Colorectal serrated lesions and polyps in the Danish population: A large nationwide register-based cohort study

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ABSTRACT

Background and study aims Colorectal serrated lesions and polyps (SPs) include hyperplastic polyps (HP), sessile serrated lesions-/+dysplasia (SSL/SSL-D), and traditional serrated adenomas (TSA). From 20% to 30% of colorectal cancers (CRC) develop from SP. We present incidence and baseline characteristics of SP in a Danish cohort.

Patients and methods We used The Danish Pathology Registry to include all SPs in the Danish population from January 1, 2000 to December 31, 2021. Based on the unique Danish personal identification number and SNOMED-codes, combined with the age and sex of patients, and date of procedure, we determined the incidence of the SP subtypes, anatomical location, and changes over time.

Results During the period from 2000 to 2021, a total of 292,761 SPs were removed from 163,840 patients: 51,649 SSLs, 5959 SSL-Ds, 224,860 HDs, and 10,293 TSAs. The median age of patients was 64.1 years (range 55.2–71.6) and 53.3% were male. We found a general increase in SPs from 3525 in 2000 to 25,853 in 2021 and a rise in the SSL proportion from 1.7% in 2006 to 38% in 2021. Half of all patients had more than one lesion at endoscopy with conventional adenomas being the most common. CRC was found along with SPs in 3.3% of procedures, while 1% to 2.5% of the patients developed metachronous CRC.

Conclusions We found an increasing number of SPs, especially SSLs. From 2019 to 2021 the number of SPs seem to stabilize, while the proportion of SSLs keeps rising. Synchronous lesions were common along all subtypes of SP.

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world and has the second highest cancer-related mortality [1]. In Denmark, more than 4000 patients are diagnosed with CRC each year [2]. Traditionally conventional adenomas (CA) are perceived as precursor lesions for CRC via the adenoma carcinoma sequence, which is still considered the primary pathway to CRC. But lately there has been more focus on the sessile serrated pathway, suggesting that serrated lesions and polyps (SPs)

are the precursors of up to 30% of CRCs [3]. The serrated pathway is also acknowledged in more recent polyp follow-up programs and screening guidelines for colorectal cancer, in which subgroups of SPs are also perceived as precursor lesions for CRC with a specified need for follow-up [4, 5, 6]. The diagnostic criteria for SPs have changed several times over the years, most recently in the WHO Classification of Tumours 5th edition from 2019 [7], dividing SPs into the following subgroups: hyperplastic polyps (HPs), sessile serrated lesions (SSLs), sessile serrated lesions with dysplasia (SSLD), and traditional serrated adenomas (TSAs) [3, 8, 9]. While small HPs (<5 mm) are still considered benign, especially if found in the distal left colon and rectum, SSLs and TSAs are considered to be CRC precursors [10, 11]. It is estimated that 10% to 20% of a given population will have one or more serrated polyps [3, 12, 13], and of these, 20% are SSLs and 4% to 8% SSLDs [12, 13]. However, these numbers are based on studies from before the 2019 WHO diagnostic criteria, and before the increased clinical focus on identifying and removing SPs, especially SSLs. These lesions can be hard to detect endoscopically, because they are often located in the right colon, often appear flat and are often covered by a mucus cap. Even after the introduction of narrow-band imaging (NBI) endoscopy, small colonic polyps ≤5 mm tend to be difficult to distinguish endoscopically [14, 15].

Most of the previous studies on the incidence and baseline characteristics of SPs are smaller studies [16, 17, 18]. Even though larger studies are emerging, the classification of SPs often still follows the former WHO 2010 diagnostic criteria, which may lead to both a lower incidence and an inaccurate interpretation of the impact of SPs as a precursor to CRC [10, 11].

The aim of this study was to describe both the incidence of SPs in the Danish population and the distribution between the subgroups HP, SSL, SSLD, and TSA in the period 2000 to 2021, including the baseline characteristics of the study population and synchronous and metachronous lesions in the subgroups.

Patients and methods

This study was a Danish nationwide register-based cohort study including patients with SPs from 2000 to 2021.

All data from pathoanatomical examinations performed at both private and public pathology departments are registered in The Danish Pathology Register (Patobank). Data are systematically coded using a Danish equivalent of the International Systematized Nomenclature of Medicine (SNOMED) (See Appendix 2 for details on the SNOMED translation) [19]. Since 1968, all Danish citizens have been registered in the Danish Civil Registration System with a unique 10-digit identification number given at birth (CPR number). All study data are linked to CPR numbers in the Danish Civil Registrations System.

We included all patients who had a colorectal serrated lesion or polyp removed between January 1, 2000 and December 31, 2021. We used the year 2000 as cutoff because the diagnosis sessile serrated polyp/adenoma/lesion was rarely used in literature before the millennium and the diagnostic data in Patobank were not nationally complete until after 1997. We excluded patients younger than age 15 years and older than age 100 years.

The following data were included from Patobank both for SP as well as subsequent CA and CRC: lesion type, anatomical location, date of removal, surgical department, pathology department, age and sex of the patient, and the full text of the macroscopic and microscopic descriptions.

The first colorectal SP was defined as the index lesion, no matter the type and subsequent types of colorectal SP. The date of the index procedure was marked as Day 0. We defined synchronous lesions as any CRC, CA, or colorectal SPs found between Days 1 and 180. Metachronous lesions were defined as any CRC, CA, or colorectal SP found on Day 181 or later, because 6 months is the cutoff for metachronous CRC in the Danish guidelines and because there is no clear consensus on the cutoff for precursor lesions. The lesions were included regardless of whether they were found at a diagnostic endoscopy, screening or follow-up endoscopy.

The primary endpoints of this study were the incidence of colorectal SPs, HPs, SSLs with and without dysplasia, and TSAs in the Danish population and the change in distribution of the different SPs during the study period.

The secondary endpoints were polyp type and the correlation with sex and age, anatomical location of the polyps, and correlation with synchronous and metachronous polyps or CRC.

Statistics

We used the statistical software R version 4.2.0 [20], R studio and the packages Tidyverse, Lubridate and TableOne to conduct the statistical analysis. Baseline characteristics were calculated as mean (SD), median (IQR) or proportion dependent on the datatype. Significance levels were calculated using chi square test or unpaired t-tests.

Ethics

Retrospective register-based investigations do not require patient consent under Danish law. The study was approved as a register-based study by Center for Regional Development (R22013405) and The Danish Data Protection Agency (P2022–346).

Results
Baseline

From January 1, 2000 to December 31, 2021, 205,357 procedures were conducted on 163,840 patients and 292,761 colorectal SPs were removed for histopathological analysis. Baseline characteristics are shown in ▶ Table 1. Sex distribution for each subtype is shown in ▶ Fig. 1. There was an overrepresentation of males for all subtypes (P <0.001). The median age of patients at the time of index lesion was 64.1 years (interquartile range [IQR] 55.2–71.6). Most polyps were removed in patients aged 50 to 74 years, with a clear spike at ages 50 and 74 years (▶ Fig. 1, **Supplementary Fig. 1**). The regional differences were small and follow the general population numbers in the Danish regions (**Supplementary Fig. 2**).

▶**Table 1** Baseline characteristics.

	Serrated polyps	Hyperplastic polyps	Sessile serrated lesion	Sessile serrated lesion with dysplasia	Traditional serrated adenoma
Patients, n	163840	137804	32955	5099	8434
Procedures, n	205357	167314	36991	5308	9237
Polyps, n	292761	224860	51649	5959	10293
Age, median (IQR)	64.1 (55.2–71.6)	63.6 (54.7–71.2)	65.1 (57.0–71.7)	68.3 (61.2–73.9)	67.4 (59.4–74.43)
Sex, male n (%)	87387 (53.3)	74435 (54.0)	16819 (51.0)	2611 (51.2)	4506 (53.4)

IQR, interquartile range.
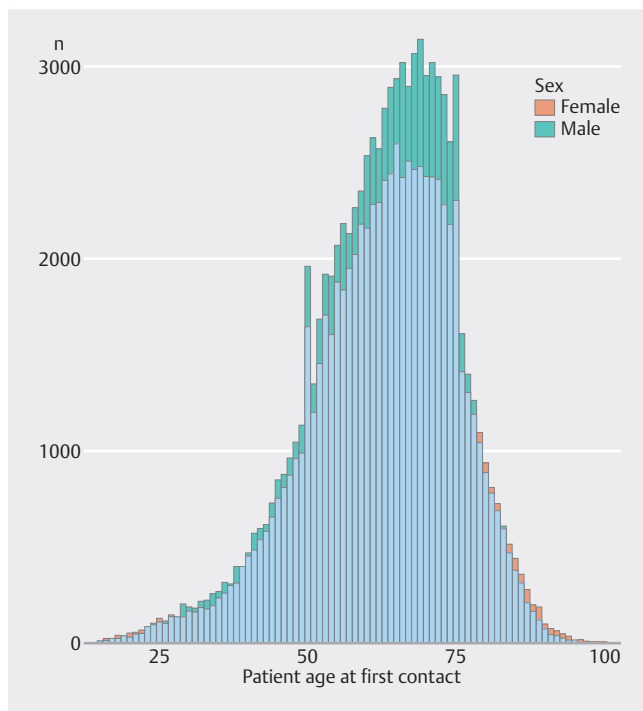
▶**Fig. 1** Patient age at first encounter divided by polyp subtype. **a** Hyperplastic polyp. **b** Sessile serrated lesion. **c** Sessile serrated lesion with dysplasia. **d** Traditional serrated adenoma. Blue, male; red, female.

Incidence during the study period

There was a 7-fold increase in the incidence of SP over the study period, from 3525 SP in 2000 to 25,853 SP in 2021 (▶**Fig. 2a**). The first polyp diagnosed as SSL was found in 2006 and a significant increase in the diagnosis was seen during the study period from a proportion of 1.7% of SPs being SSLs in 2006 to 38.3% of SPs were SSLs in 2021. From 2019 to 2021 the overall number of SPs seemed to stabilize (25 467 in 2019 and 25 853 in 2021). However, the proportion of SSLs has kept rising from 30.7% to 38.3%, while the proportion of HPs decreased from 64.7% to 56.7% ($P < 0.001$) ($P < 0.001$) (▶**Fig. 2b**).

Anatomical location of polyps

Most SPs were in the sigmoid colon and rectum, n = 159 038 (54.3%) (▶**Fig. 3**). HPs were most often located in the left colon and rectum, while SSLs and SSLDs were most often located in the right colon. Even though the lowest total number of lesions were found in the appendix, the largest proportion of SSLs were found there. Hence, 46.7% of lesions in the appendix were SSLs and 4.6% SSLDs, compared with the ascending colon, where 44.3% and 5.3% were SSLs and SSLDs, respectively.

Synchronous and metachronous lesions

In half of the procedures there was more than one lesion (▶**Table 2**). In procedures with SSLs and SSLDs, more than one lesion was detected in approximately 70% of patients. Across all SP subtypes, the most common parallel lesion type was CA, closely followed by HP. For SSL and SSLD, one-quarter of all instances had a parallel HP or SSL. The least common combination was TSA along with SSL or SSLD. SPs in general were diagnosed along CRC in 3.3% of procedures. For SSL, SSLD, and TSA, the percentages of parallel CRC were 4.2%, 6.6%, and 6.1% respectively.

Concerning metachronous lesions, 10% to 17% of all patients were diagnosed with another SP at a following examination, with very similar numbers for CA. Metachronous CRC were found in 0.5% to 2.5% of patients, most often in cases with previous TSA and least often in cases with previous SSL (▶**Table 3**).

Discussion

In this study of the incidence of SP in Denmark from 2000 to 2021, we found a general rise in the incidence of SP as well as an increase in the proportion of SSL, with a 100-fold increase from the first encounter in 2006 and a 5-fold increase from 2014 to 2021. All SP subgroups were more prevalent in males and associated with increasing age. We found the highest number of SPs in the age group that were invited to participate in the Danish screening program for CRC, with a spike at 50 and 74 years, representing the age of inclusion and the age of exclusion from the screening program, respectively. HPs and TSAs were most often found in the left colon and rectum, while SSLs and SSLD were more prevalent in the right colon. Over
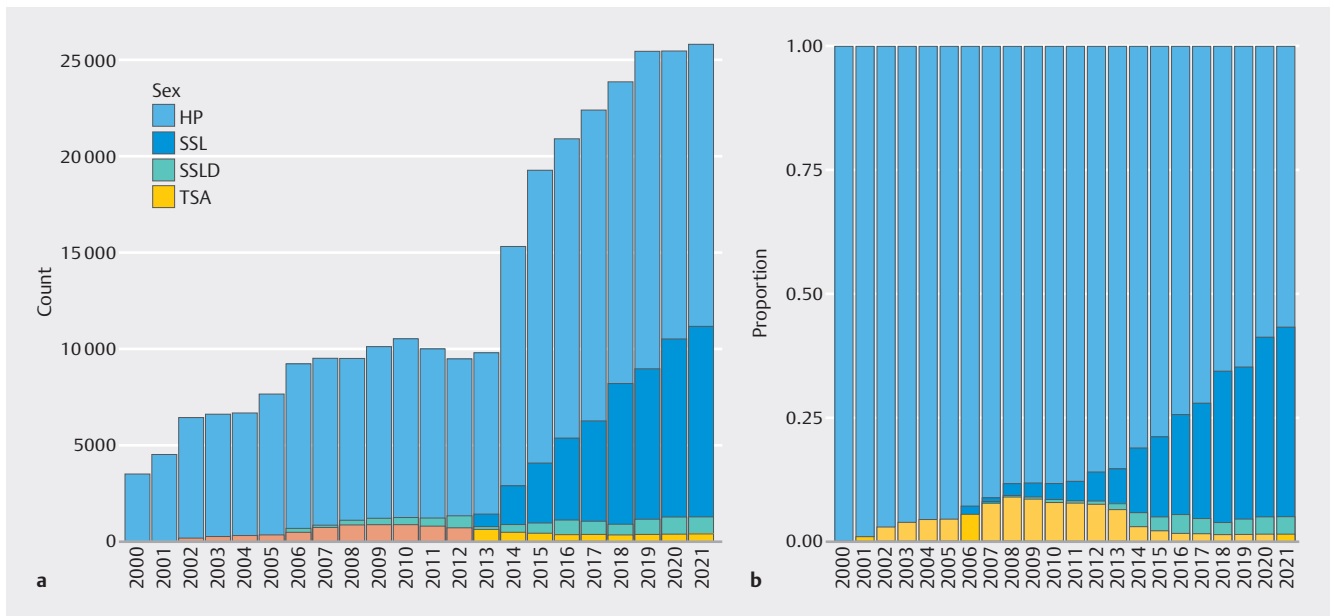
▶ **Fig. 2** Incidence of colorectal serrated lesions. **b** Fraction of incidence and changes over the study period. Red, hyperplastic polyp; green, traditional serrated adenoma; purple, sessile serrated lesion with dysplasia; blue, sessile serrated lesions without dysplasia.

▶ **Fig. 3** Location in the colorectal canal. **a** Number of polyp subtypes per colon segment. **b** Proportion of polyp subtypes per colon segment. Red, hyperplastic polyp; green, traditional serrated adenoma, purple, sessile serrated lesion with dysplasia; blue, sessile serrated lesions without dysplasia.
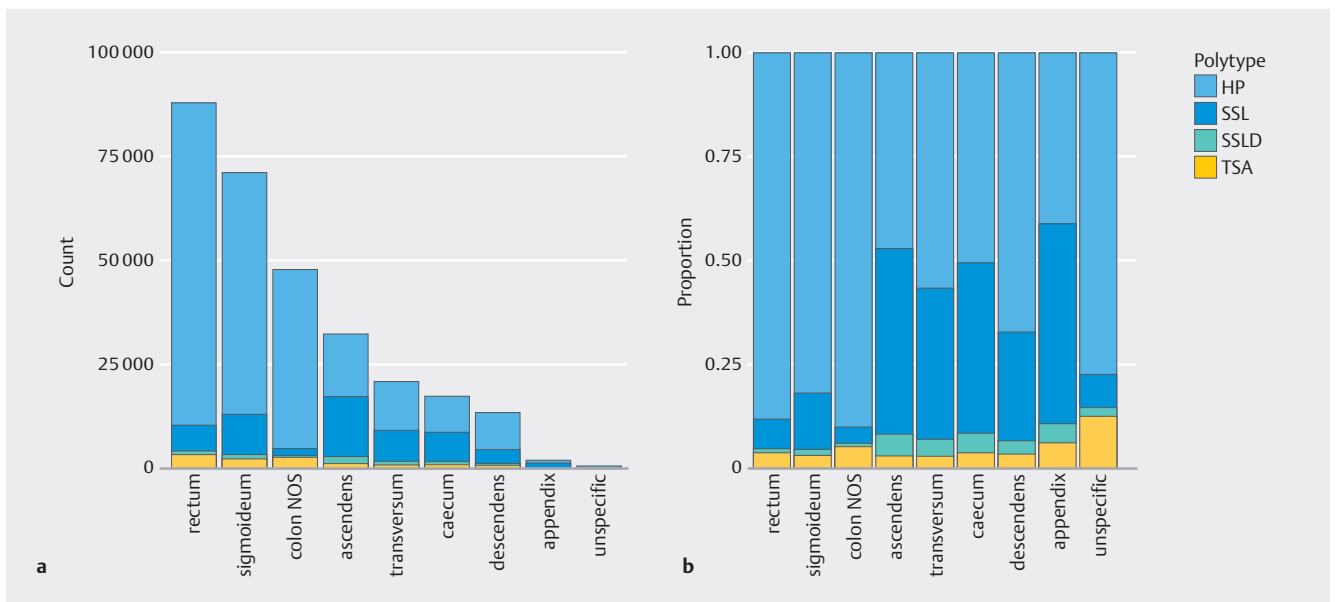
half of the patients had more than one lesion - either more than one SP, or SP synchronous with CA or CRC.

While the definitions of HP and TSA have remained largely unchanged through the years, there has been a lot of debate about the nomenclature for SSL. Through the 1990s, there was an increasing focus on a subgroup of supposed HP with malignant potential [21, 22]. Accordingly, SSPs /adenomas/lesions were described as a precursor to approximately 30% of CRCs via the serrated pathway in 1996 [23] and were named sessile ser-

rated adenomas in 2003 [24, 25]. Throughout the 2000s the diagnostic criteria and nomenclature have changed, and the current diagnostic criteria from 2019 use the term SSL and only one unequivocal crypt was needed to diagnose SSL [7, 26, 27, 28]. Although there is no fundamental disagreement regarding the clinical importance of the entity, nor regarding its progression from an early lesion to carcinoma, a difference of opinion persists regarding terminology for the lesion. Hence, the acceptance of the term SSL demonstrates considerable geo-

▶ **Table 2** Procedures with more than one lesion.

	Any colorectal serrated polyp or lesion	Hyperplastic polyps	Sessile serrated lesion	Sessile serrated lesion with dysplasia	Traditional serrated adenoma
More than one lesion	102868 (50.1)	83140 (49.7)	24623 (66.6)	3789 (71.4)	4809 (52.1)
Hyperplastic polyps		36101 (21.6)	9280(25.1)	1183 (22.3)	1706(18.5)
Sessile serrated lesion		9280(5.6)	8446 (22.8)	1483 (27.9)	424(4.6)
Sessile serrated lesion with dysplasia		1183 (0.7)	1483(4.0)	472 (8.9)	117(1.3)
Traditional serrated adenoma		1706(1.0)	424(1.2)	117 (2.2)	784 (8.5)
Any colorectal serrated polyp or lesion	50816 (24.7)	43637 (26.1)	15637 (42.3)	2448 (46.1)	2587 (28.0)
Conventional adenoma	70767 (34.5)	55730(33.3)	16696 (45.1)	2697 (50.8)	3066(33.2)
Colorectal carcinoma	6831 (3.3)	5021(3.0)	1560 (4.2)	348 (6.6)	567 (6.1)

▶ **Table 3** Patients with colorectal serrated lesions and polyps and stratified by index polyp subsequent synchronous and metachronous polyps and cancers.*

		Any colorectal serrated polyp or lesion	Hyperplastic polyps	Sessile serrated lesion	Sessile serrated lesion with dysplasia	Traditional serrated adenoma
Patients, n		163840	137804	32955	5099	8434
No subsequent lesions, n patients		96616(58.3)	79915(57.4)	16737(50.1)	1856 (35.6)	3037 (34.7)
Serrated lesions and polyps, n patients		29121(17.8)	23984 (17.4)	4771 (14.5)	942 (18.5)	1993(23.6)
	Synchronous	8044 (4.9)	6025 (4.4)	1757 (5.3)	358 (7.0)	821 (9.7)
	Metachronous	23747(14.5)	20029 (14.5)	3014 (9.1)	584 (11.4)	1171 (13.9)
Conventional adenoma, n patients		44277(27.0)	35685 (26.0)	6840 (20.8)	1357(26.6)	2900 (34.4)
	Synchronous	6040 (3.7)	4492 (3.3)	1084 (3.3)	277 (5.4)	640 (7.6)
	Metachronous	20638(12.6)	17263 (12.6)	2387 (7.2)	589 (11.6)	1515 (18.0)
Colorectal carcinoma, n patients		14633(8.9)	11572 (8.4)	2257 (6.8)	490 (9.6)	949 (14.3)
	Synchronous	3836 (2.3)	3021 (2.2)	549 (1.6)	136 (3.1)	370 (4.4)
	Metachronous	2561 (1.6)	2218 (1.6)	177 (0.5)	42 (1.0)	226 (2.7)

*Synchronous is defined as between 1 and 180 days from initial lesion. Metachronous is defined as more than 180 days from initial lesion. Proportion as part of all patients with the same index polyp type.

graphic variability. In general, acceptance appears to be greater in Europe and Asia than in the United States [29].

Based on this history, the polyps we now categorize as SSLs or SSLD may have been categorized as either HPs, TSAs, or tubulovillous adenomas before the introduction of stricter diagnostic criteria. Thus, categorizing SSL as TSA may explain why we found a crossover between proportions of TSA and SSL, with a fall in raw numbers of TSAs around 2014. The latest change in the WHO definition in 2019 may have caused SP, which formerly would have been diagnosed as HP, to be cor-

rectly diagnosed as SSL, thereby leading to the observed increase in the SSL incidence and decrease in HP incidence in the following period.

Apart from the stricter diagnostic criteria, there has been a more general clinical focus on locating and removing SSLs and SSLD, as already mentioned. This, along with the substantial technological advances with higher endoscopic image resolution and the introduction of chromoendoscopy and NBI in the 2010s [3], as well as the focus on best practice endoscopy, e. g. sufficient bowel preparation, withdrawal time, operator ex-

perience, has been shown to increase the detection rate for SSLs [4, 5]. All these factors, along with the changes in definition, may have led to the increase in incidence of serrated lesions shown in our study, reflecting a better estimate of the true incidence.

A correlation between SP and increasing age has been shown in several studies. An Australian cohort study found that SP in younger patients may have a lower potential for malignancy than in older patients [16]. In contrast, another Australian cohort study hypothesized that SSL in younger women may be part of the reason for the rising incidence of CRC in women aged < 50 years [30]. However, whether there is a difference in SSL incidence in males and females remains unclear. Most studies that have found a difference in SSL incidence between males and female were older and smaller studies [12, 17, 18, 31, 32]. One large study from Sweden found a higher incidence of SSLs in women [11]. However, none of these studies use data collected after the WHO 5th ed. 2019 definition. In our study we found a higher number of SPs of all subtypes in males compared with females, and we did not find a correlation between female sex and SSL.

In 2014 Denmark introduced the national screening program for CRC, based on the fecal immunochemical test. All Danish citizens between ages 50 and 74 years are invited to participate every second year. In case of a positive test, the citizen is offered a screening colonoscopy [33]. The impact of the introduction of the Danish screening program was obvious in our data. Hence, we found a large increase in raw numbers of SPs from 2014 onward, as well as a clear correlation between the most common SPs and the age span of patients in the screening program, most noticeable in the spikes at ages 50 and 74 years, respectively.

The Danish guidelines for follow-up of patients who have polyps removed were revised in 2023, mainly based on the recommendations in the 2020 update of the post-polypectomy colonoscopy surveillance guideline by the European Society of Gastrointestinal Endoscopy (ESGE) [4]. This revision also led to changes in the recommended follow-up program for patients with SPs. According to the 2023 Danish guidelines diminutive polyps (< 5 mm) with hyperplastic features (endoscopically) in the sigmoid colon and rectum do not need to be removed. On the other hand–and in contrast to previously–patients with SSLs ≥ 10 mm. and SSLD of any size will be offered a control colonoscopy after 3 years.

The national screening program and the recent changes in follow-up may further influence the incidence of SPs and enhance our understanding of the impact of these lesions on CRC development. This should be investigated further in future studies.

In previous studies, synchronous lesions have been found in approximately 30% of all cases of SP [34, 35]. In our study the numbers were much higher, with approximately 50% of all patients with SP having another lesion at the same procedure, either in the form of another SP, CA, or CRC. We found a low number of metachronous cancers in patients with SSLs (0.5%) and SSLD (1.0%), compared with patients with both HP (1.6%) and especially TSA (2.7%). The differences might be due to the

shorter follow-up period for SSLs and SSLD, as these were not diagnosed in Denmark before 2006 and, as hypothesized above, SSLs have been categorized as other polyp types under older classifications. Song et al found a 10-year cumulative incidence for CRC of 2.5% in patients with SSLs and 1.6% for patients with HPs [11], whereas Erichsen et al demonstrated cumulative incidences of 2.3% for SSLs and 4.4% for SSLD on reevaluated Danish material [10].

The correlation between SPs and the development of CRC needs to be further investigated, especially focusing on the diagnostic criteria of the WHO 5th ed. 2019, and how the increase in identifying and removing SPs may influence the risk of CRC in the patients. Our study has several limitations. This was a register-based cohort study, meaning the data are only as good as the initial diagnosis. The histopathological reviews were originally performed at different pathology departments in Denmark and by several different pathologists. Similarly, the endoscopic procedures or colectomies were performed by numerous different surgeons and the follow-up of the patients varied. Because the follow-up protocol was based on the initial findings, not all patients had more than one procedure. Before the focus on removal of SPs, some smaller lesions may have been left in situ or not sent for histopathological examination. In our study, this may have resulted in a lower incidence of SP, especially in the early years. The definition and subclassification of SPs have changed several times, both in 2010 and 2019. Hence, the classification from before 2019 might have been correct according to the diagnostic criteria for that time, but the diagnosis would probably be changed in some cases using the current definitions and criteria.

Conclusions

In this Danish register-based cohort study, we found an increased incidence of SPs from 2000 to 2021, with a large and still increasing proportion of SSLs. All types of SPs were found more often in men than in women. We found that 50% of all patients had more than one lesion at endoscopy, with CA being the most common. Finally, between 3.0% and 6.6% of patients have CRC found at the same time as their SP and 1% to 2.5% of patients develop metachronous CRC.

Conflict of Interest

The authors declare that they have no conflict of interest.

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