polyps were completely removed by the endoscopist and evaluated by the pathologist. Colonoscopies were excluded when a lesion suspicious for colorectal cancer was detected; caecal intubation was not achieved; Boston Bowel Preparation Score was below six; the procedure was prematurely aborted; the registered follow-up advice was referral for CT-colonography or no follow-up advice was registered; lesions were sent for pathological evaluation but pathology data were missing; or a colorectal cancer was already registered before the date of screening colonoscopy. Colonoscopies were also excluded when done by an endoscopist who had performed fewer than 75 colonoscopies for the screening programme during the study period (appendix p 2).

To calculate the interval post-colonoscopy colorectal cancer rate, we additionally excluded colonoscopies in which follow-up was less than 6 months; colorectal cancer was detected within 6 months after colonoscopy; follow-up advice was an early evaluation of the polypectomy scar for completeness; or follow-up advice was a referral for further endoscopic treatment (eg, endoscopic mucosal resection or endoscopic submucosal dissection).

The Dutch Act on Medical Research Involving Human Subjects did not apply to our study, since neither screenees nor endoscopists were exposed to any additional interventions other than standard of care. The population screening research committee of the governmental National Institute for Public Health and the Environment approved the study protocol. The privacy of people undergoing screening was guaranteed by pseudonymisation of all data before data transmission to our research team, according to the General Data Protection Regulation Act.[17]

Data collection

Data regarding screening colonoscopies were obtained from a centralised database called ScreenIT, managed by the national screening organisation. Colonoscopy data (eg, date of the procedure, caecal intubation, quality of bowel preparation, performing endoscopist, and surveillance advice), as well as polyp data (eg, location and histology), were prospectively collected in this database. Data regarding interval post-colonoscopy colorectal cancer were provided by the Netherlands Comprehensive Cancer Organization using the Netherlands Cancer Registry. This registry contains detailed information on each malignancy in the Netherlands (eg, type of cancer, location, and staging). Patient colonoscopy data were linked to cancer registry data using Dutch citizen service numbers.

Outcome definitions

All detection rates were calculated for each endoscopist individually. The PSPDR was defined as the proportion of colonoscopies in which at least one serrated polyp proximal to the descending colon was detected, confirmed by histopathology. According to the WHO definition, serrated polyps were defined as either HP, SSL, or TSA.[18] The ADR was defined as the proportion of all colonoscopies in which at least one conventional adenoma was detected, confirmed by histopathology. The SSLDR was defined as the proportion of all colonoscopies in which at least one SSL was detected, confirmed by histopathology. The SPDR was defined as the proportion of all colonoscopies in which at least one HP, SSL, or TSA was detected, confirmed by histopathology.

The World Endoscopy Organization consensus definition of post-colonoscopy colorectal cancer, the colonoscopy report, and the Dutch post-polypectomy surveillance guideline were used to define interval post-colonoscopy colorectal cancers.[4,19] An interval type post-colonoscopy colorectal cancer is a colorectal cancer case detected before the advised post-colonoscopy surveillance interval. The advised post-colonoscopy surveillance interval was based on the conclusion of the endoscopy report and, if this advice was lacking, the national guideline determined the surveillance interval.[19] In case of any discrepancy in surveillance interval between the guideline and the endoscopists' advice, as registered in the endoscopy report, the endoscopists' advice was decisive, since this was considered to be closest to clinical practice. All interval post-colonoscopy colorectal cancers

See Online for appendix

were located in the colorectum. As such, pathology-confirmed adenocarcinomas, mucinous carcinomas, undifferentiated carcinomas, and signet cell carcinomas were included. Neuroendocrine tumours, lymphomas, small-cell carcinomas, carcinoid tumours, among other tumour types, were excluded. The definition of advanced-stage interval post-colonoscopy colorectal cancers included stage III (metastasis in regional lymph node) or stage IV (metastasis to site or organ) colorectal cancer cases based on TNM classification (American Joint Committee, eighth edition).[20] Proximal interval post-colonoscopy colorectal cancers were located proximal to the descending colon, including the splenic flexure.

Statistical analysis

This was an observational retrospective study, including all patients in the screening programme period from initiation to the latest possible point in time (2014–20). Within the study period, 239 217 colonoscopies were done and 305 interval post-colonoscopy colorectal cancers were detected, which would provide us with more than 99·9% power to detect a hazard ratio (HR) of 0·95, based on the methods of Hsieh and Lavori.[21]

PSPDR is presented as the median with IQR. Additionally, the median PSPDR was evaluated for each year of inclusion. Differences were evaluated for significance with the Kruskal-Wallis test statistic, considering endoscopists who had done more than 50 colonoscopies per year.

To test the assumption that PSPDR for individual endoscopists was constant over time, we calculated and compared with PSPDR of each endoscopist in the first half (2014 to mid-2017) and second half (mid-2017 to 2020) of the study period. Shorter intervals of comparison (eg, per year) were not deemed possible, since a large subset of endoscopists did not do sufficient colonoscopies per year to calculate reliable estimates. A median difference in PSPDR of less than 2% within both time periods was considered as non-time dependent. To evaluate whether colonoscopy volume per endoscopist was correlated with the PSPDR, we calculated the Spearman correlation coefficient and interpreted its magnitude following the rules of Schober and colleagues.[22]

We used shared frailty Cox proportional hazards regression modelling to evaluate the strength of the association between the PSPDR and the risk of interval post-colonoscopy colorectal cancer. Individuals were followed up from 6 months after the colonoscopy date until the date of interval post-colonoscopy colorectal cancer diagnosis or end of follow-up (December, 2020). Models included individual age and sex as potential confounders. The individual endoscopist was included as a random effect to account for within-endoscopist clustering.

We assessed the linearity of the association between PSPDR and interval post-colonoscopy colorectal cancer by evaluating whether fractional polynomials models (ie, square or cubic transformation of the PSPDR) resulted in better model fit, considering a difference of 2 units on the Akaike Information Criterion as a meaningful improvement. Appropriateness of the proportional hazards assumption in the PSPDR model was evaluated by analysing the plots of the Schoenfeld residuals. To evaluated a time-dependent effect of the PSPDR, we did a sensitivity analysis including year of colonoscopy and the interaction with PSPDR as additional covariates in the model.

Similar analyses were done for female and male participants separately, and for the risk of advanced and non-advanced, proximal, and distal interval post-colonoscopy colorectal cancers. For ease of interpretation, endoscopists were also grouped based on PSPDR quintiles (quintile 1: 0·8–7·5%, quintile 2: 7·6–10·4%, quintile 3: 10·5–12·9%, quintile 4: 13·0–16·9%, and quintile 5: 17·0–29·1%). For these analyses, the HR for each group was compared against endoscopists in the lowest quintile.

The association between the ADR and the risk of interval post-colonoscopy colorectal cancer was evaluated using the same strategy. We calculated the Spearman correlation coefficient between PSPDR and ADR. To evaluate the additional effect of PSPDR compared to ADR, endoscopists were classified into four groups, with the median PSPDR and median ADR as cutoff values, as follows: low-PSPDR and low-ADR, low-PSPDR and high-ADR, high-PSPDR and low-ADR, and high-PSPDR and high-ADR. The HR of interval post-colonoscopy colorectal cancer was calculated for each group and compared with the group of endoscopists with a high-PSPDR and high-ADR.

Associations between the SSLDR and SPDR and the risks of interval post-colonoscopy colorectal cancer were evaluated as described. To enable a statistical comparison of these serrated polyp detection parameters on the risk of interval post-colonoscopy colorectal cancer, we used Cox regression modelling, after standardisation of each parameter ([PSPDR value−meanPSPDR]/sdPSPDR).

Analyses were done with SPSS version 26.0.0.1 and R version 4.0.3 using the coxme package. This study is registered with the Netherlands Trial Registry, NL8350.

Role of the funding source

There was no funding source for this study.

Results

Between Jan 1, 2014, and Dec 31, 2020, 329 104 colonoscopies were done, of which 51 549 were excluded. The most common reasons for excluding colonoscopies were detection of a lesion suspicious for colorectal cancer (27 322 colonoscopies) and missing pathology data for lesions sent for pathological evaluation (9840 colonoscopies). The remaining 277 555 colonoscopies were included in the PSPDR calculations (appendix p 2). These colonoscopies were done by 441 endoscopists, with a median of 542 (IQR 317–840) colonoscopies per endoscopist (table 1).

	All colonoscopies (n=277 555)	Interval post-colonoscopy colorectal cancer* (n=305)
Age, years	68 (63–72)	70 (66–74)
Sex		
Female	115 240 (42%)	130 (43%)
Male	162 315 (58%)	175 (57%)
Location of interval post-colonoscopy colorectal cancer		
Distal†	..	147 (48%)
Proximal‡	..	148 (49%)
Colorectum, not specified	..	10 (3%)
Colorectal cancer stage		
Advanced	..	177 (58%)
Non-advanced	..	121 (40%)
Data missing	..	7 (2%)
Follow-up between colonoscopy and event or end of follow-up, months	36 (21–57)	33 (21–42)
Endoscopist data (n=441)		
Total colonoscopies done	542 (317–840)	..
Proximal serrated polyp detection rate	11·9% (8·3–15·8)	..

Data are median (IQR) or n (%).*Based on 239 217 colonoscopies. †Located distal to the splenic flexure. ‡Located proximal to the descending colon, including the splenic flexure.

Table 1: **Baseline characteristics of included individuals and endoscopists**

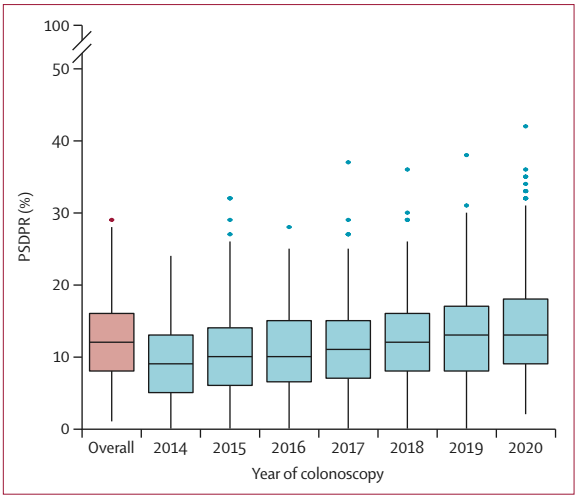

Figure 1: **Median PSPDR per year of colonoscopy**
Only endoscopists who did more than 50 colonoscopies per year within our study have been included. Error bars represent range. Dots represent outliers using a step of 1·5 times the IQR. PSPDR=proximal serrated polyp detection rate.

	Hazard ratio* (95% CI)	p value
Proximal serrated polyp detection rate	0·93 (0·90–0·95)	<0·0001
Age	1·05 (1·03–1·07)	<0·0001
Female sex†	1·06 (0·84–1·32)	0·64

PSPDR=proximal serrated polyp detection rate. *Per percentage point increase in PSPDR, per year increase in age, and for females. †Male was used as a reference.

Table 2: **Shared frailty Cox proportional hazards regression analysis of PSPDR and interval post-colonoscopy colorectal cancer**

The median PSPDR was 11·9% (IQR 8·3–15·8). During the study, the median PSPDR increased from 9·2% (IQR 5·3–13·2) in 2014 to 13·0% (9·3–17·6) in 2020 (p<0·0001; figure 1). The median difference btween the first half and second half of the study period was 1·3 percentage points (IQR –1·1 to 3·9). We determined the correlation between PSPDR and volume of colonoscopy as negligible (r=0·05; p=0·021).

239 217 colonoscopies were included for interval post-colonoscopy colorectal cancer analysis, which yielded 305 interval post-colonoscopy colorectal cancer cases. Of all interval post-colonoscopy colorectal cancer cases, 177 (58%) were advanced stage cancers. 148 (49%) interval post-colonoscopy colorectal cancers were detected in the proximal colon and 130 (43%) were detected in female patients (table 1). The median time between colonoscopy and interval post-colonoscopy colorectal cancer diagnosis or end of follow-up was 33 months (IQR 21–42).

The overall incidence of interval post-colonoscopy colorectal cancers was 4·0 cases per 10 000 person-years of follow-up. For each percentage point increase in PSPDR, the adjusted interval post-colonoscopy colorectal cancer rate was 7% lower (HR 0·93, 95% CI 0·90–0·95; p<0·0001; table 2). Evaluation for non-linearity showed no better fit for models with a square and cubic transformation of the PSPDR compared with the linear model. Schoenfeld residuals showed appropriateness of the proportional hazard assumption (appendix p 3). Timing of colonoscopy in quarters as a random effect did not affect the estimated HRs in the model (appendix p 4).

The adjusted HRs for interval post-colonoscopy colorectal cancer incidence, according to quintiles of PSPDR performance, from lowest to highest, were 1·0 (reference group), 0·95 (95% CI 0·70–1·29), 0·74 (0·53–1·03), 0·42 (0·28–0·64), and 0·34 (0·21–0·55; figure 2A). The cumulative hazard over time per quintile is shown in the appendix (p 5).

We observed a significant association between PSPDR and the incidence of advanced stage (HR 0·94, 95% CI 0·91–0·97), non-advanced stage (0·90, 0·87–0·94), proximal (0·94, 0·91–0·98), and distal interval post-colonoscopy colorectal cancers (0·91, 0·87–0·94; appendix p 6). The association between PSPDR and interval post-colonoscopy colorectal cancer was significant for both female patients (HR 0·92, 95% CI 0·88–0·95) and male patients (0·94, 0·90–0·97). Across these groups, the HRs showed an overall declining trend in the incidence of interval post-colonoscopy colorectal cancers with increasing PSPDR quintile (figure 2B–D).

The median ADR was 66·3% (IQR 61·4–69·9). Endoscopists' ADR was inversely associated with the risk

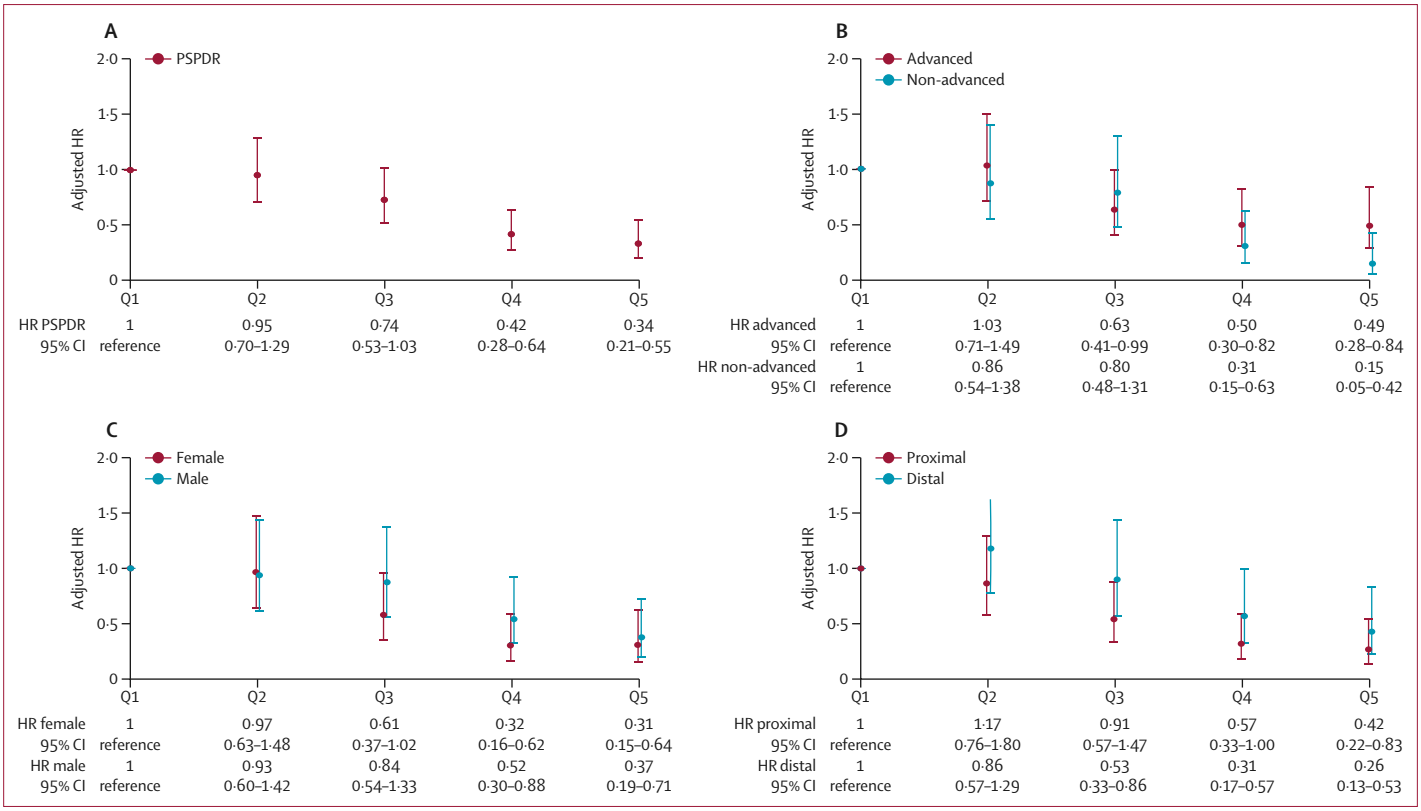

Figure 2: **Adjusted HRs for interval post-colonoscopy colorectal cancer according to quintile of PSPDR, overall (A), stratified by cancer stage (B), stratified by sex (C), and stratified by location (D)**
HRs were adjusted for sex and age (except for C), and random effect was applied to adjust for correlation within endoscopists. Proximal indicates located proximal to the descending colon, including the splenic flexure; distal indicates located distal to the splenic flexure. HR=hazard ratio. PSPDR=proximal serrated polyp detection rate.

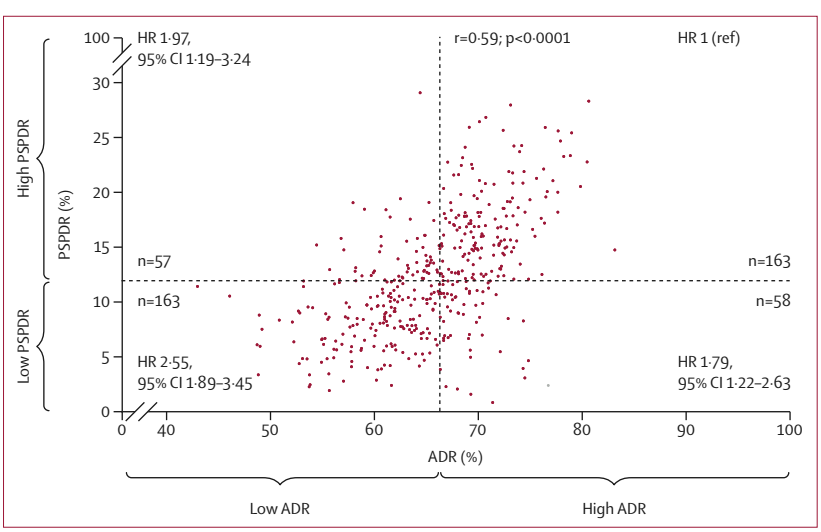

Figure 3: **Risk of interval post-colonoscopy colorectal cancer for endoscopists with a high PSPDR and a high ADR compared with endoscopists with a high PSPDR and a low ADR, low PSPDR and high ADR, or low PSPDR and low ADR**
The dashed vertical line indicates the median ADR (66·3%) and the dashed horizontal line indicates the median PSPDR (11·9%). HRs are adjusted for age and sex. Random effects were used for endoscopists. Endoscopist count per group is indicated. ADR=adenoma detection rate. HR=hazard ratio. PSPDR=proximal serrated polyp detection rate.

of interval post-colonoscopy colorectal cancers (HR 0·94, 95% CI 0·93–0·96). Correlation between PSPDR and ADR was considered moderate (r=0·59; figure 3). Compared with endoscopists with an PSDPR and ADR both above the median (163 [37%] of 441), endoscopists with a high-PSPDR and low-ADR (57 [13%] of 441; HR 1·97, 95% CI 1·19–3·24), low-PSPDR and high-ADR (58 [13%] of 441; 1·79, 1·22–2·63), and low-PSDPR and low-ADR (163 [37%] of 441; 2·55, 1·89–3·45) all had a higher interval post-colonoscopy colorectal cancer risk (figure 3).

The interval post-colonoscopy colorectal cancer risk was significantly lower for each percentage point increase in SSLDR (HR 0·91, 95% CI 0·87–0·94) and SPDR (0·96, 0·94–0·98; appendix p 7). After standardisation, PSPDR, SSLDR, and SPDR showed similar associations with the interval post-colonoscopy colorectal cancer risk (appendix p 8).

Discussion

To date, ADR has been the only polyp detection indicator to have a proven association with interval post-colonoscopy colorectal cancer incidence. In this study, we showed that the PSPDR is at least as strongly associated with interval post-colonoscopy colorectal cancer as ADR,

based on more than 230 000 colonoscopies and 305 interval post-colonoscopy colorectal cancer cases in a faecal immunochemical test-positive screening population. Each percentage point increase in the PSPDR of endoscopists was associated with a lower risk of interval post-colonoscopy colorectal cancer. Interval post-colonoscopy colorectal cancer incidence was three times higher in the lowest compared to the highest PSPDR quintile. Additional analyses showed similar results for advanced, non-advanced, proximal, and distal interval post-colonoscopy colorectal cancers, and similar differences in female individuals and male individuals.

In line with previous studies, we observed only a moderate correlation between the ADR and PSPDR.[13,23,24] This finding shows that we should not assume that endoscopists with high ADR also have a high PSPDR, and thus advocates adoption of PSPDR as a separate quality indicator. Besides, the moderate correlation would also hamper a combined analysis of the PSDPR and ADR in a regression model. The benefit of adding PSPDR to existing quality indicators is shown by the markedly increased risk of interval post-colonoscopy colorectal cancer in endoscopists with high ADR but low PSPDR, compared with endoscopists with a high ADR and high PSPDR. Hence, we propose that the PSPDR should not be considered as a surrogate parameter for ADR or vice versa, but as an additional quality indicator, to be used alongside the ADR. Based on the linear association between PSPDR and interval post-colonoscopy colorectal cancers in our study, endoscopists should pursue a PSPDR that is as high as possible. Endoscopists could use chromoendoscopy to increase their PSPDR, although implementation might be complicated due to extra labour.[25] A more promising approach might be the educational training of endoscopists, as this is a proven effecitve method to achieve a sustained improvement of the PSPDR, although these studies were done on a small scale.[26,27] Efforts should be made to develop and validate widely applicable educational programmes to improve the detection of serrated polyps. Once validated, these programmes could be offered to those endoscopists that achieve a low detection rate of serrated polyps to improve the overall quality of the screening programme.

Our data showed similar associations between interval post-colonoscopy colorectal cancer and SSLDR and SPDR, two alternative serrated polyp quality indicators. From a clinical perspective, considering ease-of-use and expected effectiveness, the PSPDR appears to be the best proxy for the detection of clinically relevant serrated polyps in daily practice. First, as pathologists have a high interobserver variability in SSL diagnosis, the SSLDR would not solely evaluate the detection by endoscopists but also the diagnostic accuracy of pathologists. Second, the SPDR as a parameter would also target irrelevant distal HPs and could wrongly encourage their removal similar to the so-called one-and-done principle in ADR.[28] Finally, we observed no statistical benefits for SSLDR and SPDR compared with the PSPDR.

Several strengths of our study should be emphasised. This study was done within the Dutch national colorectal cancer screening programme, ensuring a homogeneous population, detailed documentation (including detailed serrated polyp characteristics), and experienced, certified endoscopists and pathologists. Additionally, recent data were used, mirroring current detection rates based on up-to-date endoscopic equipment and knowledge. A limitation of the study is the fact that this was a prospective registration with prespecified variables. Therefore, not all potential confounding factors (eg, ethnicity or age of endoscopists) could be considered in our statistical model. Furthermore, the pseudonymisation of our database hampered us in verifying the legitimacy of each interval post-colonoscopy colorectal cancer case on a patient record level. However, a detailed database allowed us to reconstruct the clinical situation with high certainty. Also, the short follow-up period (median 36 months) could underestimate the incidence of interval post-colonoscopy colorectal cancers, especially with individuals given surveillance advice of 5 years or longer. Nevertheless, sufficient interval post-colonoscopy colorectal cancers were detected for robust analyses.

Notably, the accreditation programme for endoscopists in the Dutch colorectal cancer screening programme, the relatively high cutoff value of the faecal immunochemical test, the strict inclusion criteria for colonoscopies, and the exclusion of low-quality colonoscopies might have resulted in a higher PSPDR and ADR than in other studies or settings (eg, faecal immunochemical test screening with lower cutoffs, primary screening colonoscopy or diagnostic colonoscopy). As detection rates vary greatly between these colonoscopy settings and between national screening programmes, application of global benchmarks is difficult. Our data do not serve as a universal benchmark for PSPDR; such benchmarks should be determined per country and per colonoscopy setting. Nevertheless, considering a low faecal immunochemical test sensitivity for serrated polyps, the use of PSPDR as colonoscopy quality indicator seems widely applicable in other colonoscopy settings, such as faecal immunochemical test screening with lower cutoff values, primary screening, and surveillance cohorts.[29]

In conclusion, to our knowledge, our study is the first to show a strong inverse association between endoscopists' PSPDR and the incidence of interval post-colonoscopy colorectal cancer. This association cannot solely be explained by the correlation between the PSPDR and the ADR. This finding suggests that improving endoscopists' PSPDR could optimise colonoscopy effectiveness and reduce the incidence of interval post-colonoscopy colorectal cancer. Our data thus support universal adoption of PSPDR as a separate quality indicator alongside ADR. Future studies could focus on the development and validation of widely applicable

educational interventions to improve the detection of serrated polyps among low-detecting endoscopists.

Contributors

DEFWMvT and JEGIJ contributed equally to this study. ED, JEGIJ, and AGCB conceived and designed the study. DEFWMvT and AGCB managed the acquisition of the study data. DEFWMvT, JEGIJ, ED, and PMMB analysed the data. All authors contributed to data interpretation. DEFWMvT, JEGIJ, and ED drafted the manuscript. All authors provided critical revision of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. DEFWMvT and JEGIJ accessed and verified the data.

Declaration of interests

ED reports consulting fees from Fujifilm, Olympus, GI Supply, CPP-FAP, PAION, and Ambu; has served as speaker for Olympus, GI Supply, Norgine, IPSEN, PAION, and Fujifilm; has received payments as a member of the supervisory board of the eNose company; and has endoscopic equipment on loan for resesarch studies from Fujifilm. MCWS reports contracts or grants from The Netherlands Institute of Public Health and the Environment/Screening Organization, TKI/Health Holland, Dutch Gastroenterology Association, and ZonMW; and has received materials and research support from Sysmex, Sentinel, Boston Scientific, and Norgine. All other authors declared no competing interests.

Data sharing

The data that support the findings of this study are available on request from ED.

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