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Low prevalence of serrated polyposis syndrome in screening populations: a systematic review

Authors

Background and study aims: The most frequently cited prevalence for serrated polyposis syndrome (SPS) is 1 in every 3000 people screened, but this value is debated. Additionally, changes in 2010 in the World Health Organization (WHO) diagnostic criteria for SPS might affect reported prevalence. An updated estimate of SPS prevalence is necessary to predict the number of cases in screening programs.

Patients and methods: A systematic literature search was conducted in the PubMed, EMBASE, and Web of Science databases up to February 2014. Studies reporting the prevalence of SPS, as defined by WHO criteria, in screening populations were selected.

Results: Six studies reported prevalence of SPS in screening populations, varying from 0 to 0.66%. The highest prevalences (0.34% and 0.66%) were seen in studies from screening programs with patients pre-selected by fecal blood test. Primary colonoscopy-based screening programs, that have the lowest risk of bias, reported SPS prevalences ranging from 0 to 0.09%. Across studies, 56 patients were diagnosed with SPS of whom 3 presented with synchronous colorectal cancer at index endoscopy.

Conclusion: The true prevalence of SPS is unclear because of the risk of bias across studies, but is likely to be below 0.09% as derived from primary colonoscopy screening programs. The prevalence in pre-selected screening populations after positive fecal testing is higher, with reported values of 0.34% and 0.66%. Large and high quality primary colonoscopy screening studies, reporting SPS prevalence in adequately described populations, are necessary for better estimation of the true prevalence of SPS in average-risk patients.

Introduction

The presence of multiple serrated polyps in patients is associated with an increased risk of colorectal cancer (CRC). Since the recognition of this association, it has become clear that both serrated polyposis patients and their first-degree relatives have an increased risk of CRC [1,2]. The so-called serrated polyposis syndrome (SPS) is now recognised as one of the new polyposis syndromes. Since no genetic basis for SPS has been discovered thus far, diagnosis is based on clinical criteria defined by the World Health Organization (WHO) [3]. The latest WHO definition for SPS dates from 2010 and states that patients fulfill the criteria if they have at least 5 serrated polyps proximal to the sigmoid colon, of which two are at least 10 mm; or any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS; or at least 20 serrated polyps of any size distributed throughout the colon. In comparison with the previous criteria published in 2000, polyps with a serrated architecture apart from hyperplastic polyps are also included in the definition. In addition, the third criterion has been made less stringent, reducing the required serrated polyps count from 30 to 20 [4].

Since the number of colorectal screening programs is increasing worldwide, an up-to-date estimate of the prevalence of SPS is necessary to predict the number of SPS cases that may be identified in (differently organized) screening programs. As the diagnosis of SPS is often missed in daily practice, a prevalence estimate can be used to check whether there is optimal recognition of the syndrome by clinicians [5,6]. In addition, identification of SPS patients through screening programs can provide valuable information on CRC risk and prognosis as this patient population is not biased towards a more severe phenotype, which is the major problem in the cohorts of SPS patients that present to genetics clinics [7].
The prevalence of SPS is not clear at present. The most frequently cited prevalence for SPS is 1 patient in every 3000 people screened by sigmoidoscopy, but this number is debated as it is based on an abstract from 2001 with limited information on study procedures [8]. The amendment of the WHO criteria in 2010 is likely to influence prevalence numbers because less stringent criteria and new endoscopy techniques might lead to an increase in the number of cases that fulfill the criteria. No systematic discussion on the prevalence of SPS is available so far. Therefore we attempted to estimate the prevalence of SPS and the associated CRC occurrence, as defined by the previous and the new WHO criteria, in a systematic review that includes studies investigating SPS prevalence in screening populations.

Methods

Data sources and search
A systematic search was conducted in the electronic databases PubMed, EMBASE and Web of Science through February 2014 with the aid of a librarian. The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was used for all the steps reported in this review [9]. The full search strategy is presented in Appendix 1 (available online). No restrictions regarding language, year of publication, or publication type were imposed. Additional studies were sought by scanning the reference lists of included articles, reviews, and key textbooks and by searching Google Scholar. If more than one article was published from a study, the version that provided the most updated data was selected for inclusion. Additional information was extracted from all articles concerning the screening program. Conference abstracts and letters to the editor were included only if no full-text article presenting the same data was available. Two independent authors (M. V. and Y. H.) assessed the studies by title and abstract to judge whether inclusion criteria were met. Case reports and reviews were excluded as these contain no primary epidemiological data. Subsequently, the full text of potentially eligible studies was independently examined by two authors (M. V. and Y. H.), and articles presenting prevalence rates of SPS as defined by the WHO criteria in screening populations were included. Disagreements were resolved after discussion with a third author (T. B.).

Data extraction and quality assessment
Two authors (M. V. and Y. H.) independently evaluated and extracted background characteristics and outcomes from the included studies. The study characteristics extracted included: first author, year of publication, place of research, and time period, and also methods of inclusion and exclusion and study design to evaluate the generalizability of the source population. To evaluate the study process and population numbers, we assessed the number of patients approached from the source population, the reporting of responders and nonresponders, the number of patients undergoing colonoscopy or other screening tests, and the number of patients diagnosed with SPS. Critical appraisal of the studies was done using a methodological scoring system for prevalence and incidence studies as previously described [10]. Quality items evaluated were: methods of sampling, sampling frame, sample size, outcome measurement, outcome assessment, response rate, statistical reporting, and interpretation of study results [10].

Adequate sample size was calculated \((N=Z^2_{\alpha/2} \times p(1-p))/d^2;\) where \(N\) is the sample size, \(Z_{\alpha/2}\) (1.96) is the \(z\) value for 95% confidence, \(p\) the expected prevalence, and \(d\) the accuracy of the estimation) based on an estimated prevalence of 0.09% and an accuracy of 0.005%. This gave a minimum sample size of approximately 1380000, which would be considered adequate in the quality assessment. Disagreements regarding data extraction and quality assessment were resolved by discussion and consensus with a third reviewer (T.B.).

Data synthesis and analysis
The primary outcome of the study was the prevalence of SPS as defined by the WHO criteria in screening populations. Studies were grouped and analyzed based on the screening method used and the criteria used for diagnosis (WHO 2000 or WHO 2010). For point estimates of prevalence, 95% confidence intervals (95%CI) were estimated. Prevalence numbers were presented using Graphpad Prism (Version 5.03 for Windows, GraphPad Software, San Diego California USA).

Results

Study selection
Our search, described in Fig. 1, resulted in 2476 unique citations. After exclusion of 2356 articles, based on title and abstract, we evaluated the full text of the remaining 120 citations that were considered potentially relevant. One study, an abstract from 1994, was discarded because the full text was unavailable to us despite extensive searching. A total of 113 studies were excluded because no SPS prevalence rates were presented. Six studies described the prevalence rates of SPS defined by the old or new WHO criteria in screening populations and were included for analysis. One article included two databases with screened patients from different origins. We excluded the second, smaller database because the patients were included in a randomized controlled trial instead of being randomly selected for screening and this could lead to potential selection bias [11].

Study characteristics
Six studies were selected for the review, three prospective and three retrospective by nature. Of the included studies, two were described in full-text articles [11,12], two in conference abstracts [8,13] and two in letters to the editor [14,15]. Characteristics of the studies and their source populations are presented in Table 1. In four studies, patients were diagnosed with SPS as defined by the most recent WHO criteria [11,12,14,15]. In the other two studies the criteria of 2000 were used [8,13]. In two studies the second WHO criterion, based on a positive family history for SPS, was not used for diagnosis [12,14], in the remaining studies it was not reported whether this criterion was systematically assessed.

In three studies, before colonoscopy, participants had undergone an initial screening test prior to inclusion in the study. In two of these the screening method was fecal testing [14,15]. The study of Biswas et al. [14] included only persons who underwent a colonoscopy after positive findings from a guaiac fecal occult blood test (gFOBT) [14], and the study of Moreira et al. [15] included only persons with positive findings from a fecal immunochemical test (FIT). In these studies, with data from 2009 to 2012, the number of persons participating in the screening program was not re-
ported; thus it was impossible to calculate response rates and compare responders and nonresponders. The prevalence of SPS could only be calculated for those persons with a positive stool test, namely 755 (Biswas et al. [14]) and 2355 (Moreira et al. [15]). In the third study, by Lockett et al., 57,254 persons between 55 and 64 years of age were invited for sigmoidoscopy screening between 1994 and 1999 [8, 17]. All participants underwent flexible sigmoidoscopy and were referred for colonoscopy if they met any of the high risk criteria: adenoma 1 cm or larger; three or more adenomas; tubulovillous or villous histology; severe dysplasia or malignant disease; or 20 or more hyperplastic polyps proximal to the distal rectum. Although participants who did not fulfill these criteria were not further investigated, the prevalence was calculated on the total screening population leading to a higher risk of bias. Only one study used the most desirable study design by randomly selecting and inviting screening-naive individuals for a colonoscopy-based screening program [12]. The sample size was not adequate in any of the included studies.

All studies used objective and standardized criteria for assessing the presence of SPS, namely the WHO criteria of 2000 or 2010. Only one study fully described the sociodemographic characteristics of participants, thereby providing information on the applicability of the results [12].

Table 3 shows that several studies did not adequately report the response rates of participants within the screening program, making it impossible to compare responders and nonresponders. It was possible to determine the response rate of two studies [8, 12], and these rates were adequate in both studies. Overall, substantial risk of bias is likely for all included studies (Table 2).

Limited information was given across studies on quality indicators for colonoscopy. The study of Hazewinkel et al. [12] was the only study reporting unadjusted cecal intubation rate (98.7%), median withdrawal time (10 minutes), and median score (5) on the Ottawa Bowel Preparation Scale, while Orlowska et al. only reported cecal intubation rate (91.1%) [18]. Other studies reported no information on quality of colonoscopy [8] or reported only that colonoscopies were performed by experienced endoscopists [11, 15]. The study by Biswas et al. was conducted under the quality regulations of the UK National Health Service Bowel Cancer Screening Program [8].

Risk of bias within studies

Scores for quality items of the included articles are presented in Table 2. In four of the studies, the study design used a method of sampling to assemble the study population which was not ideal but was mostly comparable to the general population [12–15]. In the study by Kahi et al. [11] the route by which screening patients presented themselves for colonoscopy was unclear, leading to a higher risk of bias. Only one study used the most desirable study design by randomly selecting and inviting screening-naive individuals for a colonoscopy-based screening program [12]. The sample size was not adequate in any of the included studies.

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Table 1  Prevalence of serrated polyposis syndrome (SPS): characteristics of the included studies

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Study period</th>
<th>Publication type</th>
<th>Study design</th>
<th>Screening method</th>
<th>Age of interest, years</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>National screening program?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lockett, 2001 [8]</td>
<td>United Kingdom</td>
<td>1994–1999</td>
<td>Conference abstract</td>
<td>Prospective</td>
<td>Sigmoidoscopy</td>
<td>55 – 64</td>
<td>Unclear</td>
<td>Inability to provide informed consent; history or family history of colorectal cancer, adenomas, inflammatory bowel disease, or symptoms of colorectal cancer; severe or terminal disease; life expectancy less than 5 years; or sigmoidoscopy or colonoscopy within the previous 3 years</td>
<td>No</td>
</tr>
<tr>
<td>Orlowska, 2009 [13]</td>
<td>Poland</td>
<td>2000–2004</td>
<td>Conference abstract</td>
<td>Prospective</td>
<td>Colonoscopy</td>
<td>40 – 66</td>
<td>50 – 66 years: people in good general health and colorectal cancer was not suspected for a national screening program for colorectal cancer; 40 – 49 years: family history of cancer of any type</td>
<td>Age 50 – 66 years: recent changes in bowel habits, anemia, unexplained weight loss, bleeding in the lower gastrointestinal tract not attributable to hemorrhoids, characteristics that met the criteria for hereditary nonpolyposis colorectal cancer of familial adenomatous polyposis, inflammatory bowel disease, and colonoscopy within the preceding 10 years</td>
<td>Yes</td>
</tr>
<tr>
<td>Hazewinkel, 2014 [12]</td>
<td>Netherlands</td>
<td>2009–2010</td>
<td>Full text</td>
<td>Prospective</td>
<td>Colonoscopy</td>
<td>50 – 75</td>
<td>Randomly selected screening-naive individuals</td>
<td>Full colonic examination in the previous 5 years, scheduled for surveillance colonoscopy because of a personal history of CRC, adenomas, inflammatory bowel disease, end-stage disease with a life expectancy of less than 4 years</td>
<td>No</td>
</tr>
<tr>
<td>Biswas, 2013 [14]</td>
<td>United Kingdom</td>
<td>2010–2012</td>
<td>Letter to the editor</td>
<td>Retrospective</td>
<td>gFOBT</td>
<td>60 – 69 [16]</td>
<td>Patients with a positive gFOBT presenting for (NHS) bowel cancer screening</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; NHS, National Health Service.

Table 2  Prevalence of serrated polyposis syndrome (SPS): quality assessment of included studies.

|-------------------|-------------------------------------|------------------|----------------|---------------------|----------------------|-----------------------------|-----------------------------|-----------------------------|

* low risk of bias; + / – reporting not adequate; –, high risk of bias.
Screening Programme, with accredited endoscopists, but did not provide detailed information on quality parameters [14, 16].

**Prevalence rates**

The prevalence of SPS varied widely from 0% to 0.66% between the six studies (Fig. 2, Table 3). Because only one study reported the 95% confidence intervals for the prevalence estimate [14], we estimated the 95% confidence intervals for the other studies (Fig. 2).

The three studies in which patients were pre-selected for colonoscopy, by either sigmoidoscopy or a stool test, reported prevalences ranging from 0.03% to 0.66% [8, 14, 15]. The highest prevalence rates, 0.34% and 0.66%, were seen in two of these three studies; the two studies were based on screening programs that select patients for colonoscopy by stool test [14, 15]. The size of the included source population in the two studies was unknown and the prevalence was calculated only in the participants with a positive stool test.

Colonoscopy-based screening programs reported prevalence rates ranging from 0 to 0.09% [11–13]. One of these colonoscopy-based studies used the WHO criteria of 2000 and reported a prevalence of 0.06% [13], compared to the prevalences of 0% and 0.09% in the studies using the WHO 2010 criteria [11, 12].

**Adenomas and carcinomas**

The occurrence of adenomas and carcinomas varied between studies and was not clearly reported in some studies (Table 4). The presence of adenomas at index endoscopy varied from 7% to 80% in patients with detected SPS. Overall, 3 patients presented with synchronous CRC and SPS at index colonoscopy: only 1 patient in the population screened with sigmoidoscopy and 2 patients who had been screened with FIT [8, 15].

**Discussion**

In the current study we assessed the prevalence of SPS in population screening programs. Since we found only six studies, all with considerable risk of bias and lack of follow-up data, the true prevalence remains unclear. The prevalence of SPS in persons with detected SPS is likely to be below 0.09%, this figure being the highest reported prevalence. The prevalence in screening populations after pre-selection by positive stool testing is higher, with reported values of 0.34 and 0.66% from two studies. In screening populations few patients present with synchronous CRC at the time of SPS diagnosis. The first important finding of this study is the quantity and quality of the available studies. The number of studies investigating...
the prevalence of SPS in screening populations is low and most studies have a high risk of bias because of patient selection. Because of the essential differences between the studies, we considered that it was not appropriate to pool the data. We identified only six studies, which precluded use of a funnel plot as this requires a minimum of 10 studies [19]. To avoid missing published or unpublished studies we used Web of Science to search for abstracts presented at large conferences. In addition, references in key textbooks and review articles were screened to identify additional reports of SPS prevalence. After this extensive search we feel that, regarding prevalence rates of SPS, reporting within studies is a larger problem than publication bias. The prevalence of SPS is not the primary study outcome in two of the studies included in our review [11, 12], highlighting that more SPS prevalence rates could be calculated from other studies reporting on screening cohorts. In our search we found several studies reporting the prevalence of serrated polyps in large screening cohorts, but they did not report the numbers that fulfilled the WHO criteria [20]. Even if SPS prevalence is not the primary outcome of these studies, reporting this detail can lead to a better understanding of the burden of this polyposis syndrome. Ideally, large and high quality primary colonoscopy screening studies will prospectively report SPS prevalence in adequately described populations, so that the true prevalence of SPS in average-risk patients can be better estimated.

We observed a large difference in the prevalence of SPS between studies screening with colonoscopy and studies screening with stool tests before colonoscopy. Although it seems logical that prevalence in the latter populations would be higher, studies examining fecal occult blood tests report that their accuracy for detecting serrated polyps is low [21]. An explanation might be that SPS patients were detected because of synchronous adenomas or carcinomas. Although the presence of adenomas was high in the studies where a stool test was used to pre-select patients for colonoscopy, the number of patients presenting with CRC was not. It is likely that patients with SPS were missed when a stool test was used as screening test, leading to different prevalences in the total populations. No detailed information was available on nonresponders from the two different screening methods, making it impossible to compare the two groups. It is unclear whether nonresponders have a different SPS prevalence compared to responders in the screening programs.

Although the primary outcome of screening programs is the detection of CRC, few CRCs were detected in patients diagnosed with SPS during the screening programs. With only 5.4% of screening-identified SPS patients presenting with synchronous CRC, we noticed a large difference compared with previously described populations where CRC occurrence was much higher, ranging from 16% to 39% [1, 7, 22, 23]. This can be explained by the differences in population and method of detection. These previous studies were not conducted in screenees but in patients with a family history of CRC or with symptoms suggestive of CRC. Since these patients represent the more severe phenotypes or have a more pronounced cancer risk within their families, they are likely to have a higher risk of CRC. The screening participants in the current study are older and it is likely that SPS patients with high risk of CRC were not included because they had been diagnosed earlier and therefore were not participating in a screening program. Additionally, we cannot exclude that the SPS patients detected in the included studies might develop CRC during follow-up, since we have information only on the index colonoscopy. Another explanation for this difference might be that SPS is underdiagnosed in patients with CRC or large adenomas, as the attention of the endoscopist focuses on the major lesion while possibly overlooking synchronous serrated polyps. This is highly dependent on the awareness of the endoscopist with regard to detection of serrated polyps and serrated polyposis syndrome.

Surprisingly, we found no difference in reported prevalence of SPS between the colonoscopy-based screening program that used the 2000 WHO criteria and those that used the 2010 criteria. We expected to detect a difference in prevalence between studies using the old and new WHO criteria, because the 2010 criteria specify fewer polyps for diagnosis and hence are fulfilled more easily. Furthermore, new endoscopic techniques increase detection rates for serrated polyps. On the other hand, endoscopist awareness of the malignant potential and the discrete appearance of these polyps might be more important for their detection. The differences in source population and the overall quality of the studies could also explain why we did not detect a difference in prevalence. Another hypothesis could be that most patients who fulfill the third 2010 criterion of at least 20 polyps would still have fulfilled the criterion if 30 polyps had been needed.

In the execution of screening programs for CRC it is useful to be aware of the prevalence of SPS. Two previous studies report a significant miss rate for SPS diagnosis, citing possible reasons [5, 6]. Most importantly, unawareness of the SPS criteria can be a contributing factor to missing this diagnosis. Additionally, information from previous colonoscopies, such as polyp size, location, and histology, is not always readily available. It is important for physicians to be aware of the SPS criteria so that they can actively check whether the criteria might be fulfilled when previous colonoscopy findings are taken into account. Knowledge of the prevalence of this syndrome helps to give an indication of the number of SPS patients that are likely to be detected in screening programs. Endoscopists who identify a smaller number of SPS patients than other endoscopists might benefit from additional training in the detection of serrated polyps and the recognition of SPS [6, 24].

Important strengths of this review are that this is the first review on this topic and that we performed an extensive search for prevalence data. The most important limitation is the lack of available data as highlighted above. Additionally, sampling methods in the included studies were not intended to discover the true prevalence of SPS. An important problem within studies was the reporting of the background characteristics of the source population. Most studies did not sufficiently report the response rates for colonoscopy. Studies describing populations pre-selected with stool tests did not describe the source population, numbers of responders and nonresponders for the stool test, and the percentage of positive findings from stool tests. Another limitation was the lack of information on quality indicators for colonoscopy, which is an important issue in diagnosis of SPS. Cecum intubation rate, withdrawal time and bowel preparation quality are important because flat proximal polyps are easily missed in a polluted colon or an incomplete colonoscopy [25]. In addition, the included studies did not present follow-up data but only findings from a single screening colonoscopy on which SPS diagnosis was based. As we have outlined previously, the diagnosis of SPS can be made on a cumulative polyp count from multiple colonoscopies [26]. Therefore it is likely that more patients from these screening cohorts will fulfill the criteria during follow-up.
In conclusion, few studies are available on the prevalence of SPS, therefore the actual prevalence remains uncertain. Our analysis suggests that the prevalence of SPS found in primary screening colonoscopies is likely to be below 0.09%, while SPS prevalence found in patients after positive findings from a stool test is higher, with values of 0.34% and 0.66% being found. Patients with SPS detected through screening colonoscopy rarely present with synchronous CRC. Since several countries have implemented programs screening for colorectal cancer, an up-to-date estimate of the prevalence of SPS in different populations would be useful to predict the number of cases in various screening programs.

Competing interests: E. Dekker receives research support and equipment on loan from Olympus, F. M. Nagengast is scientific advisor to Sensus, part of COSUN. J. Drenth is supported by research grants from Novartis, Zambon, Ipsen, Otsuka, and Falk and is a consultant for Merck, Jansen, Abbvie and Norgine. The other authors have no potential conflicts of interest to disclose.

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Acknowledgement
Polat Dura is supported by a Mozaïek Grant awarded by the Netherlands Organisation for Scientific Research.

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Appendix e1
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http://dx.doi.org/10.1055/s-0034-1392411