Serrated polyps
IJspeert, J.E.G.

Citation for published version (APA):

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CHAPTER 3

Detection rate of serrated polyps and serrated polyposis syndrome in colorectal cancer screening cohorts; A European overview


Gut 2016; in press
ABSTRACT

Objective
The role of serrated polyps (SPs) as colorectal cancer precursor is increasingly recognised. However, the true prevalence of SPs is largely unknown. We aimed to evaluate the detection rate of SP subtypes as well as serrated polyposis syndrome (SPS) among European screening cohorts.

Methods
Prospectively collected screening cohorts of ≥1000 individuals were eligible for inclusion. Colonoscopies performed before 2009 and/or in individuals aged below 50 were excluded. Rate of SPs was assessed, categorised for histology, location and size. Age–sex–standardised number needed to screen (NNS) to detect SPs were calculated. Rate of SPS was assessed in cohorts with known colonoscopy follow-up data. Clinically relevant SPs (regarded as a separate entity) were defined as SPs ≥10 mm and/or SPs >5 mm in the proximal colon.

Results
Three faecal occult blood test (FOBT) screening cohorts and two primary colonoscopy screening cohorts (range 1.426–205.949 individuals) were included. Rate of SPs ranged between 15.1% and 27.2% (median 19.5%), of sessile serrated polyps between 2.2% and 4.8% (median 3.3%) and of clinically relevant SPs between 2.1% and 7.8% (median 4.6%). Rate of SPs was similar in FOBT-based cohorts as in colonoscopy screening cohorts. No apparent association between the rate of SPs and gender or age was shown. Rate of SPS ranged from 0% to 0.5%, which increased to 0.4% to 0.8% after follow-up colonoscopy.

Conclusions
The detection rate of SPs is variable among screening cohorts, and standards for reporting, detection and histopathological assessment should be established. The median rate, as found in this study, may contribute to define uniform minimum standards for males and females between 50 and 75 years of age.
BACKGROUND

Colorectal cancer (CRC) arises from colonic polyps over the course of many years, and the detection and resection of these lesions will decrease both CRC morbidity and mortality.\textsuperscript{1} Historically, adenomas were considered as the only type of polyp with malignant potential.\textsuperscript{2} For this reason, endoscopists were only prone to resect adenomas during colonoscopy.\textsuperscript{7} However, studies from the last two decades have suggested that besides adenomas, serrated polyps (SPs) are also precursors of CRC, responsible for up to 15–30% of all malignancies.\textsuperscript{3–5} These CRCs arise via the serrated neoplasia pathway, which is an autonomous sequence to CRC.\textsuperscript{6–8} Several studies have demonstrated that SPs are common precursors of colonoscopy interval cancers, cancers diagnosed within the surveillance interval after a complete colonoscopy, mainly due to their challenging clinical management.\textsuperscript{9–11} The WHO has classified SPs into hyperplastic polyps (HPs), sessile serrated polyps (SSPs) with or without dysplasia and traditional serrated adenomas (TSAs).\textsuperscript{12} This classification system is of clinical importance, since not all SP subtypes seem to possess an identical CRC potential.\textsuperscript{13,14} SSPs have been identified as the main precursors of CRC, while HPs are generally considered of less clinical importance, especially if diminutive and located in the rectosigmoid.\textsuperscript{13,14} TSAs are considered premalignant, but the prevalence of these lesions is low and their exact neoplastic potential is only marginally understood.\textsuperscript{15,16} The identification of SPs as CRC precursors has altered prevention strategies, since nowadays also the premalignant SPs should be detected and resected during colonoscopy. In addition, post-polypectomy surveillance is generally recommended after removal of SSPs or large/proximal HPs.

As a result of the difficulties in diagnosing SPs during colonoscopy, the detection rate of those lesions is widely variable among endoscopists.\textsuperscript{17–19} For instance, several studies showed that the detection rate of SPs in the proximal colon varied among endoscopists between 1% and 20%.\textsuperscript{17–19} Furthermore, pathologists experience difficulties in the differentiation of SP subtypes.\textsuperscript{20,21} As a result, the interobserver agreement in the diagnosis of SP subtypes is only moderate to low, both for expert and non-expert pathologists.\textsuperscript{20,21} The differentiation of HPs and SSPs seems to be particularly challenging.\textsuperscript{20,22} Reproducibility of the histopathological diagnosis of SPs is mandatory to enable proper surveillance intervals for individual patients. To enable guidance for standards in detection, resection and surveillance, studies that evaluate the prevalence and distribution of SP subtypes are needed. At this stage, it is unknown whether geographical differences exist within countries, potentially due to environmental and/or genetic factors, such as diet or smoking habits, justifying the conception of an international study. Second, international studies are needed to enable a proper assessment of the prevalence of individuals with serrated polyposis syndrome (SPS), a syndrome characterised by multiple SPs throughout the colon and accompanied by an increased risk of developing CRC.\textsuperscript{12,22,23} The aim of this study was to evaluate and compare the detection rate (referred to as rate) of SP subtypes as well as SPS in several European CRC screening cohorts in an attempt to better understand what is reported among Western countries and to enable guidance for detection standards.
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METHODS

Study design
This study had an international multicentre cross-sectional design using data from several prospectively collected databases. Analyses were retrospectively performed. The primary endpoint of this study was the variability in reported prevalence of SP subtypes among European CRC population-based screening cohorts. Principal investigators contributing to the European Polyp Surveillance (EPoS) trials, in which post-polypectomy surveillance intervals will be compared, were approached to submit colonoscopy data for this study. Prospectively collected cohorts that underwent colonoscopy after a positive faecal occult blood test (FOBT) in a screening programme, as well as cohorts that underwent a colonoscopy as primary screening test of at least 1000 individuals performed from 2009 onwards (within 5 years from start data collection), were eligible to be included in the analysis. Colonoscopies performed in individuals aged below 50, with IBD and/or a known hereditary CRC syndrome, were excluded from the analysis. These inclusion and exclusion criteria were composed to ensure robust and homogeneous data, collected in an era that the awareness of the malignant potential of SPs was well known. Formal ethical approval was not required, since no additional interventions were performed for the sake of this study and individual data were anonymised per centre before being centrally uploaded. This study was carried out in accordance with the ethical principles as described in the Helsinki declaration.24

Data collection
Data from five European cohorts were collected between February 2014 and February 2015. Participating centres were asked to complete a standardised electronic data-collection form including general information on the cohort and a data sheet for data input. General information included data on cohort type (eg, FOBT-based screening or primary colonoscopy screening), cohort size, individual demographics (gender and age distribution), participating centres (academic, non-academic or combined) and calendar years of data collection. Data on unadjusted caecal intubation rate (CIR), adenoma detection rate (ADR), pathologist expertise and quality of bowel preparation were gathered to enable evaluation of the general quality of included colonoscopies. For the evaluation of the primary endpoint, aggregated data concerning the rate of SPs (categorized for histology, location and size) were provided by all cohorts, stratified for patient age, gender and the presence of synchronous adenomas. This way stratum-specific endpoints could be evaluated. The rate of patients with at least one SP ≥10 mm and/or SP >5 mm located proximal to the splenic flexure was gathered from all cohorts and regarded as a separate entity (clinically relevant SPs). This definition enabled the evaluation of clinically relevant SPs, without the need of an accurate histopathological differentiation of SP subtypes. According to the study protocol from the EPoS project, these lesions justify post-polypectomy follow-up, irrespective of SP subclass (unpublished). Finally, data on the number of individuals diagnosed with SPS were collected, both for individuals diagnosed at initial colonoscopy and where possible for individuals diagnosed during follow-up after initial colonoscopy. The 2010
WHO classification was used to define the diagnosis of SPS. Individuals who only reached WHO criterion 2 (at least one SP proximal to the rectosigmoid and a first-degree relative with SPS) were excluded from analysis.

Statistical analysis
The rate of patients with SP subtypes was defined as the number of individuals with a positive finding divided by the total number of individuals and was presented as a percentage with 95% CI. Analyses based on the most advanced lesion per individual were not performed, in order not to exclude patients with SP with a concomitant diagnosis of adenomas. Therefore, one individual could be included in more than one calculation. However, if individuals had multiple polyps from the same type, these only accounted once for the calculation of the rate (ie, per patient analysis). Both the crude rate of patients with SP subtypes and the stratum-specific rate were calculated per cohort, stratified for age, gender and the co-occurrence of adenomas. Rates were presented, both for cohorts overall as well as stratified for cohort subtype. The age–sex standardised number needed to screen (NNS) for SSPs and clinically relevant SP was calculated and compared among cohorts to identify the potential structural gender and/or age differences. The NNS was calculated as 1 divided by the rate. The Mantel Haenszel OR (ORMH) was used to objectify potential trends for gender in SSP rate and clinically relevant SP rate. This analysis was restricted to individuals aged 60–69, as only this age group was represented in all cohorts.

RESULTS

Cohorts
Three FOBT-based screening cohorts and two primary colonoscopy cohorts from five European countries (UK, Spain, Italy, the Netherlands and Poland) were included. Characteristics of all cohorts are presented in Table 1. A detailed description of the relevant screening programmes can be found in earlier reports.

In the cohort from the UK, we included 205 949 colonoscopies, performed within the nationwide guaiac FOBT-based bowel cancer screening programme between 2009 and 2015 in individuals aged 60–74. In the Spanish cohort, we included 6091 colonoscopies, performed within an immunochemical FOBT-based screening programme in the region of Barcelona between 2010 and 2014 in individuals aged 50–69 years. In the Italian cohort, we included 17 623 colonoscopies, performed within an immunochemical FOBT-based screening programme in the region of Piemonte between 2009 and 2012 in individuals aged 60–70 years. In the cohort from the Netherlands, we included 1426 colonoscopies, performed between 2009 and 2010 within the colonoscopy arm of a clinical trial for the comparison of CT colonography versus colonoscopy as the method for screening in asymptomatic individuals aged 50–75 years. Data were previously described. In the Polish cohort, we included 12
361 colonoscopies, performed within the primary colonoscopy screening programme in the region of Warsaw at the Centre of Oncology Institute, between 2009 and 2012 in individuals aged 50–65 years.

The overall ADR ranged between 55.4% and 58.2% in FOBT-based screening cohorts and between 29.4% and 32.3% in primary colonoscopy cohorts. The unadjusted CIR was above 90% in all included cohorts, while the quality of bowel preparation was sufficient in >90% of individuals for all cohorts.

### Table 1 | Overview of cohorts with quality indicators

<table>
<thead>
<tr>
<th>Cohort name</th>
<th>UK</th>
<th>Spain</th>
<th>Italy</th>
<th>Netherlands</th>
<th>Poland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort type</td>
<td>gFOBT based screening</td>
<td>FIT based screening</td>
<td>FIT based screening</td>
<td>Primary colonoscopy screening</td>
<td>Primary colonoscopy screening</td>
</tr>
<tr>
<td>Cohort size, n</td>
<td>205.949</td>
<td>6.091</td>
<td>17.623</td>
<td>1.426</td>
<td>12.361</td>
</tr>
<tr>
<td>Age in years (range)</td>
<td>60-75</td>
<td>50-69</td>
<td>60-70</td>
<td>50-75</td>
<td>50-65</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>119.877 (58.2)</td>
<td>3374 (55.4)</td>
<td>9765 (55.4)</td>
<td>726 (50.9)</td>
<td>5842 (47.3)</td>
</tr>
<tr>
<td>Participating centres</td>
<td>Combined</td>
<td>Academic</td>
<td>Combined</td>
<td>Academic</td>
<td>Academic</td>
</tr>
<tr>
<td>Quality indicators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samples assessed by gastrointestinal pathologist</td>
<td>*</td>
<td>All samples</td>
<td>**</td>
<td>All samples</td>
<td>All samples</td>
</tr>
<tr>
<td>Caecal intubation, n (%)</td>
<td>199.153 (96.7)</td>
<td>5924 (97.3)</td>
<td>15988 (90.8)</td>
<td>1407 (98.7)</td>
<td>12073 (97.7)</td>
</tr>
<tr>
<td>Adequate bowel preparation, n (%)</td>
<td>198.741 (96.5)</td>
<td>5786 (95.0)</td>
<td>16470 (93.5)</td>
<td>1312 (92.0)</td>
<td>11381 (92.1)</td>
</tr>
<tr>
<td>At least 1 adenoma (ADR), n (%)</td>
<td>89.176 (43.3)</td>
<td>2869 (47.1)</td>
<td>8424 (47.8)</td>
<td>419 (29.4)</td>
<td>3993 (32.3)</td>
</tr>
</tbody>
</table>

### Crude serrated polyp rates

| At least 1 SP, n (%) | 15.1 (14.9-15.3) | 19.5 (18.5-20.5) | 17.6 (17.0-18.2) | 27.2 (24.9-29.6) | 26.6 (25.8-27.4) |
| At least 1 proximal SP | 4.7 (4.6-4.8) | 6.7 (6.1-7.4) | 9.5 (9.1-9.9) | 12.2 (10.6-14.0) | 9.7 (9.2-10.2) |
| At least 1 large SP | 1.2 (1.1-1.3) | 2.5 (2.1-2.9) | 2.1 (1.9-2.3) | 2.6 (1.8-3.6) | 1.1 (0.9-1.3) |
| At least one clinically relevant SP† | 2.1 (2.0-2.2) | 4.9 (4.4-5.5) | 7.9 (7.5-8.3) | 4.3 (3.3-5.5) | - |
| At least 1 SSP, n (%) | 15.1 (14.9-15.3) | 19.5 (18.5-20.5) | 17.6 (17.0-18.2) | 27.2 (24.9-29.6) | 26.6 (25.8-27.4) |
| At least 1 proximal SSP* | 4.7 (4.6-4.8) | 6.7 (6.1-7.4) | 9.5 (9.1-9.9) | 12.2 (10.6-14.0) | 9.7 (9.2-10.2) |
| At least 1 large SSP | 1.2 (1.1-1.3) | 2.5 (2.1-2.9) | 2.1 (1.9-2.3) | 2.6 (1.8-3.6) | 1.1 (0.9-1.3) |
| At least 1 SSP with dysplasia | 0.2 (0.2-0.2) | 0.6 (0.4-0.8) | 0.3 (0.2-0.4) | 1.5 (0.9-2.3) | 0.2 (0.1-0.3) |

* Samples assessed by a pathologist, trained and certified for participation in the nationwide population screening.
** It was not recorded whether the pathology slides were assessed by a gastrointestinal pathologist.
† At least one SP ≥10 mm OR at least one SP >5mm proximal to splenic flexure
†† SSP with high grade dysplasia only

### Crude polyp detection rates

The crude rate of patients with SP subtypes per cohort is presented in Table 1. The rate of at least one SP ranged between 15.1% and 27.2% (median 19.5%; NNS 6) among cohorts. For FOBT-based screening cohorts, the rate ranged between 15.1% and 19.5% (NNS 6–7) and for primary colonoscopy...
cohorts between 26.6% and 27.2% (NNS 4). The rate of patients with at least one clinically relevant SP could be assessed in 4/5 cohorts and ranged between 2.1% and 7.9% (median 4.6%; NNS 22) among cohorts. For FOBT-based screening cohorts, the rate ranged from 2.1% to 7.9% (NNS 13–48). This rate could also be estimated in one primary colonoscopy cohort (Dutch cohort) and was 4.3% (NNS 24). The rate of patients with at least one SSP could be assessed in 4/5 cohorts and ranged between 2.2% and 4.8% (median 3.3%; NNS 31) among cohorts. For FOBT-based screening cohorts, the rate ranged between 3.2% and 3.3% (NNS 31–32) and for primary colonoscopy cohorts between 2.2% and 4.8% (NNS 21–46). The rate of patients with at least one SSP with dysplasia could be assessed in all cohorts and ranged between 0.2% and 1.5% (median 0.4%; NNS 250). Only SSPs with high-grade dysplasia were taken into account in the Italian cohort. Finally, the rate of at least one TSA could be assessed in 3/5 cohorts and ranged between 0.1% and 0.8% (median 0.1%; NNS 1000).

<table>
<thead>
<tr>
<th>Stratum specific rate of sessile serrated polyps and clinically relevant serrated polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sessile serrated polyps</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>UK</strong>*</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Spain</strong>*</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Italy</strong>*</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Netherlands</strong>*</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Poland</strong>*</td>
</tr>
<tr>
<td>Female</td>
</tr>
</tbody>
</table>

*FOBT based screening cohorts  
**Primary colonoscopy screening cohorts  
† 49 males and 69 females aged ≥70 were merged with participants 60-69 due to small sample size

**Stratum-specific SP detection rates**

In Table 2, the rate of SSP as well as clinically relevant SP is presented, stratified for age and gender. In Figure 1A, B the corresponding age–sex–standardised NNS is presented. Uniform gender and/or age differences among cohorts were not found. Within the FOBT screening cohorts, male subjects aged 60–69 were significantly more often diagnosed with ≥1 clinically relevant SP (ORMH 1.26; 95% CI 1.19 to 1.34) and ≥1 SSP (ORMH 1.65; 95% CI 1.38 to 1.96). In the analysis for SSPs, the UK FOBT cohort could not be taken into account. Opposite to the FOBT screening cohorts, no significant gender differences within subjects aged 60–69 years were found within the primary colonoscopy cohorts.
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Figure 1 | Age–sex–standardised number needed to screen to detect one individual with sessile serrated polyps (A) or one individual with clinically relevant serrated polyps (B). IT, Italy, NL, the Netherlands; PL, Poland; SP, Spain.
Synchronous adenomas

In Figure 2, the ratio between individuals diagnosed with and without a synchronous adenoma is presented, within individuals diagnosed with subtypes of SPs. In the FOBT-based screening cohorts, 60.6–71.5% of all individuals diagnosed with any SP were also diagnosed with a synchronous adenoma, compared with 41.5–58.0% of individuals in the primary colonoscopy cohorts. In the FOBT-based screening cohorts, 66.3–78.1% of all individuals diagnosed with at least one clinically relevant SP did also have a synchronous adenoma, compared with 46.8% of individuals in the Dutch primary colonoscopy cohort. Of all individuals diagnosed with a SSP in the FOBT-based screening cohorts, 60.6–98.4% were also diagnosed with a synchronous adenoma, compared with 48.5–57.5% of individuals in the primary colonoscopy cohorts. Finally, in the FOBT-based screening cohorts 63.2–94.7% of all individuals diagnosed with a SSP containing dysplasia were also diagnosed with a synchronous adenoma, compared with 52.4–66.7% of individuals in the primary colonoscopy cohorts.

Figure 2 | Ratio between individuals diagnosed with and without a synchronous adenoma, within individuals diagnosed with subtypes of serrated polyps. AD, adenoma; IT, Italy; NL, the Netherlands; PL, Poland; SP, Spain; SSP, sessile serrated polyp.

Serrated polyposis syndrome

The number of individuals diagnosed with SPS is presented in Table 3. In total, 4/5 cohorts reported on SPS detection rate at initial colonoscopy, which ranged from 0% to 0.5%. The rate of individuals diagnosed with SPS overall (at diagnosis + during surveillance) could be assessed in two cohorts. In
the Spanish FOBT-based screening cohort, 1:127 individuals were diagnosed (0.8%; CI 0.6 to 1.1), while in the Netherlands primary colonoscopy cohort 1:238 individuals were diagnosed (0.4%; CI 0.1 to 0.9) with SPS after follow-up.

Table 3 | Individuals diagnosed with serrated polyposis syndrome

<table>
<thead>
<tr>
<th>Cohort name</th>
<th>UK</th>
<th>Spain</th>
<th>Netherlands</th>
<th>Poland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort size, n</td>
<td>205,949</td>
<td>6,091</td>
<td>1,426</td>
<td>12,361</td>
</tr>
<tr>
<td>Diagnosed at initial colonoscopy, rate (95% CI)</td>
<td>0.03 (0.02-0.04)</td>
<td>0.5 (0.3-0.7)</td>
<td>0</td>
<td>0.1 (0.0-0.2)</td>
</tr>
<tr>
<td>Diagnosed during follow-up, rate (95% CI)</td>
<td>-</td>
<td>0.3 (0.2-0.5)</td>
<td>0.4 (0.1-0.9)</td>
<td>-</td>
</tr>
<tr>
<td>Diagnosed overall rate (95% CI) (at diagnosis + during follow-up)</td>
<td>0.8 (0.6-1.1)</td>
<td>0.4 (0.1-0.9)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The information was not available for the Italian cohort.

**DISCUSSION**

In this study, we evaluated and compared the rate of SP subtypes among three FOBT-based and two primary colonoscopy CRC screening cohorts from five European countries. These cohorts are representative of current European colonoscopy practice. Within these cohorts, the rate of patients with any SP ranged between 15.1% and 27.2% (median 19.5%; NNS 6), with any SSP between 2.2% and 4.8% (median 3.3%; NNS 31), with any SSP with dysplasia between 0.2% and 1.5% (median 0.4; NNS 250) and with any clinically relevant SP between 2.1% and 7.8% (median 4.6%; NNS 22).

No structural differences were found between the FOBT-based screening cohorts and the primary colonoscopy cohorts regarding the rate of SSP or clinically relevant SP, which suggests that for now, uniform standards in SP detection could be introduced. These data are supported by a recent report, which showed that faecal blood tests are not useful as pretest to increase the detection of SPs, possibly due to the fact that these lesions only seldom bleed.31 Furthermore, in the current study no uniform gender and/or age differences in NNS were found for SSP or clinically relevant SPs. However, within the FOBT screening cohorts, male subjects aged 60–69 were slightly more often diagnosed with both polyp subtypes. Although the reason for these differences were not explored, this could potentially be explained by a well-known higher rate of synchronous advanced neoplasia among men, which is suggested to be associated with the rate of SSPs.30,32,33 However, caution is required since this association would also suggest an increased rate of SSP overall among FOBT-based cohorts compared with primary colonoscopy cohorts. Furthermore, male preference for SSP and clinically relevant SP was also not identified in other age categories. Therefore, uniform detection standards among men and women seem justified.

In a secondary analysis within individuals diagnosed with subtypes of SPs, we evaluated the ratio between individuals diagnosed with and without a synchronous adenoma. This analysis showed that
a substantial number of individuals diagnosed with clinically relevant SPs did not have a synchronous adenoma, both in FOBT and primary colonoscopy cohorts. This finding is of significance for daily practice, since for these individuals post-polypectomy surveillance intervals are based only on the characteristics of detected SPs. Finally, we showed that SPS is probably more common than earlier assumed and often diagnosed during colonoscopy follow-up. In the Spanish FOBT-based screening cohort, 1:127 individuals and in the Dutch primary colonoscopy cohort 1:238 individuals were diagnosed with SPS after follow-up.

Our analysis on clinically relevant SPs deserves further consideration. The NNS of 22, corresponding to a 4.6% rate, is only slightly inferior to the NNS of 17 shown by Regula et al\cite{29} for advanced neoplasia in a primary screening population, suggesting that clinically relevant SPs could be a reasonable target for primary colonoscopy screening.\cite{29} However, the lack of significant reduction of the NNS for clinically relevant SPs at higher age is notably different from the substantial reduction of the NNS for advanced neoplasia detection in the Regula et al\cite{29} series, passing from 30 at age <50 years to 10 at age >60 years in males. This would suggest that differently from advanced neoplasia, it may not be feasible to select the best age of screening for the detection of clinically relevant SPs, leaving uncertainty on this point. We also showed that the NNS to detect one SSP with dysplasia is over 100. This would argue against the use of such lesions as a target in CRC screening.

In the current study, five large and prospectively collected cohorts were included, enabling robust and reliable analyses. All colonoscopies were performed according to the most recent quality parameters.\cite{25,34} The unadjusted CIR was >90% in all cohorts, the bowel preparation was adequate in ≥90% of individuals and in all cohorts the ADR was amply sufficient, given the type of cohort.\cite{34} All colonoscopies were performed within an era that the neoplastic potential of SPs was well known. These cohort characteristics have substantially decreased the risk of selection bias in the performed analysis. Furthermore, the evaluation of stratum-specific rates based on age and gender has decreased the risk of confounding. Nevertheless, several limitations have to be acknowledged in this study. Other known confounders associated with SPs, such as smoking status, were not taken into account in this study.\cite{33,35} Due to the retrospective nature of the performed analyses, endoscopists and pathologists were not aware of the study and did not receive a specific training before the start of this study. Therefore, certain caution is required drawing comparisons between screening and FOBT-based cohorts. Lack of observed differences could partially be based on variation between centres as opposed to the populations actually being similar. Third, centralised pathology revision was not performed for any of the included cohorts. As mentioned earlier, the reproducibility of a homogeneous SP diagnosis is moderate to low within pathologists, which might have introduced certain information bias.\cite{20,21} As a result, the variability in reported SP rate, as found in this study, might be partly due to practice variation between pathologists rather than endoscopists. To overcome this issue, we defined a group of clinically relevant SPs that could be assessed without the need of an accurate histopathological differentiation of SP subtypes. Comparable variability was demonstrated
CHAPTER 3

for the rate of SSPs (2.2–4.8%), SSPs with dysplasia (0.2–1.5%) and clinically relevant SPs (2.1–7.8%), indicating that practice variation between endoscopists at least partially explains the variability in reported detection of all SP subtypes.

Several earlier reports have described the rate of SSPs and SSPs with dysplasia in colonoscopy cohorts.\textsuperscript{21,36–43} Most older studies report a low rate of SSPs ranging around 1%.\textsuperscript{36–40} Since these colonoscopies were performed in an era where the neoplastic potential of SPs was not well known and both pathologists as well as endoscopists were not prone to diagnose these lesions, reported rate is likely to be underestimated. More recent studies (2013-onwards) reported a rate of SSPs (range 1.9–5.3%), comparable to the reported rate as found in our study (range 2.2–4.8%).\textsuperscript{41–43} One recent study reported a rate of 8.2% after centralised pathology revision.\textsuperscript{21} In this study, each SP with at least one aberrant crypt was identified as SSP. This approach is not recommended by the WHO and might result in over diagnosis of SSPs.\textsuperscript{12} The rate of SSPs with dysplasia was reported in only one of these studies (0.6%) and also was comparable to the rate as presented in our cohorts (range 0.2–1.5%; median 0.4%). These data support the fact that the reported rates of SP subtypes, as were reported in the different cohorts, are a good representation of current practice. As a consequence, the median rate of SP subtypes, as found in this study, could contribute to define minimum colonoscopy detection standards among European countries, irrespective of colonoscopy indication. However, for each individual endoscopist the highest presented rate should be the target, since these numbers are probably a better representation of the ‘true’ prevalence of disease. Furthermore, future prospective studies that assess the effectiveness of SP resection in screening could be based on data, as presented in the current study. The results from this study show that the global clinical management of SPs may have improved in the recent years. However, more awareness among endoscopists and pathologists is still needed to facilitate more consistent and adequate practice. Future research should evaluate the potential effect of structured training for endoscopists as well as for pathologists in the clinical management of SPs on the long-term incidence of colonoscopy interval CRC. These efforts might result in standardised diagnostic conditions in the near future, both for endoscopists as well as pathologists. Global use of identical criteria to histologically classify HP, SSP and SSP with dysplasia, such as proposed by Aust et al,\textsuperscript{44} will further increase uniform practice and should be advocated.

In a recent systematic review, the rate of SPS from six screening populations was presented, showing an overall low rate of disease.\textsuperscript{45} In the FOBT-based screening cohorts, the rate of SPS ranged from 0.34% to 0.66%, while in the primary colonoscopy cohorts the rate ranged from 0% to 0.09%. In all described studies, only those polyps detected at initial colonoscopy were taken into account for the diagnosis of SPS. This approach most probably resulted in an underestimation of the true prevalence of disease. For instance, Edelstein et al showed that only 45% of individuals with SPS were diagnosed at initial colonoscopy.\textsuperscript{46} Furthermore, Vemulapalli and Rex\textsuperscript{47} showed that SPS is a common and frequently unrecognised disease among individuals with large SPs, which is often diagnosed during colonoscopy follow-up. The rate of SPS after follow-up, as reported in the Spanish FOBT-based
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screening cohort (0.8%) and in the Dutch primary colonoscopy cohort (0.4%), therefore seems to be
more accurate estimates of the true prevalence of SPS in FOBT-based preselected populations and
average-risk populations, respectively. The relatively high rate of SPS in screening populations and its
association with CRC emphasise the importance for endoscopists to recognise this disease.

In conclusion, we showed that the rate of subtypes of SPs is variable among European countries,
which is likely to be explained by inconsistency in detection, reporting and/or histopathological
differentiation of these lesions. The rate of clinically relevant SPs showed to be similar in FOBT-based
screening cohorts as in primary colonoscopy screening cohorts and was not related with gender and/
or age. The rate of SPS showed to be higher than reported in earlier studies. Awareness, training in
endoscopic detection and the global use of identical histopathology criteria are needed to improve
the clinical management of SPs and facilitate more consistent practice. The median rate of SP
subtypes, as found in this study, could contribute to define minimum standards for detection in both
males and females between 50 and 75 years in CRC screening programmes.
REFERENCES

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