Editorial

Serrated polyposis: the problem of definition and its relationship to the population at risk for syndrome-related colorectal cancer

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Serrated polyposis (SPS) is a syndrome characterised by multiple serrated polyps (MSP) in the large bowel and an increased personal and familial risk of colorectal cancer (CRC). To date efforts to estimate the level of risk associated with SPS have been carried out in the setting of an arbitrary set of clinical criteria. A recent report has presented evidence that the boundary used for meeting these criteria may need to be reconsidered.

SPS, formerly known as hyperplastic polyposis, has been recognised for decades as a risk factor for the development of CRC in both individuals (1) and their first-degree relatives (2). SPS is defined by meeting at least one of three World Health Organization (WHO) criteria for the syndrome; specifically (I) five or more histologically diagnosed serrated lesions proximal to the sigmoid colon of which two are 10 mm or more in size; (II) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS; or (III) more than 20 serrated polyps throughout the colon (3). Though there are three criteria, the first and third are used clinically to identify individuals with a threshold polyp burden (4). The criteria apply to the numbers of histologically confirmed serrated polyps of size and site but not histological subtype, in the colon of an individual, which are cumulative over their lifetime. In addition to serrated polyps, individuals with SPS frequently develop conventional adenomatous polyps which may comprise up to 50% of the polyp burden (5,6). SPS is thought to be relatively rare in the population with a prevalence of 0–0.5% reported in screening populations, rising to 0.4–0.8% after follow up colonoscopy (7). The aetiology of SPS is currently largely unknown apart from rare families where a segregating gene mutation has been reported (8). SPS has a high rate of synchronous and metachronous CRC suggesting a field defect in the colonic mucosa of individuals with this condition (9). Coupled with phenotypic variability, the lack of a genetic aetiology renders SPS one of the most poorly understood and under-recognised of the colorectal polyposes (10).

A recent article from Egoavil and colleagues writing in *Gastroenterology* (5) has highlighted the limitations within the current definition of SPS. In their report, they compared SPS patients with those having MSP but who fall short of meeting the SPS criteria. The most important finding from this work was that the risk of developing CRC in individuals with MSP is commensurate with those who meet the criteria for SPS. In addition, they further demonstrated that patients with MSP confer an equivalent risk for CRC on their first-degree relatives as do those with SPS. These results suggest that patients with MSP and their first-degree relatives would benefit from similar surveillance intervals as those applied in the setting of SPS.

Other similarities between SPS and MSP were observed including smoking history levels, body mass index and the number of colonoscopies each group underwent. The prevalence of CRC at the time of diagnosis for both SPS and MSP was not significantly different at 20.8% and 25.5% respectively (P=0.5). When risk of CRC during follow up was considered, CRC occurred in 1.9% of SPS patients (cumulative risk of 2.7%) and 2.8% of MSP patients (cumulative risk of 4.1%). Significant differences between SPS and MSP patients included a more advanced age at

diagnosis for MSP (54.9 *vs.* 48.9 years, respectively; P<0.001), a higher prevalence of diagnosis in males (70.3% *vs.* 52.8%; P=0.02), and a higher median conventional adenoma rate (P=0.002). As adenoma rate increases with age and as adenoma prevalence is higher in males, these factors may be interrelated but this was not tested in the report. Also, given that the MSP cohort of patients could have any histologic sub-type of serrated polyps, and up to 50% of the polyp burden could be adenomas, it is currently unknown whether the prevalence of adenomas in the MSP cohort of patients is influencing the personal CRC risk level. Family history of non-colonic neoplasms was also higher in MSP patients (53%) compared with 33% in individuals with SPS (P=0.02).

The study has several strong points. In defining their study cohort, the authors have excluded patients with familial adenomatous polyposis (FAP), inflammatory bowel disease, Lynch syndrome, hamartomatous polyposis and hyperplastic polyps of the recto-sigmoid only. In addition, the study drew participants from general rather than specialised clinics thus representing a real-world scenario, and decreasing selection and referral bias. However, listed among the limitations of the study by the authors is the problem (again) of arbitrary definition. In describing MSP as patients with more than ten polyps throughout the colon, 50% of which constitute a serrated subtype, but whose numbers and sizes fall short of meeting the current definition for SPS, the study has used a more relaxed but still arbitrary definition and has not identified a clinical boundary if indeed there is one. Prospective studies of colonoscopy cohorts where serrated polyps are present which include first-degree family history of CRC and other cancers would be needed to better identify the population subset where more intensive surveillance is indicated.

The importance of the WHO criteria in clinical settings lies in their use for identification of a sub-population at increased risk for CRC. Early recognition of SPS and entry into surveillance programs has produced a very low rate of incident CRC in the most recent published series (4,11,12). The current criteria have been criticised for being arbitrary and restrictive (5), as no empirical work was undertaken to generate them. Using these criteria, it may take several colonoscopies for a patient to be classified as having SPS, thus delaying their diagnosis and entry into a more intensive surveillance program. A delayed diagnosis in a proband also delays recognition of the risk for CRC in their first-degree relatives. A recent study demonstrated that 45% of patients with SPS were not diagnosed at their first procedure despite the colonoscopy being carried out by an experienced endoscopist (13).

Other factors influencing the underdiagnosis and hence diagnostic delay inherent in SPS relate to the premalignant lesion which gives the syndrome its name. Serrated polyps, particularly in the proximal colon are difficult to detect and thus reaching a threshold number is dependent upon the skill of the endoscopist. Other factors include failure to apply the current WHO criteria to patient colonoscopy results, and lack of recognition by a minority of histopathologists that the patient has features suspicious for SPS. Taken together these factors make SPS a potentially under-diagnosed syndrome of CRC predisposition (10). A proposal to counter the problem of under-diagnosis is a strategy of reassessment colonoscopy using high definition technologies within 1 year and triggered by initial findings of five or more proximal serrated polyps or two or more sessile serrated adenomas 10 mm or greater in diameter. Using this approach, diagnosis of SPS tripled from 0.3% to 0.9% (14).

Another limitation of the WHO criteria is the phenotypic variability contained within them. Implicit in the criteria as currently proposed, is a spectrum of disease which can range from a patient with a single serrated polyp proximal to the sigmoid colon (conditional upon having a first-degree relative meeting one of the other two criteria for polyp burden) through patients with a small number of large proximally located polyps to patients with hundreds of serrated polyps of any size throughout the colorectum. Thus, SPS is likely to comprise a heterogeneous group of conditions. Cases of oligo-polyposis which do not fit into any known syndromic group are relatively common, particularly involving the co-occurrence of serrated and adenomatous polyps. The presence of adenomas has been associated with an increased risk of CRC in SPS (15), and there is evidence that many CRCs in this condition arise from these pre-malignant lesions rather than from sessile serrated adenomas (9). It is therefore likely that CRC risk spans a spectrum, and that it is the characteristics of the neoplasia in an individual colon rather than simply the number of serrated polyps which determines the risk of CRC.

The lack of a known genetic basis for SPS is a major limitation in our understanding of the syndrome and the definition of its phenotypic boundaries. Familial SPS was first described by Jass and colleagues (16,17) in the mid-nineties. Later reports described an increased risk of CRC to first-degree relatives of individuals with SPS (18). Subsequently Win *et al.* (2) confirmed that SPS demonstrated multiple features of a CRC predisposition syndrome including a high prevalence of CRC, multiple neoplastic lesions including synchronous CRC, a predilection for the proximal colon and a younger age of onset for CRC than is seen in the general population coupled with an increased risk to relatives of CRC and pancreatic cancer (19). Recognition of a familial risk for CRC associated with SPS has been slow to emerge, despite the evidence of a consistent five-fold increase over the level seen in the general population (2,18). In addition, two studies have

estimated the burden of pre-malignant lesions in first-degree relatives of probands with SPS. The first showed that one third of first-degree relatives of SPS probands have serrated polyps in their proximal colon (20), and in a further study, 43% of first-degree relatives had a significant polyp at their first colonoscopy (21). Recognition of a familial risk could also be hampered by the fact that the greater majority of SPS patients do not themselves develop CRC. In SPS patients where there was a first-degree relative with CRC in the study under review here (5), 60% of the probands did not have CRC. In addition, patients who present with synchronously occurring oligo-polyposis and a CRC at their first colonoscopy are often aged over 50 and may not trigger the family history investigations that often arise when patients below age 50 present with CRC.

Families have also been described where *BRAF*-mutated CRC predominate, implicating an origin in sessile serrated polyps but not necessarily meeting the criteria for SPS (22). Further patients with *BRAF*-mutated CRC in the general population have been shown to have an increased familial risk for CRC, as do patients with at least one sessile serrated adenoma (23). These observations suggest that there may be a spectrum of risk which is independent of absolute numbers of serrated polyps *per se*, and that it may be more useful to also look at risk factors such as dysplasia in serrated polyps, size and multiplicity in a proximal location (24,25), and co-occurrence with conventional adenomas (26).

Surveillance for SPS itself is an evolving entity. Given the phenotypic heterogeneity, the current recommendation of annual surveillance for SPS patients has been questioned by a number of expert gastroenterologists, who propose that surveillance interval should be determined by risk stratification (4,27) ranging from less than 12 months to up to 2 years dependent upon early colonoscopy findings. Follow-up surveillance intervals for first-degree relatives are currently largely determined on a case-by-case basis, also dependent upon the colonoscopy findings but mindful that a genetic risk may still be present. To this end, recommendations for the surveillance of first-degree relatives of SPS probands, comprise 5-yearly colonoscopy beginning at age 40 or at age 10 years younger than the proband age at diagnosis (28). This frequency should increase if polyps are found.

The recently reported evidence for CRC risk in patients with MSP and their first-degree relatives indicates that they too might be considered for entry into a surveillance program (5). However, there are caveats to be considered as MSP criteria are also arbitrary and may lead to delayed entry to a surveillance program for some first-degree relatives. Finally, where an individual does not meet the criteria for SPS, or even for MSP, as defined by the paper under discussion here (5), clinical judgement would need to be applied. In such individuals, age at first polyps, as well as size and location of the polyps, is an early indicator as to the likelihood that an individual will progress to a diagnosis of SPS. For example, where an individual is very young and has large serrated polyps in the proximal colon, this would be a reasonable expectation, and the issue of screening first-degree relatives should be raised regardless of criteria.

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