Serrated polyps
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Prevalence, distribution and risk of sessile serrated adenomas/polyps in a centre with a high adenoma detection rate and experienced gastrointestinal pathologists

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CHAPTER 4

ABSTRACT

Background and study aims
Sessile serrated adenomas/polyps (SSA/Ps) are the precursors of 15%–30% of colorectal cancers (CRC). We aimed to determine the prevalence and distribution of SSA/Ps and to evaluate the association between SSA/Ps and the risk of synchronous advanced neoplasia at a high quality colonoscopy center.

Methods
Data from all colonoscopies performed within one dedicated colonoscopy center between 2011 and 2015 were prospectively retrieved using an automated reporting system. All lesions were assessed by an experienced gastrointestinal pathologist. Multiple logistic regression was used to evaluate influence of age, gender, and colonoscopy indication on prevalence of SSA/Ps, and to assess the association between SSA/Ps and synchronous advanced neoplasia.

Results
In total 4251 histologically confirmed polyps were resected in 3364 patients; 399 polyps were SSA/Ps (9.4%). The prevalence of SSA/Ps was 8.2% overall, increasing to 9.0% for individuals older than 50 years. SSA/P detection rate varied between 2.5% and 13.6% among endoscopists. Increased SSA/P prevalence was associated with colonoscopy indications “familial CRC risk” (odds ratio [OR] 1.52, 95% confidence interval [95%CI] 1.05–2.22; P=0.03) and “surveillance” (OR 1.73, 95%CI 1.20–2.49; P<0.01), when compared with the indication “symptoms.” The presence of synchronous advanced neoplasia was associated with SSA/Ps overall (OR 1.71, 95%CI 1.25–2.34; P=0.001), as well as with high risk SSA/Ps (defined as ≥10mm and/or with dysplasia) (OR 2.70, 95%CI 1.56–4.67; P<0.001).

Conclusion
SSA/Ps are more common than previously reported and are associated with the presence of synchronous advanced neoplasia. Endoscopists should be assiduous in identifying SSA/Ps in daily practice and should carefully look for synchronous advanced neoplasia when an SSA/P has been recognized. Results from this study can guide detection standards in general colonoscopy practice adapted to the type of patient that may predominate in an individual department.
INTRODUCTION

Colorectal cancer (CRC) is one of the most substantial causes of cancer-related morbidity and mortality in the western world. Up to 30% of all CRCs arise from serrated polyps via the serrated neoplasia pathway. Therefore, endoscopists should aim to detect and resect premalignant serrated polyp subtypes in addition to adenomas. The World Health Organization (WHO) has classified serrated polyps into hyperplastic polyps, sessile serrated adenomas/polyps (SSA/Ps) without dysplasia, SSA/Ps with dysplasia, and traditional serrated adenomas (TSA)\(^2,3\). SSA/Ps have been acknowledged as the main precursor lesion in the serrated neoplasia pathway, resulting in cancer via a stage of cytological dysplasia\(^6,7\). Most hyperplastic polyps, especially those in the recto-sigmoid, seem to have an indolent course and should be distinguished from premalignant SSA/Ps\(^8\). Both the European Society of Gastrointestinal Endoscopy as well as the US Multi-Society Task Force on Colorectal Cancer have acknowledged that SSA/Ps with dysplasia and/or those of at least 10mm in size should be approached as high risk lesions, comparable to advanced adenomas\(^9,10\). Furthermore, according to the US guideline, moderate risk SSA/Ps (<10mm and without dysplasia) should be treated as non-advanced adenomas\(^10\).

Unfortunately, both high risk as well as moderate risk SSA/Ps tend to be discrete and camouflaged lesions, which impedes their detection during colonoscopy\(^11,12\). Furthermore, SSA/Ps with dysplasia are suggested to be as often diminutive in size (<6mm) as SSA/Ps without dysplasia, also hampering the detection of the most advanced SSA/P subtypes\(^13\). Finally, the histopathologic identification of SSA/Ps tends to be difficult, for experts as well as for non-expert pathologists\(^14\). For these reasons the reported prevalence of SSA/Ps differs widely between studies, resulting in an underestimated prevalence and consequent biased analysis in most of these studies\(^11,13\). Knowledge about the prevalence and distribution of SSA/Ps is of importance to enable guidance for detection standards, ensuring high quality colonoscopies. Additionally, the risk of synchronous and metachronous advanced neoplasia in patients with SSA/Ps can only be assessed without bias if the detection rate of SSA/Ps is amply sufficient. For these reasons we aimed to prospectively determine the prevalence and distribution of high risk SSA/Ps as well as SSA/Ps overall, and to evaluate the association between SSA/P subtypes and the risk of synchronous advanced neoplasia, in general colonoscopy practice at an endoscopy center with a high adenoma detection rate and collaborating experienced gastrointestinal pathologists.

METHODS

This study has a cross-sectional design using data retrieved from a prospectively collected database. All colonoscopies were performed in adult patients at the Bergman Clinics IZA, Amsterdam, the Netherlands. This is a dedicated colonoscopy center, where colonoscopies are performed by
CHAPTER 4

endoscopists from the Academic Medical Center. At this center no colonoscopies are performed in individuals already known to have an hereditary colorectal cancer (CRC) syndrome and/or inflammatory bowel disease. All data were retrieved during standard care and no extra interventions were performed for the sake of this study. Therefore, ethical approval of the study protocol by the institutional review board was not required, in agreement with the Dutch Medical Research Involving Human Subjects Act. This study was performed in compliance with the Helsinki declaration of ethical principles.

Patient selection
All patients who received a colonoscopy between January 2011 and June 2015 were eligible for inclusion in this study. If patients received multiple colonoscopies within the timeframe, only the first colonoscopy was included to ensure a per-patient analysis. Incomplete colonoscopies were excluded. All colonoscopies done by an endoscopist who performed fewer than 40 procedures were also excluded. This meant that individual endoscopist performance could be taken into account in the logistic regression analysis that was undertaken.

Colonoscopy data
Colonoscopy data were retrieved with the use of the automated EndoALPHA reporting system (Endobase; Olympus Winter & Ibe, Hamburg, Germany). This is a completely structured reporting system and enables automatic data collection and quality assurance of all colonoscopies in daily practice. This reporting system has been described in an earlier report.

For the current study, we collected data on patient demographics (e.g. age and gender), colonoscopy indication (e.g. abdominal symptoms, surveillance, following a positive fecal immunochemical test [FIT], or familial cancer risk), and colonoscopy outcome. For each polyp we retrieved colonic location (per segment), size (as measured during endoscopy), morphology (pedunculated [Paris Ip], sessile [Paris Is], or flat [Paris IIa, IIb, or IIc]) and histopathology. Maximal insertion depth was retrieved per segment and cecal intubation was confirmed by images of the ileocecal landmarks and/or insertion into the terminal ileum. Quality of bowel preparation was assessed using the Boston Bowel Preparation Scale (BBPS). The adenoma detection rate, the mean number of detected adenomas per colonoscopy, the proximal serrated polyp detection rate (proximal to the descending colon), and the mean number of detected proximal serrated polyps were assessed, to evaluate the overall quality of performed colonoscopies. All endoscopists were aware of the clinical importance of SSA/Ps as well as the difficulties in identifying these polyps, and were instructed to resect all lesions, irrespective of size, location, and/or optical diagnosis of detected polyps.

Histopathology
All lesions were assessed by one of five experienced gastrointestinal pathologists in daily practice. The pathologists did not have a special research interest in serrated polyps. All resected lesions were
collected in separate jars, enabling high quality of care of specimens. Polyp histology was assessed based on the revised Vienna criteria, and categorized into adenomas (including grade of dysplasia and presence of a villous component), hyperplastic polyps, SSA/Ps (including the presence of dysplasia) and TSAs28. SSA/Ps were diagnosed in cases when at least two separate crypts were dilated (including T- and L-shaped crypts) and/or showed (hyper)serration in the lower part of the crypt, in accordance with the most recent WHO guideline5. Advanced adenomas were defined as adenomas with high grade dysplasia, with a villous component, and/or of at least 10mm in size. High risk SSA/Ps were defined as SSA/Ps of at least 10mm in size and/or with cytological dysplasia. A random sample of 10% of all SSPs and hyperplastic polyps <10mm was reviewed by an expert gastrointestinal pathologist who did not perform any of the initial pathology assessments (L. K.). In this way the overall quality of histopathology assessment could be evaluated.

Study outcomes and statistical analysis

The primary outcomes of this study were the prevalence, endoscopic characteristics, and distribution of subtypes of SSA/Ps, as described in general colonoscopy practice. The secondary outcome was the association between SSA/Ps and synchronous advanced neoplasia. The prevalence was calculated as the proportion of colonoscopies with a positive finding divided by the total number of performed colonoscopies and was presented as a percentage. Multiple logistic regression was used to evaluate the influence of age, gender, and colonoscopy indication on the prevalence of SSA/Ps. Estimates were adjusted for endoscopist performance in the detection of SSA/Ps. Endoscopists were subdivided into high SSA/P detectors (detection rate above the median) and low SSA/P detectors (detection rate below the median).

Endoscopic characteristics (location and morphology) were compared between moderate risk and high risk SSA/Ps using chi squared analysis. The proximal colon was defined as proximal to the descending colon. The right-sided colon was defined as proximal to the transverse colon.

The association between subtypes of SSA/Ps and synchronous advanced neoplasia (defined as advanced adenomas and/or CRC) was assessed using multiple logistic regression analysis, adjusted for age as well as gender and was presented as odds ratio (OR) with 95% confidence interval (95%CI). Sensitivity analysis was performed by means of assessment of this association for high SSA/P detectors only. Because of restrictions in cohort size, the association between SSA/Ps and advanced neoplasia when stratified for colonoscopy indication was not examined. Kappa statistics were used to compare initial and revised pathology diagnosis. A κ value <0.20 was regarded as poor agreement, 0.21 to 0.40 as fair agreement, 0.41 to 0.60 as moderate agreement, 0.61 to 0.80 as good agreement, and >0.81 as very good agreement29. SPSS version 21 was used for statistical analysis (SPSS Statistics for Windows; IBM, Armonk, New York, USA). A P value <0.05 was considered to be statistically significant.
CHAPTER 4

RESULTS

In total 3743 colonoscopies were performed at Bergman Clinics IZA between January 2011 and June 2015. Colonoscopy was incomplete in 145 cases (cecal intubation rate 96.1%; prevalence of SSA/Ps in those incomplete colonoscopies, 0.7%). In total 57 patients received two colonoscopies and 177 colonoscopies were done by an endoscopist who performed fewer than 40 colonoscopies. After excluding those three categories, a total of 3364 patients were included for analysis. The median age of patients was 60.4 years (interquartile range [IQR] 51.5–67.5) and 1597 patients (47.5%) were male. Colonoscopy indication was reported as “abdominal symptoms” in 2115 cases (62.9%), “surveillance” in 379 cases (11.3%), “colonoscopy after a positive FIT” in 461 cases (13.7%), and “familial CRC risk” in 409 cases (12.2%). The median BBPS was 8 (IQR 7–9) and bowel preparation was adequate in 91.0% of patients (BBPS≥6). Colonoscopies were performed by 25 endoscopists, with a median number of colonoscopies of 84 (range 41–554), and 10 endoscopists performed >100 colonoscopies. The median adenoma detection rate was 38.5% (range 22.5%–53.9%), while the median number of detected adenomas per colonoscopy was 0.75 (range 0.30–1.41). The median proximal serrated polyp detection rate was 9.2% (range 2.5%–19.8%), while the median number of detected proximal serrated polyps was 0.12 (range 0.03–0.35). The median SSA/P detection rate was 7.3% (range 2.5%–13.6%).

Polyp characteristics

In total 4251 polyps were resected, including 2871 adenomas (67.5%), 974 hyperplastic polyps (22.9%), 399 SSA/Ps (9.4%) and 7 TSAs (0.2%). Of all adenomas, 584 (20.3%) were regarded as advanced lesions. Of all SSA/Ps, 15 (3.8%) contained dysplasia and 74 (18.5%) were classified as high risk SSA/Ps.

Figure 1 | Colonic polyp ratios among adenomas, sessile serrated adenomas/polyps (SSA/Ps) and hyperplastic polyps.
The colonic polyp ratio between adenomas, SSA/Ps and hyperplastic polyps, stratified for colon segment, is presented in Figure 1. SSA/Ps accounted for 15.1% of polyps in the right-sided colon, 10.9% of polyps in the transverse colon and 4.6% of polyps in the left-sided colon. In total, the categorizations of 30 SSA/Ps and 87 hyperplastic polyps were revised by one expert pathologist (L.K.). The overall agreement was shown to be good (kappa 0.7). In total, 5 SSA/Ps were redefined as hyperplastic polyps, while 9 hyperplastic polyps were redefined as SSA/Ps.

The endoscopic characteristics of all detected SSA/Ps are presented in Table 1. In total, 297 SSA/Ps (75.6%) were located in the proximal colon and 96 SSA/Ps in the distal colon (24.4%). Regarding colonic segment location, the highest proportion of SSA/Ps were detected in the ascending colon (40.5%). In total, 13 SSA/Ps with dysplasia (86.6%) and 60 high risk SSA/Ps (81.1%) were located in the proximal colon. No significant difference in colonic distribution was demonstrated between high risk SSA/Ps and moderate risk SSA/Ps (P=0.15). The colonic distribution of SSA/Ps is illustrated in Figure 2 and graphically compared with the distribution of hyperplastic polyps and adenomas. The morphology of SSA/Ps was sessile in 208 (54.3%) cases and flat in 175 (45.7%) cases. No significant difference in morphology was demonstrated between high risk SSA/Ps and moderate risk SSA/Ps (P=0.14). The median size of SSA/Ps was 5mm (IQR 3–8). No significant difference in size was demonstrated for distal SSA/Ps (median 5mm, IQR 3–7) versus proximal SSA/Ps (median 5mm, IQR 3.5–8) (P=0.06). The size range of SSA/Ps with dysplasia was 2–10mm and 40% of lesions were<6mm in size.

Table 1 | Endoscopic characteristics of sessile serrated adenomas/polyps

<table>
<thead>
<tr>
<th>Location; n (%)</th>
<th>Overall (n=399)</th>
<th>Moderate-risk SSA/P (n=325)</th>
<th>High-risk SSA/P* (n=74)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>297 (75.6)</td>
<td>237 (74.4)</td>
<td>60 (81.1)</td>
<td></td>
</tr>
<tr>
<td>Cecum</td>
<td>66 (16.8)</td>
<td>49 (15.4)</td>
<td>17 (23.0)</td>
<td></td>
</tr>
<tr>
<td>Ascending colon</td>
<td>159 (40.5)</td>
<td>131 (41.1)</td>
<td>28 (37.9)</td>
<td></td>
</tr>
<tr>
<td>Transverse colon</td>
<td>72 (18.3)</td>
<td>57 (17.9)</td>
<td>15 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>96 (24.4)</td>
<td>84 (25.6)</td>
<td>14 (18.9)</td>
<td></td>
</tr>
<tr>
<td>Descending colon</td>
<td>31 (7.9)</td>
<td>23 (7.1)</td>
<td>8 (10.8)</td>
<td></td>
</tr>
<tr>
<td>Sigmoid</td>
<td>52 (13.2)</td>
<td>47 (14.7)</td>
<td>5 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>13 (3.3)</td>
<td>12 (3.8)</td>
<td>1 (1.4)</td>
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</tr>
<tr>
<td>Missing</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Morphology; n (%)</th>
<th>Overall (n=399)</th>
<th>Moderate-risk SSA/P (n=325)</th>
<th>High-risk SSA/P* (n=74)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessile</td>
<td>208 (54.3)</td>
<td>176 (56.1)</td>
<td>32 (46.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Flat</td>
<td>175 (45.7)</td>
<td>138 (43.9)</td>
<td>37 (53.6)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>16</td>
<td>11</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size in mm; median (IQR)</th>
<th>Overall (n=399)</th>
<th>Moderate-risk SSA/P (n=325)</th>
<th>High-risk SSA/P* (n=74)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>5 (3-8)</td>
<td>5 (3-6)</td>
<td>10 (10-12)</td>
<td>N/A</td>
</tr>
<tr>
<td>Distal</td>
<td>5 (3-7)</td>
<td>5 (3-5)</td>
<td>10 (10-10)</td>
<td></td>
</tr>
</tbody>
</table>

* Defined as an SSA/P with dysplasia and/or ≥10mm in size
Prevalence of SSA/Ps
The prevalence of SSA/Ps, stratified for colonoscopy indication, is presented in Table 2. The overall prevalence of SSA/Ps was 8.2%. The overall prevalence was 6.6% for proximal SSA/Ps, 1.8% for SSA/Ps≥10mm, 2.0% for high risk SSA/Ps. The prevalence of SSA/Ps ranged between 6.7% and 11.9%, depending on colonoscopy indication. Multiple logistic regression analysis showed that the prevalence of SSA/Ps was significantly higher for the indications “familial CRC risk” (OR 1.52, 95%CI 1.05–2.22; P=0.03) and for “surveillance” (OR 1.73, 95%CI 1.20–2.49; P<0.01), when compared with the indication “abdominal symptoms” (Table 3). The prevalence of SSA/Ps was not increased in FIT-based screening patients (OR 1.08, 95%CI 0.75–1.54; P=0.69) when compared with symptomatic patients. Furthermore, no significant differences were demonstrated between men and women (OR 1.04; 95% CI 0.81-1.34; P=0.74). Increasing age was associated with increasing SSA/P prevalence (OR 1.01 per year; 95%CI 1.00–1.03; P=0.02). Subsequent regression analysis showed that the prevalence of SSA/Ps was 5.2% in individuals under 50 years of age, compared with 9.0% for individuals above 50 years (adjusted OR 1.74, 95%CI 1.19–2.53; P<0.01). Within individuals aged >50 years, no significant association was demonstrated between age and the prevalence of SSA/Ps overall (adjusted OR 1.00, 95% CI 0.98–1.01; P=0.74). The prevalence of high risk SSA/Ps was 0.8% for individuals<50 years, compared with 2.3% for individuals above 50 (adjusted OR 2.28; 95%CI 0.95–5.45; P=0.06). All SSA/Ps with dysplasia were detected in individuals above the age of 50 (prevalence 0.5%). The age-standardized prevalence of SSA/Ps is demonstrated in Figure 3.

Association of SSA/Ps and advanced neoplasia
The per-patient association between SSA/Ps and synchronous advanced neoplasia is presented in Table 4. Advanced neoplasia was diagnosed in 470 patients (14.0%). CRC was diagnosed in 84 patients.
Prevalence and risk of SSP in a high quality colonoscopy centre

(2.5%) and advanced adenomas in 407 patients (12.1%). In 21.7% of patients with at least one SSA/P, synchronous advanced neoplasia was detected, compared with 13.3% for colonoscopies without a SSA/P (OR 1.71, 95%CI 1.25–2.34; P=0.001). In colonoscopies with at least one high risk SSA/P the odds for synchronous advanced neoplasia were also significantly higher, compared with colonoscopies without a high risk SSA/P present (29.9% vs. 13.6%; OR 2.70, 95%CI 1.56–4.67; P<0.001). Sensitivity analyses, in which only those patients who underwent an colonoscopy performed by a high SSA/P detector were included, showed similar risk estimates.

DISCUSSION

In this prospective study, we showed that at an endoscopy center with a high adenoma detection rate and experienced gastrointestinal pathologists, the prevalence of SSA/Ps was 8.2% overall, increasing to 9.0% for individuals above 50 years of age. The prevalence of high risk SSA/Ps was 2.0%. Per-polyp analysis showed that the typical SSA/P was sessile or flat, 5mm in size and located in the proximal colon. Both SSA/Ps overall (OR 1.71, 95%CI 1.25–2.34; P<0.001) as well as high risk SSA/Ps (OR 2.70, 95%CI 1.56–4.67; P<0.001) were associated with the presence of synchronous advanced neoplasia in a per-patient analysis.

Table 2 | Prevalence of sessile serrated adenomas/polyps per colonoscopy indication

<table>
<thead>
<tr>
<th></th>
<th>Overall; n (%)</th>
<th>Symptoms; n (%)</th>
<th>FIT screening; n (%)</th>
<th>Familial risk; n (%)</th>
<th>Surveillance; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=3364)</td>
<td>(n=2115)</td>
<td>(n=461)</td>
<td>(n=409)</td>
<td>(n=379)</td>
</tr>
<tr>
<td>≥1 SSA/P overall</td>
<td>276 (8.2)</td>
<td>141 (6.7)</td>
<td>50 (10.8)</td>
<td>40 (9.8)</td>
<td>45 (11.9)</td>
</tr>
<tr>
<td>≥1 proximal SSA/P</td>
<td>221 (6.6)</td>
<td>117 (5.5)</td>
<td>39 (8.5)</td>
<td>33 (8.1)</td>
<td>32 (8.4)</td>
</tr>
<tr>
<td>≥1 distal SSA/P</td>
<td>77 (2.3)</td>
<td>35 (1.7)</td>
<td>17 (3.7)</td>
<td>9 (2.2)</td>
<td>16 (4.2)</td>
</tr>
<tr>
<td>≥1 large SSA/P (≥10mm)</td>
<td>59 (1.8)</td>
<td>26 (1.2)</td>
<td>18 (3.9)</td>
<td>9 (2.2)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>≥1 high-risk SSA/P*</td>
<td>67 (2.0)</td>
<td>30 (1.4)</td>
<td>21 (4.6)</td>
<td>9 (2.2)</td>
<td>7 (1.8)</td>
</tr>
</tbody>
</table>

* Defined as an SSA/P with dysplasia and/or ≥10mm in size

Table 3 | Adjusted odds ratio for the detection of sessile serrated adenomas/polyps

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.01 (1.00-1.03)</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.04 (0.81-1.34)</td>
<td>0.74</td>
</tr>
<tr>
<td>Symptoms</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>FIT screening</td>
<td>1.08 (0.75-1.54)</td>
<td>0.69</td>
</tr>
<tr>
<td>Familial risk</td>
<td>1.52 (1.05-2.22)</td>
<td>0.03</td>
</tr>
<tr>
<td>Surveillance</td>
<td>1.73 (1.20-2.49)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High SSA/P detector</td>
<td>2.65 (2.00-3.50)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
TABLE 4 | Per patient association between sessile serrated adenomas/polyps and synchronous advanced neoplasia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted OR overall (95% CI)**</th>
<th>p-value</th>
<th>Adjusted OR high SSA/P detectors (95% CI)**</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 SSA/P</td>
<td>1.71 (1.25-2.34)</td>
<td>0.001</td>
<td>2.04 (1.43-2.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥1 proximal SSA/P</td>
<td>1.69 (1.20-2.39)</td>
<td>0.001</td>
<td>1.95 (1.33-2.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>≥1 large SSA/P (≥10mm)</td>
<td>2.78 (1.56-4.96)</td>
<td>&lt;0.001</td>
<td>3.05 (1.63-5.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥1 high-risk SSA/P*</td>
<td>2.70 (1.56-4.67)</td>
<td>&lt;0.001</td>
<td>3.05 (1.63-5.69)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Defined as an SSA/P with dysplasia and/or ≥10mm in size
** adjusted for age and gender

Subsequent analysis showed that the detection of SSA/Ps was associated with patient age and colonoscopy indication (namely, the indications of surveillance and familial CRC risk), while gender did not influence the prevalence of SSA/Ps. The prevalence of SSA/Ps was 9.0% for individuals above 50 years, compared with 5.2% in patients below 50. However, no age trend was seen within the group of patients older than 50 years. This observation seems to confirm recent findings, suggesting that SSA/Ps without dysplasia most often arise in middle-aged patients and have a relatively long dwell time\textsuperscript{20,30}. The association of gender and SSA/Ps was discussed in a recent review, which demonstrated conflicting results\textsuperscript{31}. However, most studies did not show a significant difference in prevalence of SSA/P between men and women, which is in agreement with findings from our study. Therefore, uniform detection standards for male and female patients seem justified. The association between colonoscopy indication and SSA/P detection is largely unexplained and should be evaluated in future research.

Variability in pathology criteria over time, as well as increasing awareness about the malignant potential of SSA/Ps and a continuing improvement in the quality of endoscopes, has contributed to
Prevalence and risk of SSP in a high quality colonoscopy centre

a wide variation in the reported prevalence of SSA/Ps within studies\textsuperscript{11,17–25}. Studies performed before publication of the most up-to-date WHO guideline\textsuperscript{5}, report an underestimated prevalence of SSA/Ps ranging between 0.6% and 3.9%\textsuperscript{18–21}. However, also in more recent studies, the reported prevalence of SSA/Ps has ranged between 2.0% and 8.1%\textsuperscript{13,17–22,25,32}. Two small studies, both including fewer than 200 patients, have even reported SSA/P prevalence from 10.6% to 13.6%\textsuperscript{12,31}. Most probably, this variability in reported SSA/P prevalence is mainly caused by variability in polyp recognition, rather than a "true" difference in prevalence of disease. In one recent study by Abdeljawad et al., all pathology specimens of polyps in the serrated class, as diagnosed in daily practice by an experienced endoscopist between 2005 and 2012, were reassessed by one expert pathologist. After re-evaluation, the determined prevalence of SSA/Ps increased from 1.5% to 8.1% in average risk individuals > 50 years of age\textsuperscript{25}. That study shows that experienced pathologists as well as endoscopists are needed to enable reliable reporting on the prevalence and distribution of SSA/Ps. For this reason, the results from most earlier reports might be subject to major bias in results. For instance, in a study by Bouwens et al. the endoscopic characteristics of SSA/Ps with and without dysplasia were compared\textsuperscript{13}. In that study it was stated that 63/170 (37.1 %) of all SSA/Ps would contain dysplasia. However, the overall reported prevalence of SSA/Ps was only 2.0%. Those results might suggest that SSA/Ps with dysplasia were more often recognized by endoscopists and/or pathologists than SSA/Ps without dysplasia. Therefore, the comparison between both types of SSA/P is subject to major selection bias and the external validity of that study is reduced. In comparison, only 5.8% of SSA/Ps showed dysplasia in the study by Abdeljawad et al, corresponding to the 3.8% of SSA/Ps as detected in the current study.

The same sort of selection bias may have also polluted the estimated association between the presence of SSA/Ps and the presence of synchronous advanced neoplasia as presented in three earlier reports\textsuperscript{17,24,34}. Buda et al. were the first to assess the association between SSA/Ps and synchronous advanced neoplasia, presenting an odds ratio of 6.0 (95%CI 1.9–19.5)\textsuperscript{24}. However, only 2.3% of individuals were diagnosed with an SSA/P. In comparison, Ng et al. showed an odds ratio between the presence of SSA/Ps and synchronous advanced neoplasia of 4.52 (95%CI 2.40–8.49), given a reported SSA/P prevalence of 1.2\textsuperscript{34}. The association, as demonstrated in both studies, is higher than that presented in the current study (OR 1.71, 95%CI 1.25–2.34; P=0.001). However, the low reported prevalence of SSA/Ps might have led to major bias in both association studies. A low prevalence suggests that the participating endoscopists mainly detected those SSA/Ps that were more easily identified (e.g. large SSA/Ps and or SSA/Ps with a dysplastic component), while the pathologists might have recognized only those SSA/Ps at a more mature stage (more affected crypts). Taking only those more advanced lesions into account would result in an artificially increased correlation between SSA/Ps and synchronous advanced neoplasia, diminishing both the internal and the external validity.

Finally, in an earlier report by our research group the association between proximal SSA/Ps (OR 3.04, 95%CI 1.50–6.15), as well as large SSA/Ps (OR 5.02, 95%CI 1.69–14.86) and synchronous advanced neoplasia was estimated in an average risk screening population\textsuperscript{17}. The reported prevalence of SSA/Ps in that study was 4.8%. Therefore the estimated associations in that study seem less biased, but...
probably still represent an artificially high association between the presence of SSA/Ps and advanced neoplasia. However, a one-to-one comparison with the results from the current study is difficult, because of the heterogeneity in study population.

In the present study, colonoscopy data were prospectively collected with the use of an automated reporting system that enabled encoded data collection and quality assurance of all colonoscopies in daily practice. The general colonoscopy quality as well as adenoma and proximal serrated polyp detection rate was high, and all lesions were assessed by an experienced gastrointestinal pathologist. Centralized pathology review by an expert pathologist showed a good agreement with original pathology diagnosis (kappa 0.70). Agreement was comparable with the interobserver agreement of five European expert pathologists, assessing serrated polyp subtypes after a diagnostic consensus meeting (kappa 0.63)\(^3\). Nevertheless, several limitations have to be acknowledged in this study. First, most patients underwent a colonoscopy for abdominal symptoms (62.9%). This may have affected the external validity of our study with regard to centers with other patient populations. We performed a stratified analysis according to colonoscopy indication to overcome this issue. Unfortunately, sample size did not allow for a stratified evaluation of the association between SSA/Ps and advanced neoplasia. Second, colonoscopies were performed by various endoscopists with SSA/P detection rates ranging from 2.5% to 13.6%. Therefore, the “true” prevalence of SSA/Ps might have been closer to 13.6 %. However, since the overall prevalence of 8.2% was reached by a group of 25 different endoscopists, the overall detection standards, as set in this study, seem to be more realistic for endoscopy units in daily practice.

The results from this study might have implications for CRC prevention strategies. We showed that, in general colonoscopy practice, SSA/Ps are more common than previously reported and associated with the presence of advanced neoplasia. For this reason, endoscopists should be focused to identifying SSA/Ps in daily practice and should carefully look for synchronous advanced neoplasia when an SSA/P has been recognized. Furthermore, CRC prevention strategies should be adjusted to enable the detection of SSA/Ps. For instance, screening tools such as computed tomographic (CT)-colonography, fecal immunochemical testing, and molecular stool testing, designed to detect adenomas and CRC, should be re-evaluated for their performance in the co-detection of SSA/Ps. Last, all international post-polypectomy guidelines should include appropriate surveillance for individuals with SSA/Ps to decrease the incidence of colonoscopy interval CRC, as incorporated in the most recent US guideline\(^4\). Future research should be performed to substantiate these goals with evidence and should enable an even better identification of those SSA/Ps truly at high risk of developing into CRC.

In conclusion, we have shown that in general colonoscopy practice the prevalence of SSA/Ps is higher than previously reported and depends on the indication for colonoscopy. Furthermore, we have shown that SSA/Ps have an evident association with the presence of synchronous advanced neoplasia, although this is lower than previously reported. The results from this study further emphasize that
CRC prevention strategies should be adjusted to enable the detection of SSA/Ps, besides adenomas and CRC. Results from this study can guide detection standards in general colonoscopy practice adapted to the type of patients that may be predominant at an individual colonoscopy center.
REFERENCES


