Risk of colorectal cancer incidence and mortality after polypectomy: a Swedish record-linkage study

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Summary

Background Long-term colorectal cancer incidence and mortality after colorectal polyp removal remains unclear. We aimed to assess colorectal cancer incidence and mortality in individuals with removal of different histological subtypes of polyps relative to the general population.

Methods We did a matched cohort study through prospective record linkage in Sweden in patients aged at least 18 years with a first diagnosis of colorectal polyps in the nationwide gastrointestinal ESPRESSO histopathology cohort (1993–2016). For each polyp case, we identified up to five matched reference individuals from the Total Population Register on the basis of birth year, age, sex, calendar year of biopsy, and county of residence. We excluded patients and reference individuals with a diagnosis of colorectal cancer either before or within the first 6 months after diagnosis of the index polyp. Polyps were classified by morphology codes into hyperplastic polyps, sessile serrated polyps, tubular adenomas, tubulovillous adenomas, and villous adenomas. Colorectal cancer cases were identified from the Swedish Cancer Registry, and cause-of-death data were retrieved from the Cause of Death Register. We collected information about the use of endoscopic examination before and after the index biopsy from the Swedish National Patient Registry, and counted the number of endoscopies done before and after the index biopsies. We calculated cumulative risk of colorectal cancer incidence and mortality at 3, 5, 10, and 15 years, and computed hazard ratios (HRs) and 95% CIs for colorectal cancer incidence and mortality using a stratified Cox proportional hazards model within each of the matched pairs.

Findings 178 377 patients with colorectal polyps and 864 831 matched reference individuals from the general population were included in our study. The mean age of patients at polyp diagnosis was 58·6 (SD 13·9) years for hyperplastic polyps, 59·7 (14·2) years for sessile serrated polyps, 63·9 (12·9) years for tubular adenomas, 67·1 (12·1) years for tubulovillous adenomas, and 68·9 (11·8) years for villous adenomas. During a median of 6·6 years (IQR 3·0–11·6) of follow-up, we documented 4278 incident colorectal cancers and 1269 colorectal cancer-related deaths in patients with a polyp, and 14 350 incident colorectal cancers and 5242 colorectal cancer deaths in general reference individuals. The 10-year cumulative incidence of colorectal cancer was 1·6% (95% CI 1·5–1·7) for hyperplastic polyps, 2·5% (1·9–3·3) for sessile serrated polyps, 2·7% (2·5–2·9) for tubular adenomas, 5·1% (4·8–5·4) for tubulovillous adenomas, and 8·6% (7·4–10·1) for villous adenomas compared with 2·1% (2·0–2·1) in reference individuals. Compared with reference individuals, patients with any polyps had an increased risk of colorectal cancer, with multivariable HR of 1·11 (95% CI 1·02–1·22) for hyperplastic polyps, 1·77 (1·34–2·34) for sessile serrated polyps, 1·41 (1·30–1·52) for tubular adenomas, 2·56 (2·36–2·78) for tubulovillous adenomas, and 3·82 (3·07–4·76) for villous adenomas ($p<0·05$ for all polyp subtypes). There was a higher proportion of incident proximal colon cancer in patients with serrated (hyperplastic and sessile) polyps (52–57%) than in those with conventional (tubular, tubulovillous, and villous) adenomas (30–46%). For colorectal cancer mortality, a positive association was found for sessile serrated polyps (HR 1·74, 95% CI 1·08–2·79), tubulovillous adenomas (1·95, 1·69–2·24), and villous adenomas (3·45, 2·40–4·95), but not for hyperplastic polyps (0·90, 0·76–1·06) or tubular adenomas (0·97, 0·84–1·12).

Interpretation In a largely screening-naive population, compared with individuals from the general population, patients with any polyps had a higher colorectal cancer incidence, and those with sessile serrated polyps, tubulovillous adenomas, and villous adenomas had a higher colorectal cancer mortality.

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Introduction

Colorectal cancer is the third most common cancer and the second leading cause of cancer death worldwide.[1] Endoscopic screening reduces colorectal cancer incidence and mortality by detection and removal of precursor lesions. Although the conventional adenoma–carcinoma sequence has been well described and accounts for the majority of cases of colorectal cancer, an alternative pathway exists for another 20–30% of cases in which sessile serrated polyps (also known as sessile

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Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 1990, and Sept 23, 2019, using the terms "colorectal cancer" and "colorectal polyp" and "endoscopy" or "colonoscopy" or "sigmoidoscopy", and "cohort". We found that most previous studies examined recurrence of colorectal neoplasia as the primary outcome and a few examined colorectal cancer as the endpoint. Also, we found only one study that assessed the long-term risk of colorectal cancer incidence after diagnosis of conventional adenomas and serrated polyps, but the study was unable to distinguish between hyperplastic polyps and sessile serrated polyps. No previous study has examined colorectal cancer mortality after removal of different subtypes of polyps.

Added value of this study

To our knowledge, this is the first study to comprehensively characterise colorectal cancer incidence and mortality in relation to different histological subtypes of polyps in a largely screening-naive population. Compared with matched reference individuals, incidence of colorectal cancer was higher in patients with any polyp subtype. The increase in risk increased with advanced histology of the index polyp. For colorectal cancer mortality, an increased risk was found in individuals with sessile serrated polyps, tubulovillous adenomas, and villous adenomas, but not those with hyperplastic polyps or tubular adenomas.

Implications of all the available evidence

The results of this study indicate that patients with sessile serrated polyps, tubulovillous adenomas, and villous adenomas might benefit from surveillance. Further studies are needed to examine the impact of colonoscopy surveillance on prevention of colorectal cancer.

serrated adenomas) represent the major precursor lesions.[2] Of note, because of their predilection for the proximal colon and their subtle and flat endoscopic appearance, sessile serrated polyps are easily missed or incompletely removed endoscopically, resulting in their disproportionate contribution to so-called interval colorectal cancers diagnosed in patients still within recommended surveillance periods after polypectomy.[3,4]

To help prevent subsequent cancer, individuals diagnosed with either conventional adenomas or sessile serrated polyps by screening endoscopy are advised to undergo colonoscopy surveillance at different intervals, depending on the most advanced findings of the index endoscopy. However, existing guidelines for colonoscopy surveillance vary widely and lack sufficient evidence.[5–10] Most supporting data are based on the risk of recurrence of advanced neoplasia after polypectomy,[11] and only a few prospective studies have examined colorectal cancer as the endpoint in individuals with conventional adenomas or sessile serrated polyps.[12–20] For sessile serrated polyps, most studies have very limited number of colorectal cancer cases (n<30),[13,15] except for a large prospective case-control study in Denmark in which there was a higher incidence of colorectal cancer in individuals with sessile serrated polyps than in those with no polyps.[16]

In 2019 we assessed colorectal cancer incidence after diagnosis of conventional adenomas and serrated polyps in three population-based cohorts and found an increased risk associated with advanced adenoma and large serrated polyps.[13] However, in that study, we were unable to distinguish between hyperplastic polyps and sessile serrated polyps and to assess colorectal cancer mortality. Therefore, comprehensive assessment of both colorectal cancer incidence and mortality after diagnosis of various polyp subtypes is absent. Such information is important to better understand the influence of different pathways on colorectal cancer and to improve the current colonoscopy surveillance guidelines for better prevention of colorectal cancer.

In this study, using prospectively collected data from national registries in Sweden, we assessed colorectal cancer incidence and mortality in individuals diagnosed with different subtypes of colorectal polyps and their matched reference individuals identified from the general population. We hypothesised that patients with a polyp had higher colorectal cancer incidence and mortality than reference individuals and that the risk increase was greater for more advanced polyps.

Methods

Study design and participants

We did a matched nationwide cohort study in Sweden using individual-level data from various national registries linked on the basis of the unique personal identity number that is assigned at birth to all Swedish residents.[21] We used data from the ESPRESSO study[22] (Epidemiology Strengthened by histoPathology Reports in Sweden), which includes data for gastrointestinal biopsies from all pathology departments in Sweden between 1965 and 2017. We identified participants with the first diagnosis of colorectal polyps aged at least 18 years in the biopsy reports (ie, index biopsy) in ESPRESSO. We excluded individuals diagnosed before 1993, because completeness of adenoma reporting was uncertain, and sessile serrated polyps were miscategorised as hyperplastic polyps before more widespread adoption of this histopathological subtype. We also excluded individuals who had a diagnosis of colorectal cancer either before or within the first 6 months after the diagnosis of the index polyp, to minimise the possibility of including individuals with synchronous cancers missed at the time of endoscopy. We further excluded individuals

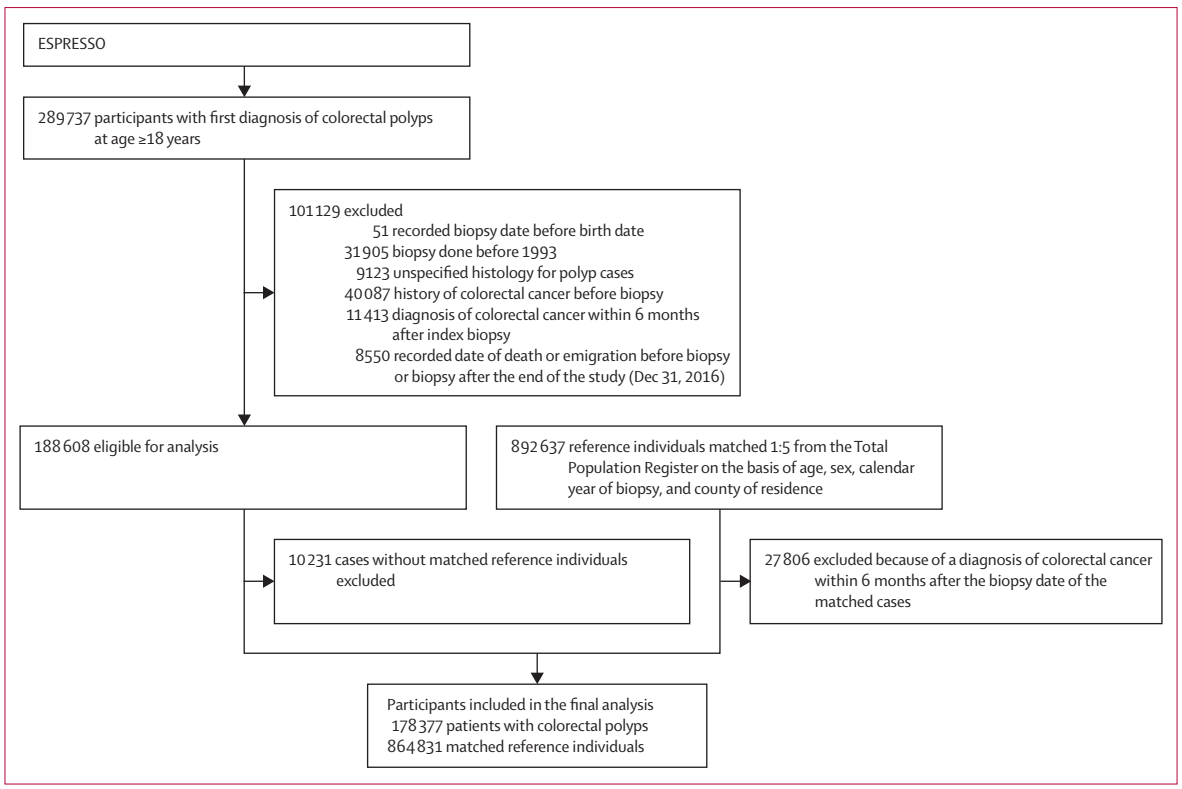


Figure 1: **Flowchart of study participant selection**
ESPRESSO=Epidemiology Strengthened by histoPathology Reports in Sweden.

with unspecified histology and erroneous records on the date of biopsies and time of follow-up. For each of the polyp cases, we identified up to five matched reference individuals from the Total Population Register on the basis of birth year, age, sex, calendar year of biopsy, and county of residence.[22] Similarly, we excluded reference individuals who were diagnosed with colorectal cancer before or within the first 6 months after the index biopsy. The study was approved by the Stockholm Ethics Review Board. Informed consent was waived by the board since the study was strictly register-based.[23]

Polyp identification and classification

In ESPRESSO, histopathological findings were defined by codes of morphology (from a Swedish modification of the Systematised Nomenclature of Medicine [SNOMED] coding system) and topography. We used topography codes of T67 (for colon) and T68 (for rectum) in combination with SNOMED codes to identify colorectal polyps.[17,18] For conventional adenomas, the SNOMED code of M82100 was used for tubular adenoma, M82630 for tubulovillous adenoma, and M82611 for villous adenoma. Patients with more than one type of conventional adenomas were classified on the basis of their most advanced endoscopic findings (the precedence order being villous adenoma, tubulovillous adenoma, and tubular adenoma).

Serrated polyps included hyperplastic polyps and sessile serrated polyps. The SNOMED code of M72040 was used for hyperplastic polyps. For sessile serrated polyps, we used the SNOMED codes of M82160 and M82130 for records from all pathology departments except those at Aleris Medilab, for which a different code (M72041) was used (Ludvigsson JF, Karolinska Institutet, personal communication). Moreover, given the evolving nature of the diagnostic criteria for sessile serrated polyps, we attempted to account for potential under-reporting in the SNOMED code by also searching various forms of serrated and gtand (part of the Swedish word for serrated) in the free text in the pathology report. We have validated this approach for sessile serrated polyp identification through manual review of pathology reports and patient charts in a random sample of 106 patients that were identified to have sessile serrated polyps on the basis of SNOMED code and free text search in ESPRESSO. A positive predictive value of 93% (95% CI 87–97) was observed.[24] Finally, patients with both conventional adenomas and serrated polyps were considered as synchronous cases. Therefore, a total of six case groups were defined for the study.

We collected location information of polyps based on the subcodes of topography: those in the caecum, ascending colon, hepatic flexure, transverse colon, or splenic flexure were classified as proximal (T671–674), polyps in

	Reference individuals (n=864 831)	Hyperplastic polyps (n=58 735)	Sessile serrated polyps (n=5181)	Tubular adenomas (n=63 753)	Tubulovillous adenomas (n=34 181)	Villous adenomas (n=2431)	Synchronous serrated polyps and conventional adenomas (n=14 096)
Age							
Mean age (years)	63·1 (13·4)	58·6 (13·9)	59·7 (14·2)	63·9 (12·9)	67·1 (12·1)	68·9 (11·8)	64·4 (11·5)
<40 years	52 052 (6·0%)	5970 (10·2%)	525 (10·1%)	2807 (4·4%)	851 (2·5%)	38 (1·6%)	398 (2·8%)
40–49 years	88 793 (10·3%)	8275 (14·1%)	672 (13·0%)	5949 (9·3%)	2062 (6·0%)	116 (4·8%)	1057 (7·5%)
50–59 years	177 833 (20·6%)	14 218 (24·2%)	1051 (20·3%)	12 378 (19·4%)	5442 (15·9%)	332 (13·7%)	2772 (19·7%)
60–69 years	264 120 (30·5%)	17 149 (29·2%)	1613 (31·1%)	19 571 (30·7%)	10 205 (29·9%)	682 (28·1%)	5060 (35·9%)
70–79 years	204 795 (23·7%)	10 139 (17·3%)	1010 (19·5%)	16 512 (25·9%)	10 509 (30·7%)	802 (33·0%)	3635 (25·8%)
≥80 years	77 238 (8·9%)	2984 (5·1%)	310 (6·0%)	6536 (10·3%)	5112 (15·0%)	461 (19·0%)	1174 (8·3%)
Birth year	1943·3 (14·7)	1947·1 (15·0)	1949·5 (15·2)	1942·1 (14·2)	1938·2 (13·8)	1934·5 (13·4)	1942·5 (12·7)
Sex							
Female	442 533 (51·2%)	31 985 (54·5%)	3001 (57·9%)	31 194 (48·9%)	17 202 (50·3%)	1308 (53·8%)	6547 (46·4%)
Male	422 298 (48·8%)	26 750 (45·5%)	2180 (42·1%)	32 559 (51·1%)	16 979 (49·7%)	1123 (46·2%)	7549 (53·6%)
Family history of colorectal cancer*	48 254 (5·6%)	5903 (10·1%)	667 (12·9%)	5854 (9·2%)	2923 (8·6%)	163 (6·7%)	1688 (12·0%)
Year of biopsy							
1993–99	..	9813 (16·7%)	450 (8·7%)	11 437 (17·9%)	7956 (23·3%)	767 (31·6%)	1691 (12·0%)
2000–04	..	12 245 (20·8%)	542 (10·5%)	11 647 (18·3%)	6186 (18·1%)	533 (21·9%)	2582 (18·3%)
2005–07	..	9175 (15·6%)	494 (9·5%)	8200 (12·9%)	3951 (11·6%)	303 (12·5%)	2107 (14·9%)
2008–10	..	10 123 (17·2%)	754 (14·6%)	10 523 (16·5%)	4834 (14·1%)	343 (14·1%)	2542 (18·0%)
2011–13	..	10 051 (17·1%)	1167 (22·5%)	11 744 (18·4%)	6030 (17·6%)	275 (11·3%)	2792 (19·8%)
2014–16	..	7328 (12·5%)	1774 (34·2%)	10 202 (16·0%)	5224 (15·3%)	210 (8·6%)	2382 (16·9%)
Polyp location							
Colon							
Unspecified sublocation	..	29 103 (49·5%)	2796 (54·0%)	38 424 (60·3%)	16 970 (49·6%)	1043 (42·9%)	7878 (55·9%)
Proximal colon	..	1795 (3·1%)	360 (6·9%)	2478 (3·9%)	1118 (3·3%)	78 (3·2%)	302 (2·1%)
Distal colon	..	3241 (5·5%)	239 (4·6%)	5349 (8·4%)	2992 (8·8%)	147 (6·0%)	572 (4·1%)
Rectum	..	22 214 (37·8%)	1269 (24·5%)	15 997 (25·1%)	11 673 (34·2%)	1073 (44·1%)	1528 (10·8%)
Multiple locations	..	2382 (4·1%)	517 (10·0%)	1505 (2·4%)	1428 (4·2%)	90 (3·7%)	3816 (27·1%)
Number of colonoscopies or sigmoidoscopies before index biopsy†							
0	854 806 (98·8%)	52 835 (90·0%)	4608 (88·9%)	58 584 (91·9%)	31 851 (93·2%)	2300 (94·6%)	13 190 (93·6%)
1	8074 (0·9%)	3698 (6·3%)	362 (7·0%)	3646 (5·7%)	1780 (5·2%)	94 (3·9%)	680 (4·8%)
2	1522 (0·2%)	987 (1·7%)	100 (1·9%)	856 (1·3%)	339 (1·0%)	23 (1·0%)	124 (0·9%)
>2	429 (0·1%)	1215 (2·1%)	111 (2·1%)	667 (1·1%)	211 (0·6%)	14 (0·6%)	102 (0·7%)
Number of colonoscopies or sigmoidoscopies after index biopsy†							
0	821 907 (95·0%)	43 595 (74·2%)	3560 (68·7%)	43 561 (68·3%)	19 572 (57·3%)	1384 (56·9%)	9220 (65·4%)
1	28 051 (3·2%)	8678 (14·8%)	992 (19·2%)	11 845 (18·6%)	7975 (23·3%)	530 (21·8%)	2847 (20·2%)
2	10 498 (1·2%)	3141 (5·4%)	335 (6·5%)	4538 (7·1%)	3522 (10·3%)	251 (10·3%)	1158 (8·2%)
>2	4375 (0·5%)	3321 (5·7%)	294 (5·7%)	3809 (6·0%)	3112 (9·1%)	266 (10·9%)	871 (6·2%)

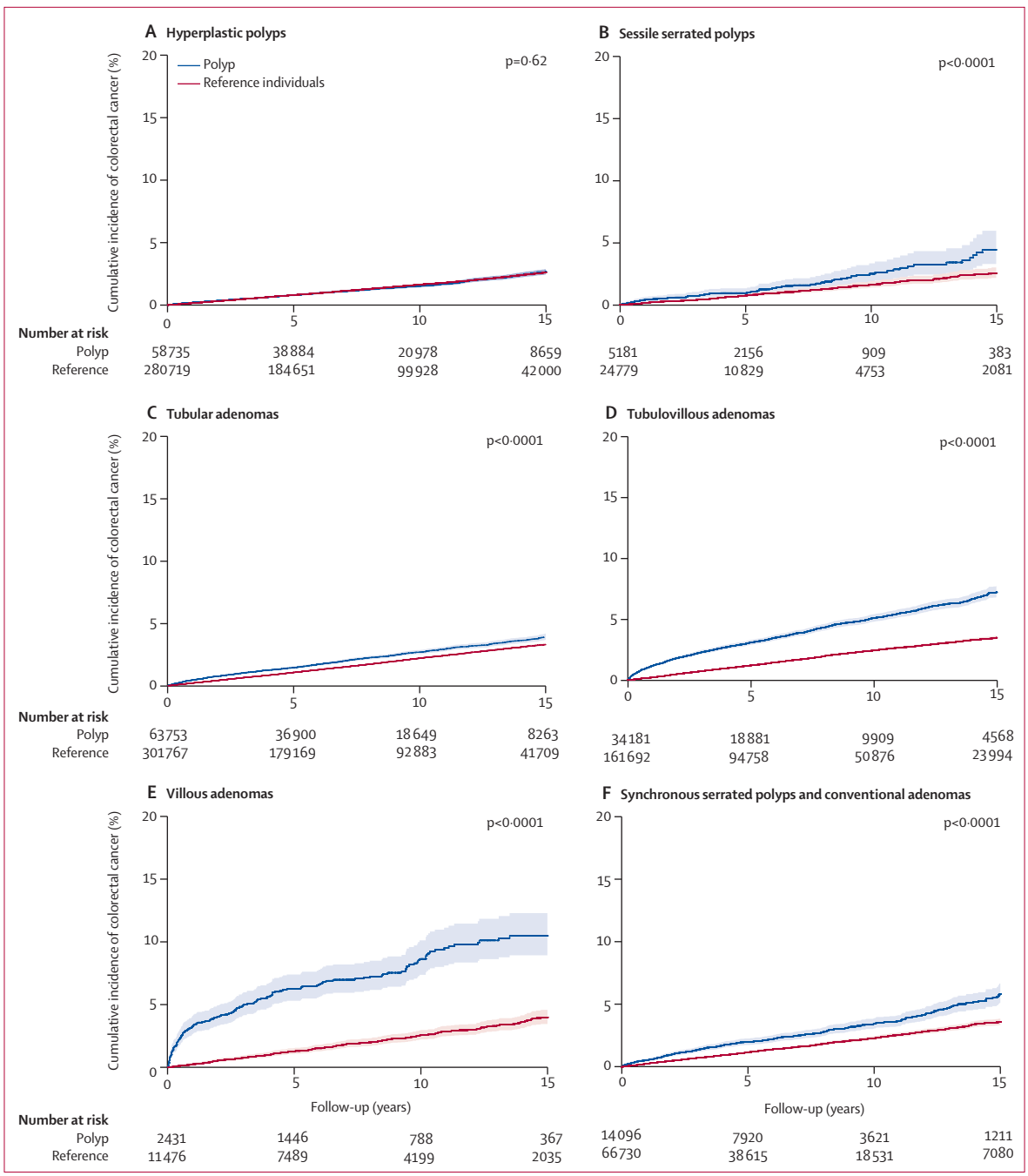
Data are mean (SD) or n (%). *Positive family history is defined as a diagnosis of colorectal cancer in parents or siblings before study baseline. †To avoid counting the diagnostic endoscopies for colorectal polyps, we excluded endoscopies performed within 30 days before and after the date of the index biopsy or colorectal cancer diagnosis.

Table 1: **Baseline characteristics of the reference individuals and participants with different polyp subtypes (n=1 043 208)**

the descending or sigmoid colon as distal (T675–677), and those in the rectum or rectosigmoid junction as rectal (T68x).

Ascertainment of colorectal cancer diagnosis and colorectal cancer death

Colorectal cancer cases were identified from the Swedish Cancer Registry, which has recorded incident malignancies in Sweden since 1958 with high completeness. The database includes coded diagnoses based on International Classification of Diseases (ICD), date of diagnosis, and cancer staging information. We used the ICD codes to identify tumour location. Cause-of-death data were retrieved from the Cause of Death Register, which comprises all deaths in Swedish residents, whether occurring in Sweden or abroad. The causes of death were coded at Statistics Sweden using the ICD codes. For colorectal cancer, the ICD-10 codes were C18,



(Figure 2 continues on next page)

C19, and C20, and the codes for earlier ICD versions were 153 and 154.

Assessment of covariates

We collected information about the use of endoscopic examination before and after the index biopsy from the Swedish National Patient Registry, which started in 1964 with complete national coverage from 1987. We used the established procedure codes to identify colonoscopy (9011, 9023, 4688, 4689, 4674, 4684, UJF32, and UJF35) and sigmoidoscopy (9012, 4685, UJF42, and UJF45). We counted the number of endoscopies done before and after the index biopsies. To avoid counting the diagnostic endoscopies for colorectal polyps or colorectal cancer, we excluded endoscopies done within 30 days before and after the date of the index biopsy or colorectal cancer diagnosis.

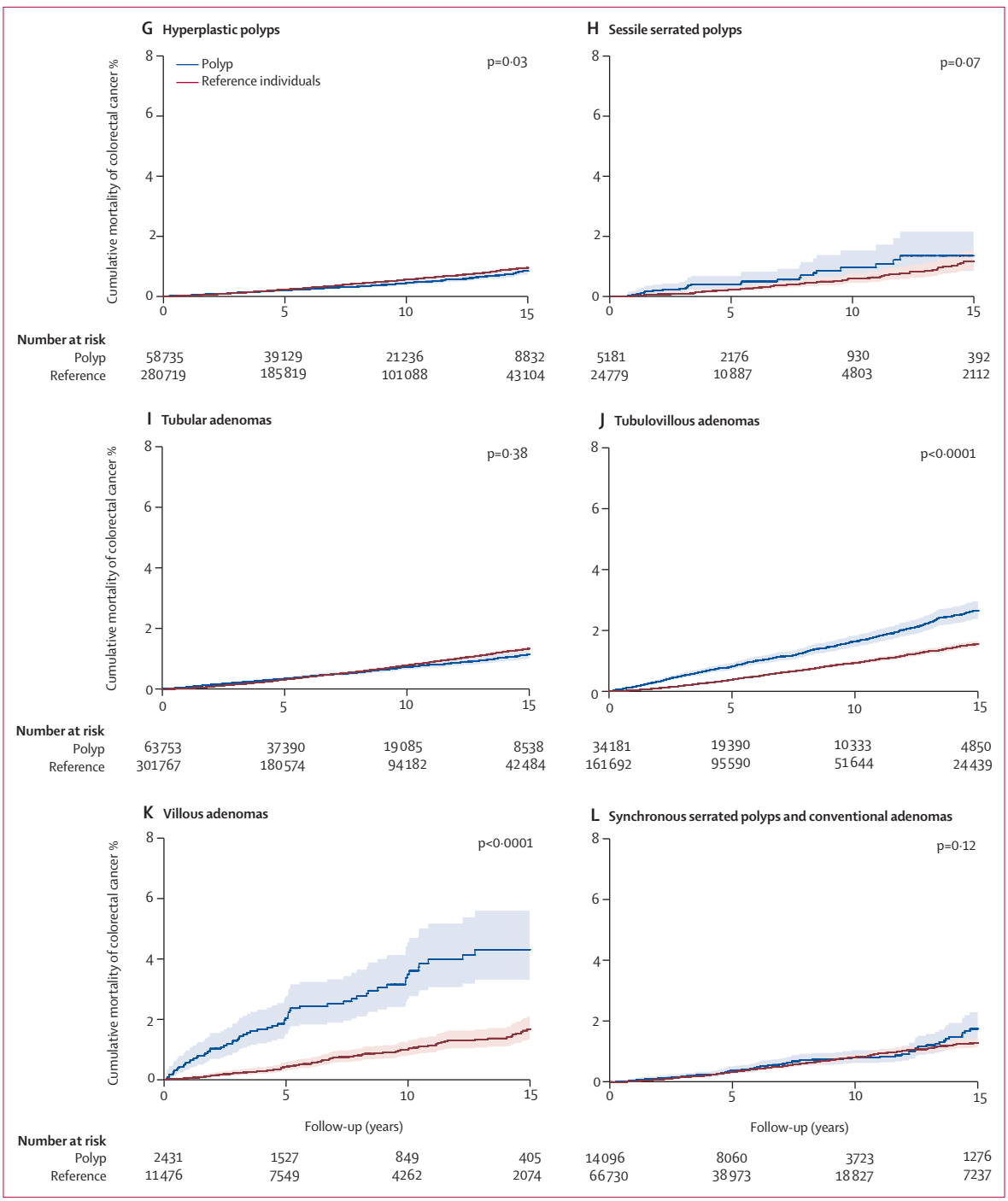


Figure 2: **Kaplan-Meier estimates of cumulative incidence (A–F) and mortality (G–L) of colorectal cancer and 95% pointwise confidence bands in each of the polyp groups (blue) and their matched reference individuals (red)**
p values for log-rank tests shown.

We assessed family history on the basis of colorectal cancer diagnosis recorded in the Cancer Registry for the parents and siblings of participants. We obtained data on education and income from the longitudinal integrated database for health insurance and labour market studies, which integrates annually updated administrative information from the labour market and educational and social sectors from 1990 onward on all individuals 16 years or older registered as residents in Sweden. Information on age, sex, date of birth, and emigration

	Reference individuals	Hyperplastic polyps	Sessile serrated polyps	Tubular adenomas	Tubulovillous adenomas	Villous adenomas	Synchronous serrated polyps and conventional adenomas
Colorectal cancer incidence							
Events (n)	14 350	878	77	1361	1406	176	380
Person-years (n)	6 780 775	492 177	28 669	475 543	250 726	18 884	97 315
Incidence rate (per 10 000 person-years)	21·2	17·8	26·9	28·6	56·1	93·2	39·0
HR (95% CI); p value*	1 (ref)	0·97 (0·90–1·05); p=0·51	1·54 (1·17–2·02); p=0·002	1·23 (1·15–1·31); p<0·0001	2·26 (2·11–2·42); p<0·0001	3·38 (2·73–4·18); p<0·0001	1·58 (1·40–1·79); <0·0001
HR (95% CI); p value†	1 (ref)	1·11 (1·02–1·22); p=0·02	1·77 (1·34–2·34); p<0·0001	1·41 (1·30–1·52); p<0·0001	2·56 (2·36–2·78); p<0·0001	3·82 (3·07–4·76); p<0·0001	1·84 (1·61–2·10); p<0·0001
Colorectal cancer mortality							
Events (n)	5242	253	26	366	461	67	96
Person-years (n)	6 836 937	496 164	28 968	482 787	258 013	19 971	99 088
Mortality rate (per 10 000 person-years)	7·7	5·1	9·0	7·6	17·9	33·5	9·7
HR (95% CI); p value*	1 (ref)	0·83 (0·72–0·95); p=0·008	1·61 (1·01–2·56); p=0·05	0·89 (0·79–1·01); p=0·06	1·83 (1·63–2·06); p<0·0001	3·30 (2·33–4·66); p<0·0001	1·11 (0·88–1·41); p=0·37
HR (95% CI); p value†	1 (ref)	0·90 (0·76–1·06); p=0·20	1·74 (1·08–2·79); p=0·02	0·97 (0·84–1·12); p=0·63	1·95 (1·69–2·24); p<0·0001	3·45 (2·40–4·95); p<0·0001	1·20 (0·93–1·55); p=0·16

HR=hazard ratio. *Matching factors including birth year, age, sex, and county of residence were automatically adjusted for by the stratified Cox regression. †Further adjusted for family history of colorectal cancer (yes, no), income levels (quintiles), education (9 years or less, 10–12 years, >12 years, data missing), number of clinic visits at baseline (quintiles), and number of colonoscopies or sigmoidoscopies at baseline (0, 1, 2, and >2).

Table 2: **Association between polyp subtypes and incidence and mortality of colorectal cancer**

status was collected from the Swedish Total Population Register maintained by Statistics Sweden.

Statistical analysis

Follow-up started at 6 months after the date of the index biopsy for polyp cases and the same date was used for matched reference individuals. We calculated person-time of follow-up until the date of colorectal cancer diagnosis (for colorectal cancer incidence analysis only), death, emigration, or the end of the study (Dec 31, 2016), whichever occurred first. We plotted Kaplan-Meier curves, and calculated cumulative risk of colorectal cancer incidence and mortality at 3, 5, 10, and 15 years. We did log-rank tests in cases and their matched reference individuals for each polyp subtype separately. We present the 10-year risk because it is the most commonly used time period for colorectal cancer and because the IQR of follow-up time in our study was 3·0–11·6 years. We computed hazard ratios (HRs) and 95% CIs for colorectal cancer incidence and mortality using stratified Cox proportional hazards model within each of the matched pairs. Therefore, the matching factors (ie, birth year, age, sex, and county of residence) were automatically controlled for.[25] We also adjusted for other potential confounding factors—family history of colorectal cancer, income (quintiles), education (9 years or less, 10–12 years, >12 years, data missing), number of clinic visits at baseline (quintiles), and number of colonoscopies or sigmoidoscopies at baseline (0, 1, 2, and >2). We used a missing indicator method to handle missing covariate data.

We calculated descriptive statistics for colorectal cancer cases by polyp subtypes. We also assessed the associations of polyp subtypes with colorectal cancer incidence according to cancer subsite by calculating the HRs based on a fully unconstrained approach, in which the confounder effects are allowed to be different in the subgroups.[26] To test whether the exposure–disease association has a trend across cancer subsites (from the proximal colon to distal colon to the rectum), we used the meta-regression method with a subgroup-specific random-effect term and calculated the p value for heterogeneity.[26] We did a sensitivity analysis by excluding person-years accumulated during the first year after polyp diagnosis and an exploratory analysis in patients with a combination of conventional adenomas and sessile serrated polyps. Finally, we stratified analysis according to age, sex, and year of the index biopsies, and calculated $p_{interaction}$ using the Wald test for the product term between stratified variable (binary or continuous) and exposure groups.

We used SAS 9.4 for all analyses. All statistical tests were two-sided. A p value of less than 0·05 was considered statistically significant.

Role of the funding source

The study sponsors had no role in the study design, data collection, data analysis, interpretation of data, writing of the report, and the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

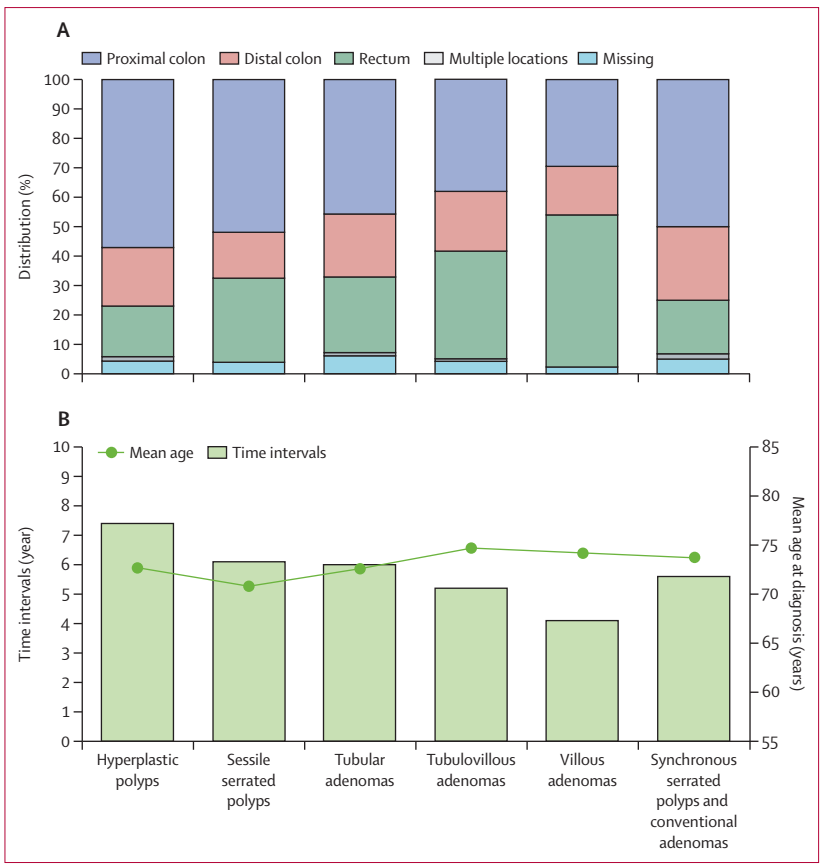


Figure 3: **Distribution of subsite (A) and age and time interval (B) of colorectal cancer diagnosis after polypectomy in each polyp group**
p<0·0001 for tests across polyp groups by subsite, time interval, and age at colorectal cancer diagnosis.

See Online for appendix

Results

178 377 patients with colorectal polyps and 864 831 reference individuals from the general population were included in the final analysis (figure 1). Table 1 shows the basic characteristics of the study participants at the time of matching. Compared with patients with conventional adenomas, those with hyperplastic polyps and sessile serrated polyps were younger and more likely to be female. A greater proportion of patients with sessile serrated polyps were diagnosed in more recent years than other polyp groups. By anatomical location, villous adenomas were more likely to be in the rectum than other polyps. Most patients with polyps did not have a history of colonoscopy or sigmoidoscopy before index polypectomy.

During a median of 6·6 years (IQR 3·0–11·6) of follow-up, we documented 4278 incident colorectal cancers and 1269 colorectal cancer deaths in patients with a polyp, and 14 350 incident colorectal cancers and 5242 colorectal cancer deaths in general reference individuals. Figure 2 shows the Kaplan-Meier curves of colorectal cancer incidence and mortality. We show 10-year risk throughout the Article and detailed data on cumulative incidence at 3, 5, 10, and 15 years are also provided in the appendix (p 1). Compared with the general reference individuals, individuals in all polyp groups except for those with hyperplastic polyps had a higher incidence of colorectal cancer (p<0·0001) but only individuals with tubulovillous and villous adenomas had higher mortality (figure 2). The cumulative incidence of colorectal cancer at 10 years was 1·6% (95% CI 1·5–1·7) for hyperplastic polyps, 2·5% (1·9–3·3) for sessile serrated polyps, 2·7% (2·5–2·9) for tubular adenomas, 5·1% (4·8–5·4) for tubulovillous adenomas, 8·6% (7·4–10·1) for villous adenomas, and 3·5% (3·1–3·9) for synchronous conventional adenomas and serrated polyps, compared with 2·1% (2·0–2·1) for general reference individuals (appendix p 1). For colorectal cancer mortality, compared with general reference individuals (0·7% [95% CI 0·7–0·8] at 10 years), there was a lower cumulative estimate for hyperplastic polyps (0·4%, 0·4–0·5) and a higher estimate for sessile serrated polyp (1·0%, 0·6–1·5), tubulovillous adenomas (1·6%, 1·5–1·8), and villous adenomas (3·5%, 2·7–4·5; appendix p 1).

Table 2 shows the association of different polyp subtypes with colorectal cancer incidence and mortality. After adjustment for potential confounders, all polyp subtypes had a positive association with colorectal cancer incidence, with a multivariable HR of 1·11 (95% CI 1·02–1·22; p=0·02) for hyperplastic polyps, 1·77 (1·34–2·34, p<0·0001) for sessile serrated polyps, 1·41 (1·30–1·52; p<0·0001) for tubular adenomas, 2·56 (2·36–2·78; p<0·0001) for tubulovillous adenomas, and 3·82 (3·07–4·76; p<0·0001) for villous adenomas (table 2). For colorectal cancer mortality, a positive association was found for sessile serrated polyps (multivariable HR 1·74, 95% CI 1·08–2·79; p=0·02), tubulovillous adenomas (1·95, 1·69–2·24; p<0·0001), and villous adenomas (3·45, 2·40–4·95, p<0·0001), but not hyperplastic polyps (0·90, 0·76–1·06, p=0·20) or tubular adenomas (0·97, 0·84–1·12, p=0·63; table 2). When examined by time since baseline, the associations were generally stronger for earlier years than for later years after polyp diagnosis (appendix p 1). For example, the HR of colorectal cancer mortality associated with sessile serrated polyps decreased from 3·99 (95% CI 1·64–9·71) at 3 years to 1·91 (1·16–3·12) at 15 years from polyp diagnosis.

In a sensitivity analysis, we excluded person-years accumulated during the first year after polyp diagnosis. The results were largely unchanged except for modest attenuation for villous adenomas in relation to colorectal cancer incidence (HR 2·70, 95% CI 2·11–3·46). Given previous data indicating a higher risk of polyp recurrence in patients with a combination of conventional adenomas and sessile serrated polyps,[27] we did an exploratory analysis in these patients (n=1817) and found an HR of 2·15 (95% CI 1·51–3·05) for colorectal cancer incidence and 1·71 (0·91–3·21) for colorectal cancer mortality.

	Reference individuals	Hyperplastic polyps	Sessile serrated polyps	Tubular adenomas	Tubulovillous adenomas	Villous adenomas	Synchronous serrated polyps and conventional adenomas
Proximal colon cancer							
Cases (n)	5040	501	40	622	535	52	190
HR (95% CI); p value*	1 (ref)	2·14 (1·90–2·42); p<0·0001	2·77 (1·84–4·18); p<0·0001	2·08 (1·86–2·33); p<0·0001	3·27 (2·88–3·71); p<0·0001	3·69 (2·52–5·42); p<0·0001	3·21 (2·63–3·91); p<0·0001
Distal colon cancer							
Cases (n)	4061	175	12	291	286	29	95
HR (95% CI); p value*	1 (ref)	0·81 (0·68–0·97); p=0·02	1·11 (0·57–2·18); p=0·75	1·18 (1·02–1·36); p=0·02	2·35 (2·01–2·74); p<0·0001	2·70 (1·68–4·34); p<0·0001	1·79 (1·40–2·30); p<0·0001
Rectal cancer							
Cases (n)	4687	151	22	350	514	91	69
HR (95% CI); p value*	1 (ref)	0·62 (0·52–0·74); p<0·0001	1·73 (1·05–2·84); p=0·03	1·28 (1·12–1·46); p<0·0001	3·45 (3·04–3·92); p<0·0001	7·49 (5·28–10·63); p<0·0001	1·12 (0·85–1·48); p=0·43
p for heterogeneity†	..	<0·0001	0·05	<0·0001	<0·0001	<0·0001	<0·0001

HR=hazard ratio. *Adjusted for family history of colorectal cancer (yes, no), income levels (quintiles), education (9 years or less, 10–12 years, >12 years, data missing), number of clinic visits at baseline (quintiles), and number of colonoscopies or sigmoidoscopies at baseline (0, 1, 2, and >2). The matching factors including birth year, age, sex, and county of residence were automatically adjusted for by the stratified Cox regression. †p for heterogeneity was calculated to assess whether there was a trend across the ordinal subtypes in the polyp–colorectal cancer association using the meta-regression method with a subtype-specific random effect term.

Table 3: **Association between polyp subtypes and incidence of colorectal cancer by cancer subsite**

Figure 3 and appendix (p 2) show characteristics of incident colorectal cancer. The subsite distribution of colorectal cancer varied across polyp subtypes, with a higher proportion of proximal colon cancer in hyperplastic polyps (501 [57%] of 878) and sessile serrated polyps (40 [52%] of 77) than in tubular, tubulovillous, and villous adenomas (30–46%). The mean time interval between polyp diagnosis and colorectal cancer diagnosis was highest for hyperplastic polyps (7·4 [SD 5·4] years); it was 6·1 (5·3) years for sessile serrated polyps, 6·0 (5·2) years for tubular adenomas, 5·2 (4·9) years for tubulovillous adenomas, and was lowest for villous adenomas (4·1 [4·1] years). The mean age at colorectal cancer diagnosis ranged from 70·8 [SD 11·3] years for sessile serrated polyps to 74·6 [11·1] years for tubulovillous adenomas (appendix p 2).

Table 3 shows the results of the subgroup analysis. When colorectal cancer cases were classified by cancer subsite, we found that hyperplastic polyps, sessile serrated polyps, tubular adenomas, and synchronous polyps were more strongly associated with risk of proximal colon cancer than distal colon or rectal cancer; whereas tubulovillous and villous adenomas were more strongly associated with rectal cancer than colon cancer.

Appendix (p 3) shows the stratified association between polyp subtypes and colorectal cancer incidence. A generally stronger association was found for younger (<65 years) than for older (≥65 years) individuals, for women than men, and for polyps diagnosed before 2003 than after 2003. For colorectal cancer mortality, no large difference across these strata was observed, except for an age-varying association for sessile serrated polyps ($p_{interaction}$ =0·008), which were associated increased mortality in individuals older than 65 years but lower mortality in those younger than 65 years (appendix p 4). However, given the large number of statistical tests, these results should be interpreted cautiously.

Discussion

Using data from a nationwide histopathology cohort in Sweden, we found that compared with individuals from the general population, incidence of colorectal cancer was significantly higher in patients with any polyps, and those with sessile serrated polyps, tubulovillous adenomas, and villous adenomas had significantly higher risk of colorectal cancer mortality. The risk of both colorectal cancer incidence and mortality increased by advanced histology for both conventional adenomas (tubular adenomas to tubulovillous adenomas to villous adenomas) and serrated polyps (from hyperplastic polyps to sessile serrated polyps), whereas the time interval between polyp diagnosis and subsequent colorectal cancer diagnosis decreased by advanced histology. Moreover, patients with hyperplastic polyps and sessile serrated polyps were more likely to develop proximal colon cancer than those with some conventional adenomas. Our findings provide novel data on the long-term risk of colorectal cancer after polypectomy in a largely screening-naive population.

Consistent with our findings, most previous studies of conventional adenomas found that patients with advanced adenomas had higher incidence and mortality of colorectal cancer than the general population or individuals with no polyps.[12,13,17–20] However, the findings for small tubular adenomas remain inconsistent, with a lower colorectal cancer risk observed in some studies[17–20] but not others.[12–14] In this study, tubular adenomas were associated with higher colorectal cancer incidence, but not colorectal

cancer mortality, compared with the general population. However, because of the absence of information on polyp size, we were unable to distinguish small from large tubular adenomas, the latter of which have been the predominant subtype linked to higher risk of colorectal cancer.[13] Our observed association for colorectal cancer incidence in tubular adenoma could possibly have been driven predominantly by large tubular adenomas, especially since no organised screening in Sweden was done during most of the study period and most endoscopies were probably done to evaluate symptoms more commonly associated with large polyps. Moreover, we found that the increased colorectal cancer risk associated with tubular adenomas was restricted to adenoma cases diagnosed before but not after 2003. This time trend might reflect increased use of surveillance and improved quality of endoscopic examination over time. Indeed, the adenoma detection rate, a key quality indicator for colonoscopy, has been inversely associated with the risk of post-colonoscopy colorectal cancer.[28] A lower rate of post-colonoscopy colorectal cancer has been observed following the introduction of colonoscopy quality improvement initatives.[29] Further studies quantifying the influence of changes in colonoscopy quality on the risk of post-polypectomy colorectal cancer are warranted.

By contrast with conventional adenomas, the natural history of serrated polyps is less understood. So far only three prospective studies have examined the long-term incidence of colorectal cancer in individuals with serrated polyps.[13,15,16] Two of them[13,15] did not distinguish hyperplastic polyps from sessile serrated polyps because of absence of consensus in the diagnostic criteria for sessile serrated polyps during most of the study period, and found an increased risk of colorectal cancer associated with large serrated polyps, which have been proposed as an indicator for sessile serrated polyps. Another nationwide case-control study nested in individuals who had received colonoscopies in Denmark found an increased colorectal cancer risk in patients with sessile serrated polyps compared with those with no polyp.[16] Consistent with these findings, we found that both hyperplastic polyps and sessile serrated polyps were associated with higher risk of colorectal cancer. The positive association for hyperplastic polyps is at least partly due to misdiagnosis of true sessile serrated polyps, as indicated by the much stronger association for sessile serrated polyps than hyperplastic polyps; the lack of association for hyperplastic polyps diagnosed since 2003 when sessile serrated polyps became more widely recognised; and the absence of association for hyperplastic polyps with colorectal cancer mortality.

Also, in support of the role of serrated polyps in the development of proximal colon cancer,[3,16] we found a higher proportion of diagnosis of proximal colon cancer in patients with hyperplastic polyps (57%) and sessile serrated polyp (52%) than adenomas (30–46%), and that the increased cancer risk for hyperplastic polyps was restricted to the proximal colon (HR 2·14, 95% CI 1·90–2·42); p<0·0001). Moreover, we report a novel observation for an increased mortality of colorectal cancer associated with sessile serrated polyp (1·74, 1·08–2·79; p=0·02; multivariable-adjusted model), particularly within the first 3 years after diagnosis (3·99, 1·64–9·71). Given the subtle endoscopic appearance, sessile serrated polyps are more likely to be missed and incompletely removed than are conventional adenomas. Also, the molecular features of sessile serrated polyps (eg, *BRAF* mutation) might induce more rapid malignant transformation, in as soon as 8 months.[30] As a result, sessile serrated polyps have been shown to contribute disproportionately to post-colonoscopy cancers.[4] Consistent with these data, our findings suggest the importance of surveillance and improved colonoscopy performance for prevention of post-colonoscopy colorectal cancer associated with sessile serrated polyps.[3] However, patients with hyperplastic polyps did not show any increase in colorectal cancer mortality and thus might not warrant intensive surveillance, although we were unable to specifically assess large or proximal hyperplastic polyps.

Our study has several strengths, including the nationwide population-based design, large sample size, long-term and complete follow-up, high validity of the cancer register, examination of both colorectal cancer incidence and mortality, as well as the ability to adjust for factors that might influence colorectal cancer risk. Some limitations of our study need to be noted. First, we used individuals drawn from the general population as the reference group. Thus, the risk of colorectal cancer in relation to polyps might have been underestimated because of the established benefit of endoscopic examination itself and the possibility that some reference individuals might have had undiagnosed polyps because of the absence of colonoscopies. However, because patients with polyps are more likely to receive surveillance endoscopy, there is a risk of detection bias driving the effect estimates for colorectal cancer incidence. This risk might be another explanation for our observation that hyperplastic polyps and tubular adenomas were associated with increased risk of colorectal cancer incidence but not colorectal cancer mortality, which is not affected by detection bias. Second, we did not have any information on other factors that might influence colorectal cancer risk, including polyp size and multiplicity, quality and indication of endoscopy, and lifestyle risk factors (eg, smoking, obesity, and diet). Of note, villous histology has been associated with large size and high-grade dysplasia. Third, the endoscopy data were based on procedure coding and subject to measurement error. Finally, our results might not be generalisable to populations in which screening endoscopy is common.

In conclusion, patients with any polyp subtype had a higher risk of colorectal cancer incidence than the refrence individuals in this largely screening-naive population. The risk elevation increased with advanced histology for both conventional adenomas and serrated

polyps. In contrast, the risk of colorectal cancer mortality was increased only in patients with sessile serrated polyps, tubulovillous adenomas, or villous adenomas. Our findings suggest that patients with any of the latter three lesions might benefit from colonoscopy surveillance.

Contributors

MS did the literature search and figures and wrote the manuscript. MS, LE, and JFL designed the study. JFL collected the data and supervised the study. MS analysed the data. MS, LE, SRB, LHN, ADJ, KS, JN, ATC, and JFL interpreted the data. MS, LE, SRB, LHN, ADJ, KS, JN, ATC, and JFL critically revised the Article for important intellectual content. MS and JFL obtained the funding. ATC and JFL provided administrative, technical, or material support.

Declaration of interests

MS reports personal fees from Shire, Synergy, and Bayer Pharma, and grants from AstraZeneca, Takeda, and Gelesis, outside the submitted work. ATC reports grants from Bayer Pharma and personal fees from Pfizer, Janssen Pharmaceuticals, and Boeringher Ingelheim, outside the submitted work. JFL coordinates a study on behalf of the Swedish inflammatory bowel disease quality register (SWIBREG) that has received funding from Janssen corporation. All other authors declare no competing interests.

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