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PREVENTION AND EARLY DETECTION

A Comparison of Risk Classification Systems of Colorectal Adenomas: A Case-Cohort Study

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BACKGROUND & AIMS: Because post-polypectomy surveillance uses a growing proportion of colonoscopy capacity, more targeted surveillance is warranted. We therefore compared surveillance burden and cancer detection using 3 different adenoma classification systems. **METHODS:** In a case-cohort study among individuals who had adenomas removed between 1993 and 2007, we included 675 individuals with colorectal cancer (cases) diagnosed a median of 5.6 years after adenoma removal and 906 randomly selected individuals (subcohort). We compared colorectal cancer incidence among high- and low-risk individuals defined according to the traditional (high-risk: diameter ≥10 mm, high-grade dysplasia, villous growth pattern, or 3 or more adenomas), European Society of Gastrointestinal Endoscopy (ESGE) 2020 (high-risk: diameter ≥10 mm, high-grade dysplasia, or 5 or more adenomas), and novel (high-risk: diameter ≥20 mm or high-grade dysplasia) classification systems. For the different classification systems, we calculated the number of individuals recommended frequent surveillance colonoscopy and estimated number of delayed cancer diagnoses. **RESULTS:** Four hundred and thirty individuals with adenomas (52.7%) were high risk based on the traditional classification, 369 (45.2%) were high risk based on the ESGE 2020 classification, and 220 (27.0%) were high risk based on the novel classification. Using the traditional, ESGE 2020, and novel classifications, the colorectal cancer incidences per 100,000 person-years were 479, 552, and 690 among high-risk individuals, and 123, 124, and 179 among low-risk individuals, respectively. Compared with the traditional classification, the number of individuals who needed frequent surveillance was reduced by 13.9% and 44.2%, respectively, and 1 (3.4%) and 7 (24.1%) cancer diagnoses were delayed using the ESGE 2020 and novel classifications. **CONCLUSIONS:** Using the ESGE 2020 and novel risk classifications will substantially reduce resources needed for colonoscopy surveillance after adenoma removal.

Keywords: Colorectal Cancer; Screening; Surveillance; Adenoma; Case-Cohort.

Colorectal cancer is the third most common malignancy worldwide, and the second most common cause of cancer-related death.[1] Colorectal cancer screening aims to reduce colorectal cancer incidence through removal of adenomas, as well as to reduce colorectal cancer mortality through early detection of cancer and by lowering the incidence of cancer. Screening programs with fecal occult blood tests, sigmoidoscopy, or colonoscopy have been introduced in many countries.[2]

Because individuals who have had adenomas removed are considered at increased risk of developing new adenomas that might progress to colorectal cancer, they are recommended surveillance colonoscopy. With increased screening activity, the prevalence of individuals recommended surveillance is rapidly increasing. Such surveillance uses a large and growing proportion of colonoscopy capacity, thus reducing resources available for diagnostic and therapeutic procedures.[3] Therefore, more accurate identification of individuals with increased risk of developing colorectal cancer is warranted, and colonoscopy surveillance should be reserved for this group.[4]

We used a previously established, large, population-based cohort of adenoma patients in Norway[5,6] and designed a case-cohort study with abstraction of detailed information on adenoma characteristics. We then compared the ability to identify individuals at risk; the need for intensive surveillance colonoscopy; and the number of delayed cancer diagnoses among the traditional,[7,8] European Society of Gastrointestinal Endoscopy (ESGE) 2020,[9] and a novel classification system.[10]

Abbreviations used in this paper: **ESGE, European Society of Gastrointestinal Endoscopy; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology, Third Revision; IQR, interquartile range.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

As more individuals are being screened, more adenomas are found. More targeted surveillance is therefore warranted. We compare 3 adenoma risk classification systems: the traditional, the European Society of Gastrointestinal Endoscopy (ESGE) 2020, and a novel system.

NEW FINDINGS

Compared with the traditional system, surveillance was reduced by 14% and 44% using the ESGE 2020 and the novel systems, respectively, and 1 (3.4%) and 7 (24.1%) cancer diagnoses were delayed.

LIMITATIONS

The individuals included in this study had less-intense surveillance than what is recommended today. Some individuals did not have a full colonoscopy at adenoma removal.

CLINICAL RESEARCH RELEVANCE

Using the ESGE 2020 and novel risk classifications of individuals after adenoma removal will reduce the need for colonoscopy resources for surveillance and resources may be better used for diagnostic and therapeutic purposes.

BASIC RESEARCH RELEVANCE

The present risk classifications are based on clinical and pathologic features of the removed adenoma. The inclusion of biomarkers in the risk classifications may further improve the performance.

Methods

The Setting

Norway has a public, single-payer health care system with universal coverage. All residents are assigned a unique national registration number, including information on sex and date of birth. Using this registration number, we linked residents in nationwide registries on cancer, population, and cause of death, and hospital databases. All hospitals in Norway introduced electronic patient records around the year 2000. Before that, patient records were paper-based.

The Cancer Registry of Norway contains data on individuals diagnosed with cancer. Reporting of all incident cancer cases is mandatory, therefore, registration is close to 100% complete.[11] All colorectal adenomas were also registered in the Cancer Registry between 1993 and 2007. The Registry classifies all cancers and adenomas according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3).[12]

During the study period, no colorectal cancer screening program existed in Norway. Thus, individuals who had adenomas removed were referred to colonoscopy due to clinical indications. However, between 1999 and 2001, 2208 individuals (5.5% of the full cohort) (Figure 1) with adenomas were identified in a regional randomized sigmoidoscopy screening trial.[13]

Before 2013, Norwegian guidelines recommended surveillance colonoscopy for individuals younger than 75 years, 10 years after removal of advanced adenomas (high-grade dysplasia, villous growth pattern, or size ≥10 mm in diameter), and 5 years after removal of 3 or more adenomas.[14] Surveillance was not recommended for patients with 1 or 2 non-advanced adenomas. In 2013, ESGE guidelines[7] were implemented in Norway, and in 2020 the updated ESGE guidelines were introduced.[9]

Study Design

Risk classification systems and surveillance recommendations. Current surveillance guidelines recommend colonoscopic surveillance at 7- to 10-year intervals for low-risk individuals and 3- to 5-year intervals for high-risk individuals.[9,15] Low-risk individuals were defined in 2012 by the US Multi-Society Task Force and in 2013 by the ESGE as individuals who had 1 or 2 tubulous adenomas <10 mm in diameter with low-grade dysplasia removed and high-risk individuals had 3 or more adenomas removed, or an adenoma ≥10 mm in diameter, (tubulo-)villous growth pattern, or high-grade dysplasia—the traditional classification.[7,8] However, in 2020, the ESGE changed the definition of low risk to individuals who had 1–4 adenomas removed with low-grade dysplasia and diameter <10 mm, and high-risk individuals had 5 or more adenomas removed, or adenomas that were ≥10 mm in diameter, or with high-grade dysplasia—the ESGE 2020 classification.[9]

A novel classification, based on data from the Polish colorectal cancer screening program, classified individuals who had adenomas with high-grade dysplasia or diameter ≥20 mm removed as high-risk because this was the only group with increased risk of colorectal cancer.[10] All others were classified as low-risk individuals. Compared with the traditional classification, this novel classification reduced the need for surveillance colonoscopies by 74% in the Polish screening cohort.

Adenoma cohort. The design of the Norwegian adenoma cohort is described elsewhere.[5,6] In brief, we retrieved information from the Cancer Registry on all individuals 40 years or older who had 1 or more colorectal adenomas removed between January 1, 1993 and December 31, 2007. Individuals were identified by topographical ICD-O-3 codes 180, 182–189, 199, or 209, combined with morphological ICD-O-3 codes 8140, 8210, 8211, 8261, or 8263 (ie, adenomas). Individuals with sessile serrated lesions were not included, as these were not recorded in the Cancer Registry. We excluded individuals with familial adenomatous polyposis through linkage with the Norwegian Polyposis Registry. Complete follow-up for colorectal cancer incidence and mortality and all-cause mortality was achieved through linkage to the Cancer Registry and the Norwegian Cause of Death Registry, both updated through December 31, 2018.

Case-cohort study. For this study, we restricted the adenoma cohort to individuals who lived in 10 of 19 counties in Norway. These counties were selected as they represented geographical variation and constituted 79% of the country's population at the same time as traveling for data collection was confined.[16] We then randomly selected 950 individuals who had been diagnosed with colorectal cancer by December 31, 2014 (cases), and 1100 individuals, regardless of colorectal cancer status (subcohort, sample fraction 2.7%) (Figure 1). The study used a case-cohort design.[17] We retrieved contact information for all individuals in the case-cohort study from the

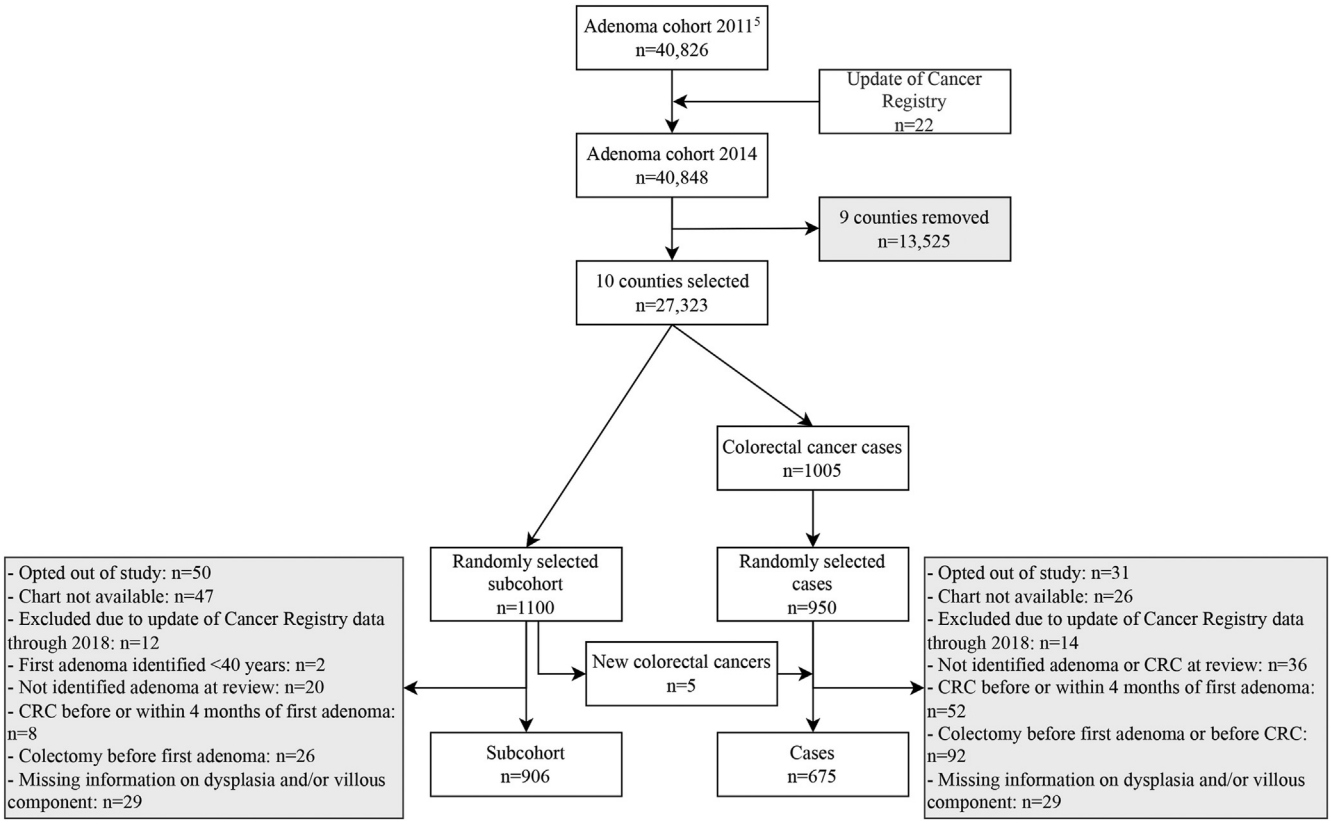

Figure 1. Flow chart of subcohort and colorectal cancer cases from the full adenoma cohort. Ten of 19 counties were selected for the case-cohort study, as these counties represented geographical variation and constituted 79% of the country's population, at the same time as traveling for data collection was confined. Five individuals who were randomly selected for the subcohort developed colorectal cancer after the random selection and were added to the cases, in addition to being a part of the subcohort.

Norwegian Population Registry and informed all living individuals about the study and gave them the opportunity to opt out, which 81 individuals did.

We performed a manual review of all hospital patient records for each individual in the case-cohort study, including histopathology, using a structured electronic case report form. The data collection included information on general health (eg, comorbidities, body mass index, smoking status, selected prescription and over-the-counter drugs, and history of colorectal cancer among first-degree relatives), lower endoscopic procedures including and after the first adenoma removal (eg, date, indication, type of endoscopic procedure, quality of bowel preparation, and level of endoscopic intubation), and colorectal surgery (eg, date, indication, and type of surgery). Detailed clinical and histopathological data on all polyps and colorectal tumors were registered. Level of endoscopic intubation was registered as the most proximal colonic segment mentioned explicitly, for example, if an adenoma was found in the right flexure and the more proximal parts of the colon was not mentioned, right flexure was registered as the deepest level of intubation. If exact polyp size was not stated in the endoscopy report, "small" was interpreted as polyps $\leq$5 mm and registered as 5 mm and "large" was interpreted as $\geq$10 mm and registered as 10 mm. Hence, we included a sensitivity analysis, excluding all adenomas registered as 10 mm in our risk estimates. As is done in the Cancer Registry, we pooled all adenoma reports within 4 months as 1 adenoma occurrence, and classified any adenoma occurrence in the same colorectal segment according to the most advanced characteristic.

We excluded individuals for whom hospital patient records were unavailable or when entries in the Cancer Registry were later removed. Based on the manual chart review, we also excluded patients with a first adenoma diagnosis before age 40 years, patients for whom no adenoma was confirmed at chart review, patients with colorectal cancer diagnosed before the first adenoma, patients who had colectomy performed before the first adenoma, or patients for whom information about grade of dysplasia and/or growth pattern of the first adenoma was missing (Figure 1). Thus, we included 675 individuals in the case group (with colorectal cancer) and 906 individuals in the subcohort (including both individuals with and without colorectal cancer). Of all individuals with colorectal cancer, 245 died of the cancer during follow-up.

All individuals were followed from date of first adenoma removal until date of colectomy, date of death, date of emigration, or date of chart review (fall 2017 to summer 2018), whichever occurred first.

End Points

Colorectal cancer incidence was our primary end point.

Ethics and Approvals

The study was approved by the Regional Ethics Committee of South-Eastern Norway (2014/2352). All living individuals included were provided with written information about the study and could opt out of the study.

Statistical Analyses

Case-cohort analysis. We used Cox proportional hazard regression with Prentice weighting[17–19] to compare colorectal cancer incidence between the low- and high-risk groups according to the traditional, ESGE 2020, and novel classifications. For observations where adenoma size was missing, we did not use any imputation method because the data were not missing at random, but rather created a separate category for missing size and included it as an independent categorical variable in the models.

All multivariable models were adjusted for sex and age group (ie, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80 years or older) at first adenoma removal. We calculated the Harrell's Concordance Statistic based on predictions from the models to compare the risk classification systems.

We performed sensitivity analyses where we censored follow-up time at the date of second adenoma removal and where we excluded individuals who had adenomas registered as large or 10 mm.

Application of the risk classification systems to the subcohort. We used Cox proportional hazard regression to compare colorectal cancer incidence between the low- and high-risk groups defined according to the traditional, ESGE 2020, and novel classifications in the subcohort. Individuals who could not be classified as either low or high risk according to 1 or more of the classification systems due to missing information on adenoma size were excluded from the analyses.

The absolute reduction in the number of individuals recommended intensive colonoscopy surveillance was calculated as the difference in number of individuals between the traditional and the 2 newer high-risk groups. The relative reduction in number of individuals recommended intensive colonoscopy surveillance was calculated as the absolute change divided by the number of individuals in the traditional high-risk group.

To estimate the number of delayed cancer diagnoses, we assumed that:

- all individuals complied with surveillance;
- colonoscopy has 100% sensitivity for adenomas; and
- all cancers in individuals that were classified as high risk using the traditional classification but low risk using the newer classifications would present as an adenoma at the first high-risk surveillance colonoscopy and develop into a cancer before the first low-risk surveillance. Thus, all cancers diagnosed among individuals reclassified from high risk to low risk would have been prevented at surveillance using the traditional classification.

The number of delayed cancer diagnoses was calculated as the difference in colorectal cancer incidence in the newer low-risk groups compared with the traditional low-risk group.

All hypotheses were tested at .05 significance level. All analyses were performed using Stata software, version 16.1 (StataCorp, College Station, TX).

Results

Case-Cohort Study Characteristics

Nine hundred and six individuals of the subcohort met our eligibility criteria and were included in the analysis (Figure 1). They were followed for a median of 12.7 years after adenoma removal (interquartile range [IQR], 6.3–16.6 years). In the subcohort, 468 (51.7%) were women and 438 (48.3%) were men, and median age at first adenoma removal was 64.1 years (IQR, 56.6–73.9 years) (Table 1). Thirty-two individuals in the subcohort had colorectal cancer and were thus also included as cases in the analyses; 27 were identified from the Cancer Registry and randomly sampled as cases and 5 were diagnosed during the time interval between the random sampling of cases and chart review and were thus identified as cases during chart review (Figure 1).

A random sample of 950 individuals who developed colorectal cancer were selected from the full cohort, of which 675 met our eligibility criteria and were included as cases in the analysis (Figure 1). Median time from first adenoma removal to colorectal cancer diagnosis was 5.6 years (IQR, 2.3–10.1 years). The cases consisted of 373 women (55.3%) and 302 men (44.7%), and median age at first adenoma removal was 68.7 years (IQR, 60.7–75.7 years).

At the time of first adenoma removal, a full colonoscopy was performed in 84.2% of the subcohort and 83.4% of the cases. The rest had a sigmoidoscopy or rectoscopy, however, 94.6% and 95.1%, respectively, had a colonoscopy within the first year. The quality of bowel preparation was similar in the 2 groups. In the subcohort, 49.8% of the individuals were in the high-risk group according to the traditional classification compared with 67.1% of the cases. One hundred twenty-six individuals (13.9%) in the subcohort and 118 individuals (17.5%) among the cases had adenomas that were large or 10 mm in size, and 130 individuals (14.4%) in the subcohort and 141 individuals (20.9%) among the cases had no information on adenoma size. See Table 1 for more details on patient characteristics.

Traditional Risk Classification

In the case-cohort analysis, the colorectal cancer incidence was higher in the high-risk than in the low-risk group (hazard ratio [HR], 2.59; 95% CI, 2.00–2.34) (Table 2, Supplementary Tables 1–3). Harrell's Concordance Statistic showed 66.3% (95% CI, 64.0%–68.6%) prediction ability (Table 2).

In the subcohort, 430 individuals classified as high risk according to the traditional classification contributed 4588 person-years of follow-up (median, 11.9 years; IQR, 4.5–15.9 years), and 386 individuals classified as low-risk contributed 4862 person-years of follow-up (median, 13.3 years; IQR, 8.9–17.1 years). Cancer incidence was 479 cases per 100,000 person-years (95% CI, 316–728 cases) in the high-risk group compared with 123 cases (95% CI, 55–275 cases) in the low-risk group (Figure 2, Supplementary Figure 1, and Table 3).

European Society of Gastrointestinal Endoscopy 2020 Risk Classification

In the case-cohort analysis, the colorectal cancer incidence was higher in the high-risk than in the low-risk group

(HR, 2.68; 95% CI, 2.06–3.49) (Table 2, Supplementary Tables 1–3). Harrell's Concordance Statistic showed 66.7% (95% CI, 64.4%–69.0%) prediction ability (Table 2).

In the subcohort, 369 individuals classified as high risk according to the ESGE 2020 classification contributed 3804 person-years of follow-up (median, 11.4 years; IQR, 3.2–15.7 years) and 447 individuals in the low-risk group contributed 5647 person-years of follow-up (median, 13.3 years; IQR 9.0–17.1 years). Cancer incidence was 552 cases per 100,000 person-years (95% CI, 360–847 cases) in the high-risk group compared with 124 cases (95% CI, 59–260 cases) in the low-risk group (Figure 2, Supplementary Figure 2, Table 3).

Novel Risk Classification

In the case-cohort analysis, the colorectal cancer incidence was higher in the high-risk than in the low-risk group (HR, 2.86; 95% CI, 2.18–3.75) (Table 2, Supplementary Tables 1–3). Harrell's Concordance Statistic showed 66.0% (95% CI, 63.7%–68.3%) prediction ability (Table 2).

In the subcohort, 220 individuals classified as high-risk according to the novel classification contributed 2175 person-years of follow-up (median, 10.6 years; IQR, 2.3–15.3 years) and 596 individuals in the low-risk group contributed 7275 person-years of follow-up (median, 13.1 years; IQR, 7.9–17.1 years). Six hundred and ninety colorectal cancer cases per 100,000 person-years (95% CI, 416–1144 cases) occurred in the high-risk group, compared with 179 cases (95% CI, 104–308 cases) in the low-risk group (Figure 2, Supplementary Figure 3, Table 3).

Sensitivity Analyses

Sensitivity analyses, censoring at second adenoma removal (Supplementary Tables 4–6), or excluding individuals with adenomas registered as large or 10 mm (data not shown) showed similar results.

Surveillance Burden and Cancer Detection Using the Different Risk Classification Systems

In the subcohort, 90 individuals could not be classified according to one of the classification systems due to missing information on adenoma size and were thus excluded from comparisons of surveillance burden and cancer detection after adenoma removal. Of the included individuals, the traditional high-risk group comprised 52.7% of individuals with adenomas compared with 45.2% based on the ESGE 2020 classification and 27.0% based on the novel risk classification (Table 3).

The number of individuals classified as high risk, and thus recommended intensive surveillance colonoscopy, was reduced by 7.5 percentage points (95% CI, 2.6–12.3 percentage points; a 13.9% relative reduction) using the ESGE 2020 classification and 26.8 percentage points (95% CI, 22.1–31.6 percentage points; a 44.2% relative reduction) using the novel classification compared with the traditional classification (Table 3).

One diagnosis of colorectal cancer (3.4%) would have been delayed using the ESGE 2020 classification and 7 diagnoses of colorectal cancer (24.1%) would have been delayed using the novel classification compared with the traditional classification. These cancers included 1 stage II

Table 1. Baseline Characteristics of Subcohort and Colorectal Cancer Cases

	Subcohort		Cases	
Characteristic	n	%	n	%
Total	906	100.0	675	100.0
Colorectal cancer cases	32	3.5	675	100.0
Sex				
Female	468	51.7	373	55.3
Male	438	48.3	302	44.7
Age group at first adenoma removal				
40–49 y	84	9.3	33	4.9
50–59 y	248	27.4	125	18.5
60–69 y	257	28.4	204	30.2
70–79 y	227	25.1	216	32.0
80 y or older	90	9.9	97	14.4
Year of first adenoma removal				
1999 or before	273	30.1	319	47.3
2000 or after	633	69.9	356	52.7
No. of adenoma occurrences				
1	583	64.4	406	60.2
2	197	21.7	150	22.2
≥3	126	13.9	119	17.6
Index endoscopy characteristic				
Colonoscopy	763	84.2	563	83.4
Bowel preparation[a]				
Good	332	43.5	229	40.7
Medium	96	12.6	95	16.9
Poor	37	4.9	26	4.6
Unknown	298	39.1	213	37.8
Level of endoscopic intubation[b]				
Cecum	594	65.6	385	57.0
Right colon[c]	645	71.2	443	65.6
Left colon[c]	240	26.5	207	30.7
Unknown	21	2.3	25	3.7
Index adenoma characteristic				
High-risk (traditional)	451	49.8	453	67.1
Advanced adenoma	433	47.8	438	64.9
Villous or tubulovillous	232	25.6	269	39.9
High-grade dysplasia	152	16.8	193	28.6
Size				
<10 mm	468	51.7	220	32.6
11–19 mm[c]	67	7.4	54	8.0
Large/10 mm[d]	126	13.9	118	17.5
≥20 mm	115	12.7	142	21.0
Missing	130	14.4	141	20.9
No. of adenomas				
1–2	841	92.8	595	88.2
≥3	65	7.2	80	11.9

[a]Registered for colonoscopies only.
[b]Segment mentioned explicitly.
[c]Right colon: proximal to splenic flexure; left colon: splenic flexure and distally.
[d]Adenomas registered as 10 mm excluded due to mix of adenomas actually measured to 10 mm and adenomas registered as "large."

Table 2. HR (95% CI) for Colorectal Cancer Incidence Using the Traditional, ESGE 2020, and Novel Classification Systems, With the Respective Low-Risk Group as Reference

Variable	HR (95% CI)	*P* value	*C*-statistic (95% CI)
Risk classification system			
Traditional high risk[a]	2.59 (2.00–3.34)	<.001	0.663 (0.640–0.686)
ESGE 2020 high risk[b]	2.68 (2.06–3.49)	<.001	0.667 (0.644–0.690)
Novel high risk[c]	2.86 (2.18–3.75)	<.001	0.660 (0.637–0.683)

NOTE. Multivariable Cox proportional hazard models with Prentice weighting, adjusted for sex and age. Individuals with adenomas with missing size or size registered as large/10 mm are removed.
[a]Three or more adenomas or an adenoma ≥10 mm or villous/tubulovillous or with high-grade dysplasia.
[b]Five or more adenomas or an adenoma ≥10 mm or with high-grade dysplasia.
[c]High-grade dysplasia and <20 mm or ≥20 mm.

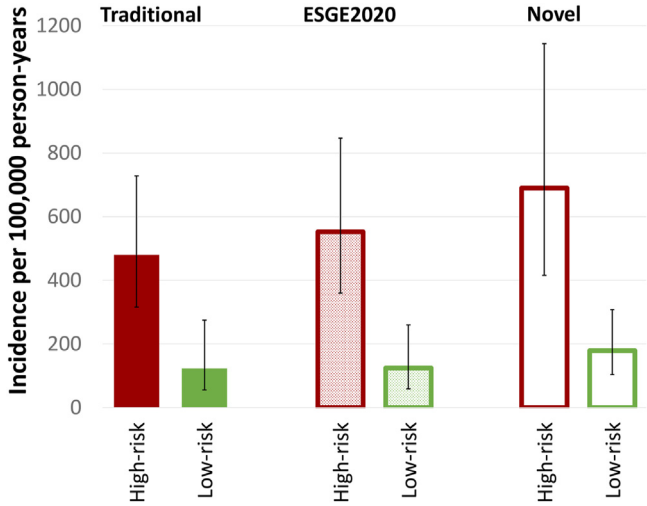

Figure 2. The incidence of colorectal cancer per 100,000 person-years with 95% CI after adenoma removal. Individuals were grouped into high-risk groups (*red bars*) and low-risk groups (*green bars*), using the traditional (*full color*), ESGE 2020 (*dotted*) and novel (*blank*) risk classification systems.

cancer, 5 stage III cancers, and 1 stage IV cancers, of which 2 were diagnosed more than 10 years after adenoma removal. This corresponds to 1.0 (95% CI, 0.5–2.0) delayed cancer diagnosis per 100,000 person-years using the ESGE 2020 classification, and 4.3 (95% CI, 2.5–7.4) delayed cancer diagnoses per 100,000 person-years using the novel classification (Table 3).

Discussion

We found that the 2 newer, simpler classification systems to guide surveillance colonoscopy after adenoma removal may be more accurate in identifying individuals in need of intensive surveillance. The need for frequent surveillance was reduced by 14%–44% with the newer classifications compared with the traditional classification, and the colorectal cancer incidence among those individuals not recommended intensive surveillance was well below that of the general population. In our subcohort of individuals followed after adenoma removal, the proportion that was classified as high risk varied grossly, between 53% and 27% with the different classifications. If 1000 individuals are screened, 200–300 individuals will be diagnosed with an adenoma.[20,21] Thus, using the traditional classification 100–160 individuals will be recommended first surveillance at 3 years.[4] With the ESGE 2020 classification, this is reduced to 90–140 of the 1000 screened individuals and with the novel classification, only 50–80 of the 1000 screened individuals would require surveillance at 3 years. Our comparisons show prediction ability of future colorectal cancer of 66%–67% for all 3 classification systems (Table 2). Implementation of these newer classifications will reserve more colonoscopy capacity for diagnostic and therapeutic purposes and reduce the potential harm of colonoscopy for the individual.

The potential cost of using a more restrictive high-risk definition is reduced adenoma detection and resection among those who are no longer identified as high risk. This would entail an increased colorectal cancer incidence in the low-risk groups. We have estimated that 3.4% and 24.1% of colorectal cancer diagnoses may have been delayed due to reclassification to low risk in the ESGE 2020 and the novel classifications, respectively. However, because we wanted to provide conservative estimates of the benefit to harm ratio of the newer risk classifications, we chose assumptions in our calculation that are likely to overestimate the number of delayed cancers.

In the current study, the absolute yearly risk of colorectal cancer among individuals with low-risk adenomas was 0.12% using the traditional and ESGE 2020 classifications, and 0.18% using the novel classification. In comparison, the average yearly absolute risk of colorectal cancer in the age-matched general population used as comparison for the full adenoma cohort was 0.27% for women and 0.33% for men.[6] Thus, the risk of colorectal cancer among the low-risk individuals is well below that of the general population regardless of which classification system is used. There is no universal answer to what is considered an acceptable risk without surveillance; this is a value-sensitive question and answers may differ between individuals and cultures.

Ideally, we should be able to separate a small high-risk group of individuals with a clearly elevated risk of future colorectal cancer and a low-risk group with risk similar to the background population. However, all of the present classification systems misclassify a large portion of individuals, that is, those in the high-risk group who will never develop cancer and those in the low-risk group who will eventually develop cancer. We therefore observed a seemingly counterintuitive phenomenon, known as Will Rogers phenomenon or stage migration.[22] Going from the traditional to the novel classification, the risk increased for both

Table 3. Clinical Implications of Using the Newer Risk Classification Systems

Variable	Risk classification system		
	Traditional	ESGE 2020	Novel
Low-risk individuals, n (%)	386 (47.3)	447 (54.8)	596 (73.0)
High-risk individuals, n (%)	430 (52.7)	369 (45.2)	220 (27.0)
Average yearly risk of cancer			
Low-risk individuals, % (95% CI)	0.12 (0.06–0.27)	0.12 (0.06–0.26)	0.18 (0.10–0.31)
High-risk individuals, % (95% CI)	0.48 (0.32–0.73)	0.55 (0.36–0.85)	0.69 (0.42–1.14)
Absolute reduction in intensive surveillance colonoscopy, % (95% CI)	0 (ref)	7.5 (2.6–12.3)	26.8 (22.1–31.6)
Relative reduction in intensive surveillance colonoscopy, % (95% CI)	0 (ref)	13.9 (5.1–22.0)	44.2 (37.2–50.5)
Delayed cancer diagnoses, n (%)[a]	0 (ref)	1 (3.4)	7 (24.1)

[a]Assuming that all individuals complied with surveillance, that colonoscopy have 100% sensitivity for adenomas, and that all cancers who were moved from high risk to low risk would present as an adenoma at the surveillance colonoscopy, but develop into a cancer before the next screening.

groups; the low-risk group increased from 0.12% to 0.18% and the high-risk group increased from 0.48% to 0.69%. This is because the individuals with the lowest risk in the high-risk group are moved to the low-risk group, with the result of a higher average risk in both risk groups.

Other risk classification systems for colorectal adenomas have been suggested.[23,24] However, because these systems have been developed and validated with surrogate end points (eg, adenomas and advanced neoplasia), their usefulness as a tool to reduce colorectal cancer incidence and mortality, and simultaneously optimize resource utilization, is unknown. Strengths of the ESGE 2020 and the novel risk classifications are their simplicity and availability for all clinicians, thorough testing in different populations based on relevant end points, and effective reduction in the need for surveillance colonoscopy.

Strengths of this study includes the long-term follow-up and detailed, high-quality data acquired by a standardized, complete chart review. By using the case-cohort design, we were able to retain the validity of a cohort study, drastically reduce the workload, and overcome the limitations of missing information on size and number of adenomas in the cohort based on the Cancer Registry.[5,6]

A limitation of this study is, firstly, that our cohort of individuals who have had adenomas removed had less intensive surveillance than what is recommended today. This might lead to higher estimates of the risk of colorectal cancer in all groups. Secondly, some individuals in our study did not have a full colonoscopy at the time of first adenoma removal (15.8% in the subcohort vs 16.6% among the cases); however, most individuals (94.6% in the subcohort and 95.1% among the cases) had a full colonoscopy within 1 year of the first adenoma removal. Thirdly, information on dysplasia and/or growth pattern was not reported in some of the patient records, which prevented us from accurately classifying these individuals as low or high risk. The number of individuals with missing information on dysplasia and/or growth pattern was small (2.6% in the subcohort and 3.0% in the cases) and would probably not influence our results. Fourthly, information on the size of adenoma was not reported in some of the patient records. In our analysis, we found that these individuals had an HR of colorectal cancer incidence closer to the high-risk group than the low-risk group for all classifications, indicating that this group constituted more high-risk than low-risk adenomas. Thus, the removal of these individuals in our comparison most likely reduces the chance of overestimating the risk of high-risk individuals for all comparisons (Supplementary Tables 1–3). Lastly, in some endoscopy reports, the size of the adenoma was described as "large" or "small" rather than numerically. These were classified by the data abstractors according to the abstraction procedure manual as 5 mm and 10 mm, respectively. Adenomas with diameter $\geq$10 mm are high risk in the traditional and ESGE 2020 classification systems, thus all large adenomas are classified as high risk. However, adenomas with a diameter of 10 mm are classified as low risk in the novel classification. When applying the novel classification to this data set, some large adenomas (those that are truly $\geq$20 mm) with low-grade dysplasia may be misclassified as low risk. Therefore, our results may overestimate the risk of colorectal cancer in the novel low-risk group.

In summary, we found that the 2 newer risk classification systems reduced the number of individuals in need of intensive surveillance colonoscopy by 14%–44% compared with the traditional risk classification, at the cost of 1.0–4.3 delayed cancer diagnoses per 100,000 person-years. Still, the risk of colorectal cancer in the ESGE 2020 and novel low-risk groups are considerably lower than in the Norwegian screening-naïve general population. Using the newer risk classifications with similar prediction ability of colorectal cancer incidence will reduce the need for colonoscopy resources for surveillance, which may be better used for diagnostic and therapeutic purposes. The acceptable risk level at which no surveillance is needed must be considered when implementing surveillance risk classifications.

Interventional studies are ultimately needed to test the effect of different classification systems on outcomes that are important to both patients and health care providers. An efficient approach is to use a learning health system to perform randomized testing and follow-up of the different risk classifications.[25]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.04.028.

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Henriette C. Jodal and Paulina Wieszczy-Szczepanik contributed equally to this work.

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Conflicts of interest

The authors disclose no conflicts.

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Data Availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Supplementary Material

Developing the Model

Statistical Analysis

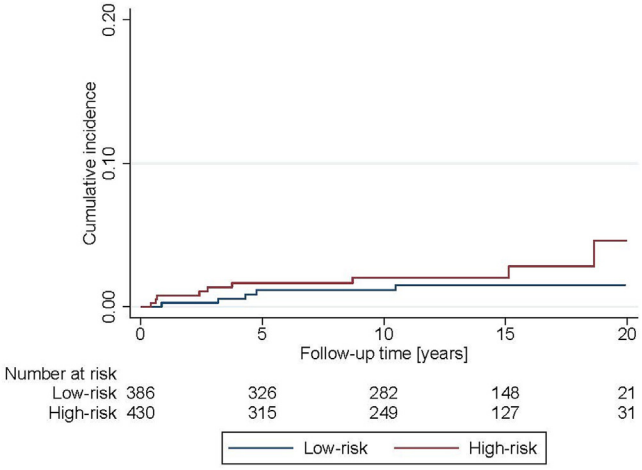
We performed Cox proportional hazard regression with Prentice weighting[17–19] to compare HRs and 95% CIs for colorectal cancer incidence. After the report of development of the novel classification,[10] we included sex, age group, and adenoma characteristics (ie, dysplasia, growth pattern, adenoma size, and number of adenomas) as variables. For observations where adenoma size was missing, we did not use any imputation method because the data were not missing at random, but rather created a separate category for missing size and included it as an independent categorical variable in the models.

In sensitivity analyses, we censored follow-up time at the date of second adenoma removal.

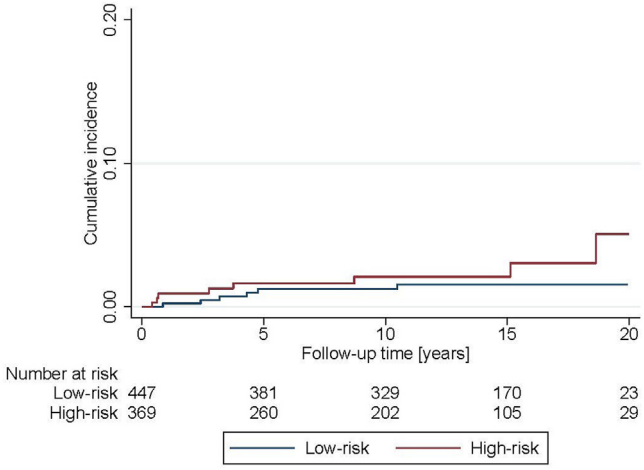
Results

In the multivariable model of colorectal cancer incidence using Cox proportional hazard models with Prentice weighting, adjusting for sex, age, and adenoma characteristics, adenomas with missing size (HR, 2.09; 95% CI, 1.51–2.90), size ≥20 mm (HR, 2.07; 95% CI, 1.43–2.99), and "large" or size 10 mm (HR, 1.69; 95% CI, 1.19–2.39) was associated with increased risk of colorectal cancer incidence, in addition to villous or tubulovillous growth pattern (HR, 1.59; 95% CI, 1.21–2.08) and ≥3 adenomas (HR, 1.91; 95% CI, 1.27–2.88) (Supplementary Table 7).

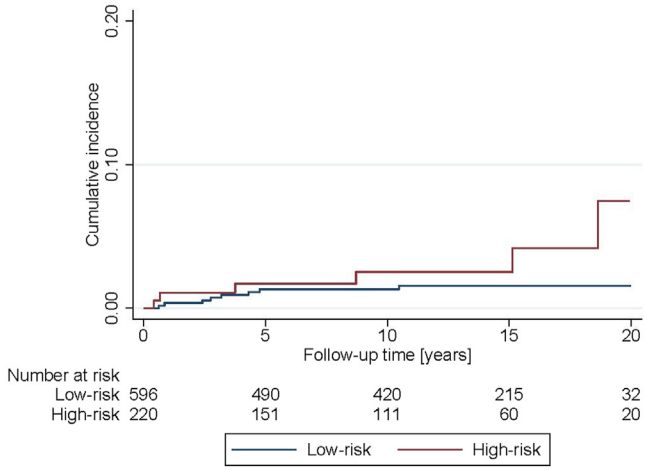
Sensitivity analysis censoring at second adenoma removal showed similar results, except that adenomas with high-grade dysplasia were also associated with increased risk of colorectal cancer incidence (HR, 1.42; 95% CI, 1.01–2.01) (Supplementary Table 8).



Supplementary Figure 1. Kaplan-Meier curve for colorectal cancer incidence in the subcohort using the traditional classification system. Log-rank $P < .001$.



Supplementary Figure 2. Kaplan-Meier curve for colorectal cancer incidence in the subcohort using the ESGE 2020 classification system. Log-rank $P < .001$.



Supplementary Figure 3. Kaplan-Meier curve for colorectal cancer incidence in the subcohort using the novel classification system. Log-rank $P < .001$.

Supplementary Table 1. Univariable and Multivariable HRs for Traditional Classification System for Colorectal Cancer: Cox Proportional Hazard Models With Prentice Weighting

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Female	1.00	—	1.00	—
Male	0.90 (0.73–1.11)	.34	1.00 (0.79–1.25)	.98
Age group				
40–49 y	1.00	—	1.00	—
50–59 y	1.33 (0.84–2.09)	.22	1.35 (0.84–2.15)	.21
60–69 y	2.46 (1.58–3.84)	<.001	2.39 (1.52–3.78)	<.001
70–79 y	4.33 (2.76–6.82)	<.001	4.11 (2.58–6.54)	<.001
80 y or older	8.53 (5.02–14.48)	<.001	7.59 (4.42–13.03)	<.001
Traditional classification				
Low risk[a]	1.00	—	1.00	—
High risk[b]	2.83 (2.24–3.58)	<.001	2.54 (2.00–3.23)	<.001
Missing size[c]	2.15 (1.44–3.22)	<.001	2.22 (1.47–3.37)	<.001

[a]Low risk: 1–2 tubular adenomas <10 mm with low-grade dysplasia.
[b]High risk: ≥3 adenomas or adenoma ≥10 mm or villous/tubulovillous or with high-grade dysplasia.
[c]Only for 1–2 tubular adenomas with low-grade dysplasia.

Supplementary Table 2. Univariable and Multivariable HRs for ESGE 2020 Classification System for Colorectal Cancer: Cox Proportional Hazard Models With Prentice Weighting

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Female	1.00	—	1.00	—
Male	0.90 (0.73–1.11)	.34	1.00 (0.79–1.25)	.99
Age group				
40–49 y	1.00	—	1.00	—
50–59 y	1.33 (0.84–2.09)	.22	1.36 (0.85–2.17)	.20
60–69 y	2.46 (1.58–3.84)	<.001	2.37 (1.50–3.75)	<.001
70–79 y	4.33 (2.76–6.82)	<.001	4.06 (2.55–6.47)	<.001
80 y or older	8.53 (5.02–14.48)	<.001	7.30 (4.24–12.59)	<.001
ESGE 2020 classification				
Low risk[a]	1.00	—	1.00	—
High risk[b]	2.92 (2.32–3.68)	<.001	2.57 (2.02–3.26)	<.001
Missing size[c]	2.53 (1.79–3.58)	<.001	2.44 (1.71–3.49)	<.001

[a]Low risk: ≤5 adenomas <10 mm with low-grade dysplasia.
[b]High risk: ≥5 adenomas or adenoma ≥10 mm or with high-grade dysplasia.
[c]Only for ≤5 adenomas with low-grade dysplasia.

Supplementary Table 3. Univariable and Multivariable HRs for Novel Classification System for Colorectal Cancer: Cox Proportional Hazard Models With Prentice Weighting

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Female	1.00	—	1.00	—
Male	0.90 (0.73–1.11)	.34	1.01 (0.80–1.27)	.94
Age group				
40–49 y	1.00	—	1.00	—
50–59 y	1.33 (0.84–2.09)	.22	1.38 (0.86–2.21)	.18
60–69 y	2.46 (1.58–3.84)	<.001	2.62 (1.65–4.15)	<.001
70–79 y	4.33 (2.76–6.82)	<.001	4.09 (2.57–6.51)	<.001
80 y or older	8.53 (5.02–14.48)	<.001	7.69 (4.43–13.35)	<.001
Novel classification				
Low-grade dysplasia and <20 mm	1.00	—	1.00	—
High-grade dysplasia and <20 mm	2.48 (1.82–3.39)	<.001	2.26 (1.63–3.13)	<.001
≥20 mm	3.00 (2.21–4.06)	<.001	2.56 (1.86–3.54)	<.001
Missing size[a]	2.05 (1.47–2.85)	<.001	2.03 (1.44–2.85)	<.001

[a]Only for adenomas with low-grade dysplasia.

Supplementary Table 4. Univariable and Multivariable HRs for Traditional Classification System for Colorectal Cancer, With Follow-Up Time Censored at Second Adenoma Removal: Cox Proportional Hazard Models With Prentice Weighting

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Female	1.00	—	1.00	—
Male	0.99 (0.79–1.25)	.96	1.19 (0.92–1.53)	.18
Age group				
40–49 y	1.00	—	1.00	—
50–59 y	1.09 (0.65–1.82)	.75	1.13 (0.67–1.91)	.65
60–69 y	2.35 (1.44–3.84)	.001	2.26 (1.36–3.74)	.002
70–79 y	4.00 (2.43–6.58)	<.001	3.91 (2.35–6.52)	<.001
80 y or older	7.96 (4.51–14.05)	<.001	7.33 (4.12–13.03)	<.001
Traditional classification				
Low risk[a]	1.00	—	1.00	—
High risk[b]	3.02 (2.33–3.91)	<.001	2.69 (2.05–3.52)	<.001
Missing size[c]	2.42 (1.56–3.76)	<.001	2.42 (1.51–3.86)	<.001

[a]Low risk: 1–2 tubular adenomas <10 mm with low-grade dysplasia.
[b]High risk: ≥3 adenomas or adenoma ≥10 mm or villous/tubulovillous or with high-grade dysplasia.
[c]Only for 1–2 tubular adenomas with low-grade dysplasia.

Supplementary Table 5. Univariable and Multivariable HRs for ESGE 2020 Classification System for Colorectal Cancer, With Follow-Up Time Censored at Second Adenoma Removal: Cox Proportional Hazard Models With Prentice Weighting

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Female	1.00	—	1.00	—
Male	0.99 (0.79–1.25)	.96	1.20 (0.93–1.55)	.16
Age group				
40–49 y	1.00	—	1.00	—
50–59 y	1.09 (0.65–1.82)	.75	1.12 (0.66–1.91)	.66
60–69 y	2.35 (1.44–3.84)	.001	2.24 (1.35–3.71)	.002
70–79 y	4.00 (2.43–6.58)	<.001	3.87 (2.32–6.44)	<.001
80 y or older	7.96 (4.51–14.05)	<.001	7.06 (3.96–12.59)	<.001
ESGE 2020 classification				
Low risk[a]	1.00	—	1.00	—
High risk[b]	3.03 (2.35–3.91)	<.001	2.66 (2.03–3.47)	<.001
Missing size[c]	2.65 (1.81–3.89)	<.001	2.47 (1.65–3.69)	<.001

[a]Low risk: ≤5 adenomas <10 mm with low-grade dysplasia.
[b]High risk: ≥5 adenomas or adenoma ≥10 mm or with high-grade dysplasia.
[c]Only for ≤5 adenomas with low-grade dysplasia.

Supplementary Table 6. Univariable and Multivariable HRs for Novel Classification System for Colorectal Cancer Using Follow-Up Time Censored at Second Adenoma Removal: Cox Proportional Hazard Models With Prentice Weighting

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Female	1.00	—	1.00	—
Male	0.99 (0.79–1.25)	.96	1.22 (0.94–1.57)	.134
Age group				
40–49 y	1.00	—	1.00	—
50–59 y	1.09 (0.65–1.82)	.75	1.12 (0.66–1.89)	.68
60–69 y	2.35 (1.44–3.84)	.001	2.44 (1.47–4.03)	.001
70–79 y	4.00 (2.43–6.58)	<.001	3.88 (2.33–6.44)	<.001
80 y or older	7.96 (4.51–14.05)	<.001	7.65 (4.28–13.67)	<.001
Novel classification				
Low-grade dysplasia and <20 mm	1.00	—	1.00	—
High-grade dysplasia and <20 mm	2.63 (1.85–3.74)	<.001	2.54 (1.75–3.67)	<.001
≥20 mm	2.90 (2.06–4.06)	<.001	2.46 (1.72–3.53)	<.001
Missing size[a]	2.11 (1.47–3.05)	<.001	2.02 (1.37–2.98)	<.001

[a]Only for adenomas with low-grade dysplasia.

Supplementary Table 7. Univariable and Multivariable HRs for Risk of Colorectal Cancer: The First Step in Developing the Novel Classification—Cox Proportional Hazard Models With Prentice Weighting

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Female	1.00	—	1.00	—
Male	0.90 (0.73–1.11)	.34	1.01 (0.79–1.27)	.96
Age group				
40–49 y	1.00	—	1.00	—
50–59 y	1.33 (0.84–2.09)	.22	1.36 (0.84–2.21)	.22
60–69 y	2.46 (1.58–3.84)	<.001	2.50 (1.55–4.03)	<.001
70–79 y	4.33 (2.76–6.82)	<.001	3.83 (2.36–6.21)	<.001
80 y or older	8.53 (5.02–14.48)	<.001	6.99 (3.97–12.33)	<.001
Dysplasia				
Low-grade	1.00	—	1.00	—
High-grade	2.35 (1.81–3.04)	<.001	1.32 (0.97–1.80)	.081
Growth pattern				
Tubular	1.00	—	1.00	—
Villous or tubulovillous	2.29 (1.82–2.87)	<.001	1.59 (1.21–2.08)	.001
Adenoma size				
1–9 mm	1.00	—	1.00	—
11–19 mm	1.90 (1.27–2.85)	.002	1.19 (0.76–1.87)	.45
Large/10 mm	2.36 (1.73–3.23)	<.001	1.69 (1.19–2.39)	.003
≥20 mm	3.48 (2.54–4.77)	<.001	2.07 (1.43–2.99)	<.001
Missing	2.50 (1.85–3.38)	<.001	2.09 (1.51–2.90)	<.001
No of adenomas				
1–2	1.00	—	1.00	—
≥3	2.09 (1.44–3.03)	<.001	1.91 (1.27–2.88)	.002

Supplementary Table 8. Univariable and Multivariable HRs for Risk of Colorectal Cancer, With Follow-Up Time Censored at Second Adenoma Removal: The First Step in Developing the Novel Classification—Cox Proportional Hazard Models With Prentice Weighting

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex				
Female	1.00	—	1.00	—
Male	0.99 (0.79-1.25)	.96	1.18 (0.91–1.54)	.21
Age group				
40–49 y	1.00	—	1.00	—
50–59 y	1.09 (0.65–1.82)	.75	1.08 (0.63–1.84)	.78
60–69 y	2.35 (1.44–3.84)	.001	2.21 (1.33–3.69)	.002
70–79 y	4.00 (2.43–6.58)	<.001	3.47 (2.07–5.84)	<.001
80 y or older	7.96 (4.51–14.05)	<.001	6.36 (3.51–11.53)	<.001
Dysplasia				
Low-grade	1.00	—	1.00	—
High-grade	2.51 (1.88–3.36)	<.001	1.42 (1.01–2.01)	.046
Growth pattern				
Tubular	1.00	—	1.00	—
Villous or tubulovillous	2.25 (1.74–2.90)	<.001	1.50 (1.11–2.04)	.009
Adenoma size				
1–9 mm	1.00	—	1.00	—
11–19 mm	2.60 (1.65–4.09)	.001	1.63 (0.99–2.67)	.055
Large/10 mm	2.33 (1.64–3.30)	<.001	1.62 (1.09–2.44)	.016
≥20 mm	3.44 (2.42–4.89)	<.001	1.94 (1.27–2.97)	.002
Missing	2.70 (1.93–3.77)	<.001	2.19 (1.52–3.16)	<.001
No. of adenomas				
1–2	1.00	—	1.00	—
≥3	2.65 (1.74–4.03)	<0.001	1.96 (1.22–3.16)	.005