Polyp characteristics at screening colonoscopy and post-colonoscopy colorectal cancer mortality: a retrospective cohort study

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Background and Aims: Polyp size and high-grade dysplasia in polyps at screening colonoscopy are considered risk factors for post-colonoscopy colorectal cancer (PCCRC) development and death, which might be averted by surveillance colonoscopy. However, robust evidence backing these risk factors is lacking. We aimed to investigate whether polyp size or dysplasia grade is associated with PCCRC mortality.

Methods: This was a retrospective study including individuals of the Austrian Quality Certificate for Screening Colonoscopy who underwent a colonoscopy between January 2007 and December 2020. We investigated the association of polyp size and dysplasia in polyps with PCCRC mortality according to Cox regression analysis. In addition, whether patients with certain polyp characteristics had similar risk for CRC death compared with the Austrian population was assessed by calculating standardized mortality ratios (SMRs).

Results: A total of 316,001 individuals were included. After a median follow-up time of 5.27 years (95% confidence interval [CI], 5.25-5.29), a significant association of polyps 10 to 20 mm (hazard ratio, 4.00; 95% CI, 2.46-6.50; $P < .001$) as well as high-grade dysplasia (hazard ratio, 6.61; 95% CI, 3.31-13.2; $P < .001$) with PCCRC death was observed. PCCRC mortality was significantly lower than the expected CRC mortality in the general population in patients with polyps <10 mm and without high-grade dysplasia (SMR, .27; 95% CI, .21-.33; $P < .001$), which was not observed for patients with polyps ≥10 mm or with high-grade dysplasia (SMR, 2.05; 95% CI, 1.64-2.57; $P < .001$).

Conclusions: Polyp size ≥10 mm and high-grade dysplasia are associated with PCCRC mortality in screening patients. The data suggest that these patients might benefit most from surveillance colonoscopy. (Gastrointest Endosc 2023;97:1109-18.)

Abbreviations: CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; HR, hazard ratio; ICD-10, International Classification of Diseases, Tenth Revision; PCCRC, post-colonoscopy colorectal cancer; SMR, standardized mortality ratio; SSL, sessile serrated lesion; WHO, World Health Organization.

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Although successful screening has been implemented in many countries, colorectal cancer (CRC) accounts for 1 in 10 cancer deaths worldwide.[1] In the United States alone, approximately 1 in every 12 cancer-associated deaths can be attributed to CRC.[2] CRC screening including high-quality colonoscopy with complete removal of polyps is considered the reference standard for the reduction of CRC incidence and mortality. Nonetheless, a small proportion of screening participants will develop CRC despite screening colonoscopy with polypectomy having been performed, so-called post-colonoscopy CRC (PCCRC).[3] Previous studies on metachronous neoplasia as well as PCCRC incidence and mortality after screening colonoscopy have shown that the colonoscopy quality provided, as well as lesion characteristics of the polyps, contributes to PCCRC occurrence.[4-6]

To reduce PCCRC risk, surveillance colonoscopy should be performed in patients at risk for PCCRC. Studies of long-term PCCRC incidence and mortality, however, have mainly focused on predefined risk groups, and there is a lack of studies examining the association of single polyp features with PCCRC outcome. According to society guidelines, screening and subsequent surveillance colonoscopies after 3 years are recommended for individuals with large adenomas and serrated polyps with a cutoff of 10 mm, adenomas with high-grade dysplasia (HGD) or serrated polyps with dysplasia, or, according to some guidelines, villous histology.[7-9] Estimates quantify the volume of surveillance colonoscopies to be as high as 25% of all colonoscopies performed.[10] Furthermore, the number of individuals being eligible for screening is expected to rise, with new screening recommendations extending the age period to individuals aged 45 years.[11] This highlights the need for guidelines to define a precise risk group of patients who need to be followed up closely, while other patients can return to screening. One study described that the high-risk definition could be narrowed down to only patients with adenomas >20 mm or with HGD, although the data backing this strategy are scarce.[12]

The aim of the current study was to identify patients who might be most likely to benefit from post-colonoscopy surveillance by characterizing the association of polyp characteristics with PCCRC death and quantifying the burden of PCCRC deaths compared with CRC deaths in the Austrian population.

METHODS

Study population, design, and setting

CRC screening in Austria is recommended starting at the age of 50 years for both men and women. Austria has an opportunistic screening program in which every insured person at screening age can undergo primary colonoscopy screening with a primary care physician's referral. Because Austria has a single payer healthcare system with almost full coverage of the population, the screening program is offered to almost all eligible individuals. In addition to social insurance–based screening opportunities, individuals can opt for a private or "self-paid" screening colonoscopy in which referrals are not necessary.

Patients were enrolled in the current study whose colonoscopy was performed within the Austrian national CRC screening and quality assurance program. Details of the program have been provided elsewhere.[13] In brief, endoscopists submit data on screening colonoscopies of average-risk individuals (excluding patients with hereditary cancer syndromes and patients with inflammatory bowel diseases) for quality assurance purposes. Details regarding bowel preparation were routinely recorded starting in 2012. Patient records of performed colonoscopies, including patient age, sex, procedure metrics (cecal intubation, adverse events, bowel preparation, and sedation), and, if applicable, polyp characteristics (size, location, removal technique, and histologic workup), are uploaded to a database.

This was a retrospective cohort study. Colonoscopies were performed by gastroenterologists, surgeons, and internal medicine physicians in 263 private practices, 11 outpatient healthcare centers, and 86 hospitals. Patients were included who had a screening colonoscopy performed between January 2007 and December 2020. Of 385,438 eligible colonoscopies, we excluded patients who had inadequate bowel preparation (poor and insufficient bowel preparation on the Aronchick scale), those who had CRC detected at screening, patients with incomplete colonoscopies (as defined by insufficient depiction of the cecum), patients whose first record was a surveillance colonoscopy, patients who did not have complete polypectomy at screening, and individuals <50 years of age. Details of the study population are presented in Figure 1. Only the first screening colonoscopy (ie, the index colonoscopy) of every patient was used; hence patients' surveillance colonoscopies were not included in our analyses.

The study was approved by the Ethics Committee of the Medical University of Vienna (EK 1794/2019).

Definitions of variables

Baseline variables included age, sex, polyp size, location, polyp count, histologic type, and grade of dysplasia. The count of polyps was categorized into either 1 to 2, 3 to 4, or ≥5. Polyp size was assessed during endoscopy, during which endoscopists estimate polyp size with standard aids (forceps or snare) and report size according to 4 predefined categories (<5 mm, 5-9 mm, 10-20 mm, or >20 mm). In 2012, a separate variable for dysplasia grade was introduced for colonoscopy records: serrated polyps could either show high-grade, low-grade, or no dysplasia; and adenomas could be classified as having HGD or low-grade dysplasia. However, until 2012, *high-grade intraepithelial neoplasia* was the term used for any polyp with HGD, in line with the 3rd edition of the World Health Organization (WHO) classification of tumors of the digestive system.[14] In those lesions, the underlying histologic growth pattern is unknown; thus, we

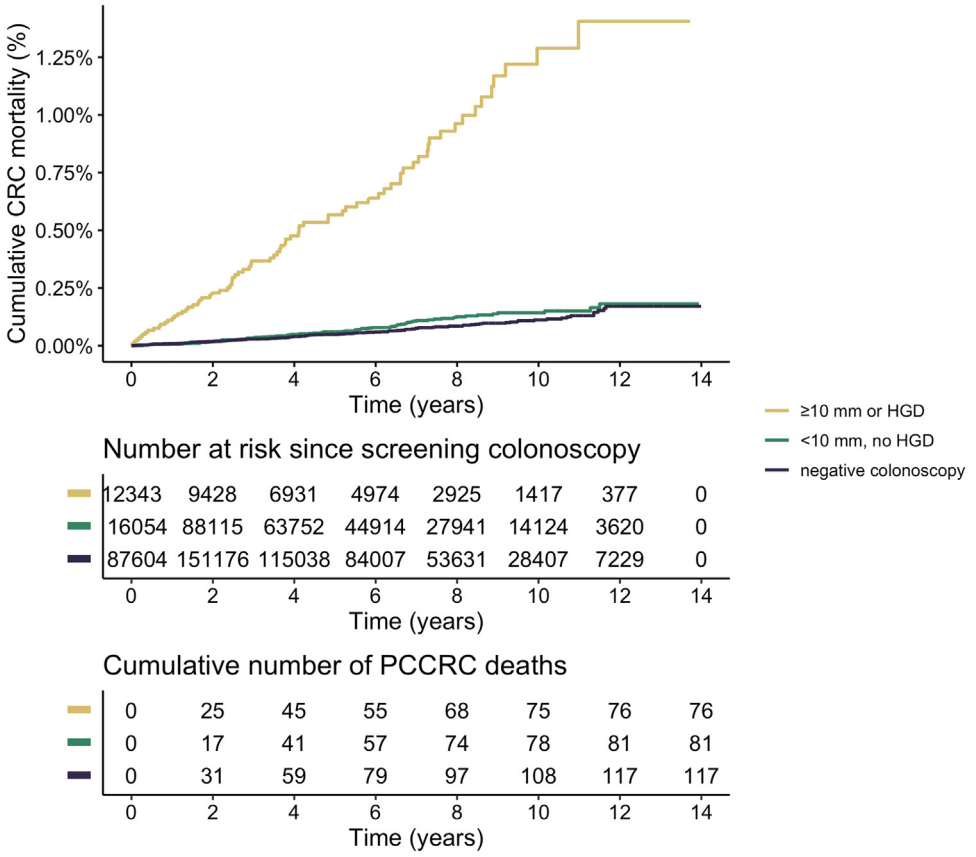

Figure 1. Cumulative colorectal cancer (CRC) mortality in percent in patients with a negative colonoscopy, with polyps <10 mm and no highgrade dysplasia, or polyps 10 mm with or without high-grade dysplasia. Patients were stratified according to polyp characteristics at screening colonoscopy. Current guidelines consider patients with adenomas 10 mm or with high-grade dysplasia and serrated polyps 10 mm or with dysplasia as high risk.7 PCCRC, Post-colonoscopy colorectal cancer.

could not perform analyses of the impact of dysplasia grade according to histologic type. The histologic type of polyps of the most severe pathology was recorded (ranked according to grade of dysplasia). Adenomas were classified as either tubular, tubulovillous, or villous, and serrated polyps were classified as sessile serrated lesions (SSLs; formerly sessile serrated adenomas) and traditional serrated adenomas. Hyperplastic polyps were recorded as a separate category; therefore, hyperplastic polyps and adenomas or SSLs/traditional serrated adenomas could be reported concomitantly. The location of polyps was classified as either distal (sigmoid and rectum), proximal (descending, transverse, ascending colon, and cecum), or both segments.

CRC mortality

In Austria, deaths are recorded in a central registry by a national institution, Statistics Austria. In this registry, date and cause of death are denoted according to the International Classification of Diseases, Tenth Revision (ICD-10), by the WHO. For this study, data from the registry were linked to records in the database, and a PCCRC-related mortality event was defined as a CRC-related death entry of the ICD-10 codes C18, C19, and C20. According to the World Endoscopy Organization consensus statement, PCCRC is defined as CRC identified in an individual with a prior colonoscopy in which no CRC had been detected.[3] All patients with screening-detected CRC were excluded. Therefore, CRC deaths in this study were only attributable to PCCRC death. Causes of death in any other ICD-10 category were considered as death from other causes.

Statistical analysis

Follow-up was determined as the time between screening colonoscopy and occurrence of death of CRC, death of other causes, or the end of the study period (December 31, 2020). Patients with no record of any-cause death were followed up until the end of the study period. To identify an association of polyp size or grade of dysplasia with PCCRC mortality, a cause-specific Cox proportional hazards model adjusted for patient's sex and age was used. Given the count of 274 deaths during the study period, we had a power of >99.9% to detect a hazard ratio (HR) of 2.0 according to Hsieh and Lavori.[15] HRs are reported with 95% confidence intervals (CIs). The proportional hazards assumption was

verified by (1) plotting scaled Schoenfeld residuals against transformed time; and (2) the Schoenfeld test.

Because surveillance colonoscopy can affect CRC risk, a sensitivity analysis was performed in which patients were censored at the first follow-up colonoscopy that was performed. We grouped patients with characteristics associated with PCCRC death (polyp ≥10 mm or HGD) and obtained cumulative incidences of PCCRC death at 5 and 10 years of follow-up. Cumulative incidence of PCCRC death was estimated with death from causes other than CRC as the competing risk. Likewise, 5- and 10-year estimates were calculated for patients with a polyp <10 mm and no HGD, and patients with a negative colonoscopy. Differences in cumulative incidence between groups were calculated by subtracting the estimates at 5 and 10 years, and 95% CIs were obtained from the sum of variances of risk in both groups.

Patients after a negative screening colonoscopy have a very small residual risk of CRC death, which might lead to high estimates of risk differences for CRC death compared with patients with high-risk polyps.[16] We therefore considered the general Austrian population as a comparator to calculate standardized mortality ratios (SMRs) of PCCRC death. The SMR adjusted for age, sex, and year was calculated by dividing PCCRC deaths in the cohort by expected CRC deaths according to the age-, year-, and sex-specific mortality rates per person-years of the Austrian population within groups of polyp findings. SMRs with 95% Wald CIs were calculated assuming that mortality rates follow a Poisson distribution. For all statistical tests, a significance level of .05 was set. Regarding the issue of multiple statistical testing of outcome data, the results of the cause-specific multivariable Cox proportional hazards regression analysis constitute the main results, with other results to be considered secondary (and to be taken as descriptive, only). We therefore did not correct any significance levels, and all *P* values are uncorrected for multiple testing. Analyses were performed by using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), with the package popEpi (version 0.4-9) and the package cmprsk (version 2.2-10).

RESULTS

Baseline findings

Cohort characteristics are shown in Table 1. Between January 2007 and December 2020, a total of 316,001 colonoscopies were performed by 239 endoscopists and were included in the analysis; of these, 162,644 (51.5%) were performed on female patients. For patients in whom bowel preparation details were available, 37.6% (n = 86,607) had an excellent bowel preparation, 50.7% (n = 116,671) had a good bowel preparation, and in 27,011 (11.7%) patients, bowel preparation was fair. The median age at colonoscopy was 59.7 (interquartile range, 54.0-67.3) years. No polyp was detected in 187,601 (59.4%) colonoscopies. The number of colonoscopies with polyps 10 to 20 mm and >20 mm was low, with only 8392 (2.7%) patients having polyps 10 to 20 mm and 3192 (1.0%) having polyps >20 mm at screening. HGD was found in 1532 (.5%) patients. The distribution of polyp histology of the whole cohort was 57,727 (18.3%) tubular adenomas, 10,105 (3.2%) tubulovillous adenomas, and 543 (.2%) villous adenomas. A total of 5061 (1.6%) patients had SSLs, 876 (.3%) had traditional serrated adenomas, and 45,609 (14.4%) had hyperplastic polyps without synchronous adenomas or other serrated polyps.

Endoscopies were mostly performed in private practices (n = 239,182). The median adenoma detection rate was 20.1% (interquartile range, 15.8%-26.5%), and the median serrated polyp detection rate was 17.9% (interquartile range, 12.5%-24.5%) (Supplementary Table 1, available online at www.giejournal.org). In a survey on endoscopic preferences conducted between January 2021 and December 2021, 31.74% of hospitals regularly used chromoendoscopy and 4.76% used computer-aided detection (CAD), whereas chromoendoscopy was used by 13.69% of private practices and computer-assisted detection colonoscopy by 2.38%.

Association of polyp finding with CRC mortality

The median follow-up time was 5.27 years (95% CI, 5.25-5.29), with an interquartile range of 2.48 years (95% CI, 2.46-2.49) and 8.49 years (95% CI, 8.47-8.50). At the end of the study period, 274 CRC deaths were observed. Being diagnosed with an adenoma or serrated polyp 10 to 20 mm (HR, 4.00; 95% CI, 2.46-6.50; $P < .001$) or >20 mm (HR, 18.1; 95% CI, 11.2-29.1; $P < .001$) at screening was significantly associated with PCCRC death, whereas the diagnosis of any polyp <10 mm was not significantly associated with PCCRC death (HR, 1.11; 95% CI, .83-1.49; $P = .5$), compared with patients with no polyps. The diagnosis of polyps with low-grade dysplasia (HR, 1.13; 95% CI, .85-1.51; $P = .4$) did not show significantly increased hazards for PCCRC death (Table 2). In the group of patients with polyps ≥10 mm or HGD (n = 12,606), 263 had a follow-up colonoscopy recorded. When patients were censored at surveillance colonoscopy for our sensitivity analysis, the estimates were comparable to our main analysis for polyps 10 to 20 mm (HR, 4.40; 95% CI, 2.71-7.12; $P < .001$) and HGD (HR, 7.10; 95% CI, 3.57-14.13; $P < .001$) (Supplementary Table 2).

Cumulative incidence of PCCRC death

When patients were stratified according to polyp findings, patients with a polyp ≥10 mm or with HGD detected at screening had a cumulative incidence of PCCRC death of .56% (95% CI, .54-.58) (Table 3) at 5 years and 1.22% (95% CI, 1.19-1.26) at 10 years. In contrast, in patients with polyps <10 mm and no HGD was detected, the cumulative incidence of PCCRC death was lower after 5 years (.06; 95% CI, .06-.06) as well as after 10 years (.14%; 95% CI, .14-.14). After a negative colonoscopy, cumulative incidence of PCCRC death was .05% (95% CI, .05-.05) at 5 years and .11% (95% CI, .11-.11) at 10 years.

TABLE 1. Baseline findings

Characteristic	Overall (N = 316,001)	Person-years	CRC deaths	CRC deaths per 100,000 person-years
Age, y				
Mean ± SD	61.3 ± 8.50	–	–	–
Median (Q1, Q3)	59.7 (54.0, 67.3)	–	–	–
Sex				
Female	162,644 (51.5%)	889,625.67	101	11.35
Male	153,357 (48.5%)	837,624.70	173	20.65
Polyp count				
No polyp	187,601 (59.3%)	1,064,736.53	117	10.99
1-4	120,271 (38.1%)	624,557.03	141	22.58
≥5	8129 (2.6%)	37,956.80	16	42.15
Polyp size				
No polyp	187,601 (59.3%)	1,064,736.53	117	10.99
<10 mm	116,813 (37.0%)	602,445.65	84	13.94
10-20 mm	8392 (2.7%)	43,269.64	24	55.47
>20 mm	3192 (1.0%)	16,761.88	49	292.33
Dysplasia				
None	246,264 (77.9%)	1,364,323.84	189	13.85
LGD	68,205 (21.6%)	355,118.98	74	20.84
HGD	1532 (.5%)	7807.55	11	140.89
Histologic type				
Tubular	57,727 (18.3%)	285,281.98	55	19.28
Tubulovillous	10,105 (3.2%)	63,520.30	19	29.91
Villous	543 (.2%)	2735.15	0	.00
Hyperplastic polyp	45,609 (14.4%)	244,678.48	28	11.44
SSL	5061 (1.6%)	16,923.12	4	23.64
TSA	876 (.3%)	2983.60	0	.00
Serrated adenoma, not specified*	385 (.1%)	3559.41	2	56.19
HGIEN†	449 (.1%)	4261.56	7	164.26
Location				
No polyp	187,601 (59.4%)	1,064,736.53	117	10.99
Distal and proximal segment	38,759 (12.3%)	175,346.96	44	25.09
Distal segment	60,808 (19.2%)	340,860.24	87	25.52
Proximal segment	28,826 (9.1%)	146,222.68	26	17.78

CRC, Colorectal cancer; *SD*, standard deviation; *Q1*, first quartile; *Q3*, third quartile; *LGD*, low-grade dysplasia; *HGD*, high-grade dysplasia; *SSL*, sessile serrated lesion; *TSA*, traditional serrated adenoma; *HGIEN*, high-grade intraepithelial neoplasia.

*SSLs and TSAs were recorded as serrated adenomas until 2012.

†In line with the 3rd edition of the World Health Organization classification of tumors of the digestive system, [12] *high-grade intraepithelial neoplasia* was the term used for any polyp with HGD until 2012.

Figure 2 shows the cumulative incidence of PCCRC death according to polyp findings over the whole study period. At 5 years, the incidence of PCCRC death was higher in patients with polyps ≥10 mm or HGD compared with patients with polyps <10 mm and no HGD (difference in cumulative incidence, .5%; 95% CI, .34-.65). At 10 years, the difference in cumulative incidences rose to 1.08% (95% CI, .76-1.41). We performed an additional analysis to investigate whether the endoscopist's specialty had an influence on PCCRC mortality. We found that cumulative incidence of PCCRC death was higher in the group of endoscopists practicing surgery at 4 to 12 years of follow-up (Supplementary Figure 1, available online at www.giejournal.org) despite comparable screening adenoma detection rates between surgeons and

TABLE 2. Multivariable hazard ratios with 95% CIs for polyp size and grade of dysplasia

Characteristic	Hazard ratio	95% CI	*P* value
Polyp size			
No polyp	—	—	
<10 mm	1.11	.83-1.49	.5
10-20 mm	4.00	2.46-6.50	<.001
>20 mm	18.1	11.2-29.1	<.001
Dysplasia grade			
None	—	—	
Low-grade	1.13	.85, 1.51	.4
High-grade	6.61	3.31-13.2	<.001

Categories are given of patients diagnosed with at least 1 polyp <10 mm, 10 to 20 mm, or >20 mm, at least 1 with low-grade or high-grade dysplasia adjusted for patient sex and age.
CI, Confidence interval.

TABLE 3. Cumulative incidence of CRC death in strata of polyp size and grade of dysplasia as well as risk differences between groups at 5 and 10 years of follow-up

Category	Cumulative incidence of PCCRC death at 5 years in percent (95% CI)	Cumulative incidence of PCCRC death at 10 years in percent (95% CI)
≥10 mm or HGD	.56 (.54-.58)	1.22 (1.19-1.26)
<10 mm, no HGD	.06 (.06-.06)	.14 (.14-.14)
Negative colonoscopy	.05 (.05-.05)	.11 (.11-.11)
	Risk difference at 5 years (95% CI)	**Risk difference at 10 years (95% CI)**
≥10 mm or HGD vs <10 mm, no HGD	.5 (.34-.65)	1.08 (.76-1.41)

The risk difference in cumulative mortality was compared between patients who had polyps ≥10 mm or with HGD detected at screening colonoscopy, and those with polyps <10 mm and no HGD.
CRC, Colorectal cancer; *CI*, confidence interval; *HGD*, high-grade dysplasia.

endoscopists of the internal medicine specialty (Supplementary Table 1, available online at www.giejournal.org). However, at 13 years of follow-up, the cumulative incidence of PCCRC death was similar in internal medicine (.21%; 95% CI, .21-.21) and surgery (.21%; 95% CI, .20-.22).

SMRs according to polyp finding

We observed 15.87 deaths per 100,000 person-years in our cohort, although 47.6 deaths per 100,000 were expected. The overall SMR for PCCRC death of the cohort was .33 (95% CI, .30-.37). When patients were stratified according to findings at screening colonoscopy, patients who had polyps <10 mm and no HGD had an SMR significantly lower than that of the general population (SMR, .27; 95% CI, .21-.33; $P < .001$). After a negative colonoscopy, findings were comparable (SMR, .24; 95% CI, .2-.29; $P < .001$). The observed mortality in patients who had polyps ≥10 mm or with HGD was higher than that of the general population (SMR, 2.05; 95% CI, 1.64-2.57; $P < .001$) (Table 4). In contrast, for patients with at least 1 advanced adenoma (tubulovillous/villous adenoma, polyp ≥10 mm, or HGD), mortality was not significantly higher compared with the expected mortality from the population (SMR, 1.22; 95% CI, .98-1.52; $P = .074$).

DISCUSSION

Polyp size and dysplasia grade are considered the main contributors to PCCRC development after screening colonoscopy.[12] In this study, we compared CRC mortality outcomes in screening patients, stratified according to lesion size and grade of dysplasia at screening colonoscopy, and assessed their association with PCCRC death. The PCCRC mortality in our cohort was compared with the CRC mortality in the Austrian population. We found that polyp size of at least 10 mm (HR, 4.00; 95% CI, 2.46-6.50; $P < .001$) and the presence of HGD (HR, 6.61; 95% CI, 3.31-13.2; $P < .001$) in polyps was associated with PCCRC death. The 10-year cumulative incidence of PCCRC death was highest in patients with polyps ≥10 mm or with HGD (1.22%; 95% CI, 1.19-1.26) compared with patients with polyps <10 mm and in whom no highly dysplastic polyp was found (.14%; 95% CI, .14-.14). A similar pattern was observed for PCCRC mortality compared with the CRC mortality in the general population, in which patients with polyps ≥10 mm or HGD had a higher mortality (SMR, 2.05; 95% CI, 1.64-2.57; $P < .001$).

Although it occurs very rarely, PCCRC is an issue that gastroenterological societies are aiming to reduce by

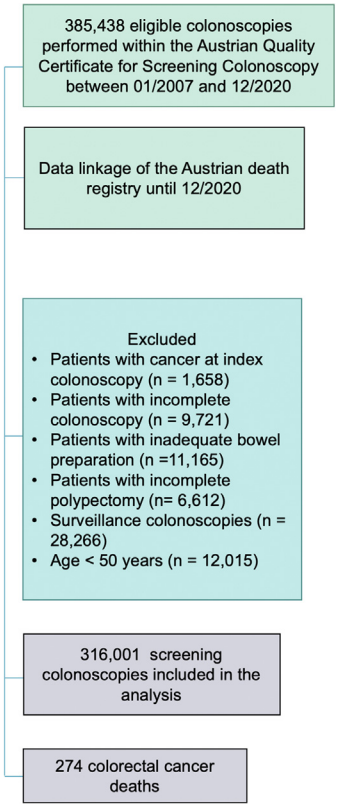

Figure 2. Study cohort characteristics.

recommending surveillance colonoscopy for high-risk patients. The purpose of a well-performing screening program is to lower rates of cancer-specific mortality; however, little robust evidence of polyp findings and their cutoffs that are associated with mortality outcomes in screening patients exists. Recent reports of PCCRC incidence and mortality after colonoscopy have focused on outcomes in predefined proposed risk groups.[4,17,18] We found that there is an association between polyp size as well as grade of dysplasia with PCCRC mortality. We found no significant association with PCCRC death of patients with polyps <10 mm (HR, 1.11; 95% CI, .83-1.49; $P = .5$). This might imply that a size cutoff of 10 mm could be most appropriate to opt for surveillance colonoscopy.[7,8] Reasons for PCCRC development are still poorly understood. The WHO considers 2 main pillars of PCCRC development: procedural characteristics, on one hand, in which lesions are either "undetected" due to low quality of the colonoscopy or detected but incompletely resected; in case the procedure quality was sufficient, on the other hand, poor adherence to surveillance recommendations or improper surveillance intervals might be culprits for PCCRC.[3] In our cohort, only high-quality colonoscopies were included, and endoscopists reported that polyps were completely removed in 81.1% of patients. However, because it is not mandatory for endoscopists to report surveillance colonoscopies of patients with polyps, we cannot exclude that some patients missed a follow-up colonoscopy to resect newly developed polyps. In addition, the database lacks assessment of resection margins by the pathologists, and resection techniques such as piecemeal EMR are not recorded (Supplementary Table 3, available online at www.giejournal.org).

Although a lower risk of PCCRC death compared with CRC mortality in the general population could be observed in patients with polyps <10 mm (96.3% of patients) without HGD (99.5% of patients), this was not observed for patients with larger or highly dysplastic polyps. Instead, the observed count of CRC deaths in this subgroup was higher than what was expected in the general population, although these patients had a screening colonoscopy. These patients might need more stringent surveillance management to reduce the risk of PCCRC death below the general risk of CRC death in the largely unscreened population. In contrast, when applying the definition of advanced adenomas (adenomas with villous/tubulovillous histology, adenomas with HGD, and size ≥10 mm) to our cohort, PCCRC mortality was not significantly higher in relation to the CRC mortality in the population. In a previous study, we found that a high-risk classification excluding villous histology had a stronger association with PCCRC death, whereas there was no significant increase in PCCRC mortality when patients without villous polyps were moved to the low-risk group.[19] These data suggest that stratification based only on polyp size and dysplasia grade helps separate out a small group with high residual risk of CRC. However, more studies are needed to investigate the effectiveness and harms of colonoscopy surveillance in this subgroup.

The comparison of observed and expected CRC mortality in the population should be regarded with caution, as Austria has an opportunistic screening program. This program might introduce a self-selection bias, as screening participants are believed to be healthier than those not choosing preventative services. The risk for CRC death in the cohort might therefore be lower than the risk in the whole population.[16,20]

One study has investigated the impact of polyp size on incident CRC and CRC mortality in screening patients, finding only small but significantly higher hazards for CRC death after the diagnosis of polyps <20 mm and without HGD compared with patients without adenomas.[12] The authors proposed to narrow down the classification of high-risk patients at need for surveillance to those with polyps ≥20 mm or HGD. However, in our study, the association of polyp size with PCCRC mortality was strong already for individuals with polyps 10 to 20 mm (HR, 4.00; 95% CI, 2.46-6.50; $P < .001$). These data support a more stringent approach of high-risk classification, in line with current guideline recommendations of a 3-year surveillance interval by the U.S. Multi-Society Task Force on Colorectal Cancer, with a cutoff of 10 mm.[7] However, more studies are needed to determine CRC mortality among different screening populations in various size categories.

TABLE 4. Comparison of CRC mortality to the general Austrian population

Category	Observed CRC deaths	Expected CRC deaths	Person-years	SMR (95% CI)	*P* value
≥10 mm or HGD	76	37.04	64,015.66	2.05 (1.64-2.57)	<.001
<10 mm, no HGD	81	303.87	598,333.63	.27 (.21-.33)	<.001
Advanced adenoma	80	65.51	108,421.1	1.22 (.98-1.52)	.07395
Nonadvanced adenoma	77	275.41	553,942.6	.28 (.22-.35)	<.001
Negative colonoscopy	117	481.16	1,064,587.91	.24 (.2-.29)	<.001

Annual CRC mortality rates were calculated according to category of polyp findings (≥10 mm or HGD/<10 mm, no HGD, advanced adenoma or no advanced adenoma) and for patients with a negative colonoscopy. Advanced adenomas were defined as polyps with tubulovillous or villous histology, HGD, or a polyp ≥10 mm. SMRs were adjusted for 5-year age group, sex, and year of death.
CRC, Colorectal cancer; *SMR*, standardized mortality ratio; *CI*, confidence interval; *HGD*, high-grade dysplasia.

In colorectal polyps, size alone is strongly associated with grade of dysplasia, a feature indicating increased malignant potential.[21,22] Individuals who are being diagnosed with polyps ≥10 mm at screening colonoscopy might therefore be the subjects in whom this threshold of carcinogenesis has been passed. However, there is a lack of robust studies that evaluate tumor biology in polyps for markers indicating likelihood of malignant transformation and its effect on long-term PCCRC occurrence. Many studies that investigated the impact of dysplasia grade on the risk of malignancy were either of small sample size or based on the occurrence of advanced adenomas as an outcome measure.[23,24] The association of HGD with CRC mortality in our cohort is strong (HR, 6.61; 95% CI, 3.31-13.2; $P < .001$) and in line with previous evidence of 2 large screening cohorts in terms of CRC incidence[12,25] and mortality.[12]

The current study has some limitations. First, we do not have complete information on count of adenomas, as this variable was only introduced later in the database. We therefore could not include this variable in the regression analyses. However, the consideration of multiplicity as a standalone risk factor for PCCRC mortality is debated.[7,12] Adenoma multiplicity (≥3) failed to show an association with CRC in patients with nonadvanced adenomas (adenomas <10 mm, without HGD) in a trial of 15,935 flexible sigmoidoscopy participants, highlighting that the occurrence of multiple adenomas alone might not confer a higher risk for CRC mortality, unless at least 1 polyp with advanced pathology is identified.[17]

A second limitation is the assessment of polyp size. Lesion size of colorectal polyps was assessed during endoscopy and not by the referred pathologist. The standard practice for size determination in Austria is measurement during colonoscopy, a source of bias for several reasons. When size categories are present, endoscopists tend to assign some diameters more frequently than others, leading to overestimation and underestimation of true size.[26-29] Furthermore, image distortion through the endoscope lens makes polyp size determination dependent on the angle of view.[30] Size measurements of pathology, however, are also prone to error. Polyp resection leads to skewed tissue, and cover slide application leads to sample spread.[31,32] To date, there is no standard for the correct measurement of polyp size. Third, a limitation is the lack of incident CRC after colonoscopy, as it might have added valuable information in terms of risk factors associated with the occurrence of PCCRC alone. Knowledge about incident CRC in our cohort, especially stages that patients presented with at PCCRC diagnosis, would have helped to better characterize disease progression from screening-detected polyps to CRC death. In addition, we did not have complete information on surveillance visits of patients after the index colonoscopy, which would have helped to further stratify risk. A study from the United Kingdom suggests that a single surveillance colonoscopy can reduce PCCRC risk by one-half in high-risk patients.[33] However, in this study, patients with incomplete colonoscopy or HGD with no information on polyp size were considered high-risk patients, whereas in our study, only complete colonoscopies were included.

Another limitation is that we are unable to assess the histologic types of SSL and traditional serrated adenoma, as these categories were introduced in the reporting form in 2012. Furthermore, because this was a retrospective study conducted during a time period in which the distinction of hyperplastic polyps from sessile serrated lesions was evolving, we cannot exclude possible misclassifications of SSL as HP. The grading of SSL is no longer recommended in the current WHO classification of digestive tumors from 2019; however, SSL had a dysplasia grade assigned in our cohort. The grading of serrated polyps did adhere to the previous WHO classification from 2010.[34] The recommendation to not grade SSL is due to interobserver variation in grading assessment, and currently any SSL exhibiting dysplasia is considered a malignant progression to CRC.[35] Society guidelines of the European Society of Gastrointestinal Endoscopy, the U.S. Multi-Society Task Force on Colorectal Cancer, and the British Society of Gastroenterology recommend surveillance colonoscopy for patients with serrated polyps with any kind of dysplasia, as the risk for CRC might be equal or even higher compared with patients with adenomas. However, size in SSLs is also a main determinant for synchronous dysplasia, and increasing size confers higher CRC risk.[36,37] Patients with hereditary cancer or polyp syndromes are not eligible

for inclusion in the database. However, a limitation of this study is the lack of information on genetic testing to exclude incidental or new diagnoses of these conditions.

In conclusion, this study is a large analysis of CRC mortality outcome after the diagnosis of colorectal polyps of different size cutoffs (<10 mm, 10-20 mm, or >20 mm) as well as dysplasia grades (low-grade dysplasia or HGD). We conclude that polyp size as well as polyp dysplasia are associated with CRC death after screening colonoscopy. Patients with polyps ≥10 mm or with HGD might benefit most from surveillance colonoscopy. Future studies will elucidate the mechanisms of PCCRC development in these high-risk patients.

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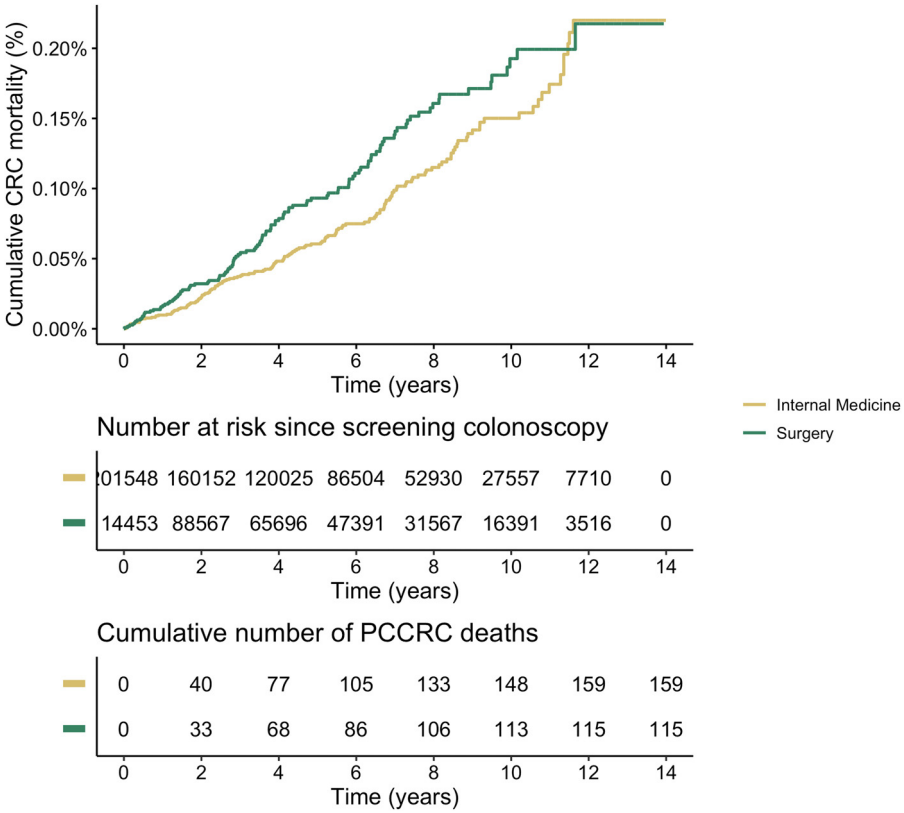

Supplementary Figure 1. Cumulative incidence of post-colonoscopy colorectal cancer (PCCRC) death according to endoscopy specialty. In Austria, screening colonoscopies can be performed by physicians practicing either internal medicine or surgery. *CRC*, Colorectal cancer.

SUPPLEMENTARY TABLE 1. Baseline adenoma detection rate (rate of detected villous, tubulovillous, and tubular adenomas) and serrated polyp detection rate (rate of detected sessile serrated lesions, traditional serrated adenomas, and hyperplastic polyps) by specialty in internal medicine or surgery as well as endoscopists' setting

	Internal medicine (n = 201,548)	Surgery (n = 114,453)	Hospital (n = 66,129)	Private practice (n = 239,182)	Outpatient clinic (n = 10,690)	Overall (N = 316,001)
Adenoma detection rate						
Mean ± SD	21.3 ± 8.03	20.5 ± 8.03	21.5 ± 7.25	20.8 ± 8.33	22.3 ± 5.42	21.0 ± 8.04
Median (Q1, Q3)	20.9 (16.0, 26.9)	19.4 (15.7, 25.3)	20.5 (16.6, 25.9)	19.8 (15.4, 26.8)	21.3 (20.4, 24.0)	20.1 (15.8, 26.5)
Serrated polyp detection rate						
Mean ± SD	19.4 ± 10.6	19.7 ± 10.2	17.9 ± 7.95	19.8 ± 11.1	21.2 ± 6.79	19.5 ± 10.4
Median (Q1, Q3)	17.9 (12.2, 24.5)	17.9 (13.2, 24.6)	16.2 (12.6, 22.5)	18.1 (12.1, 25.0)	19.4 (17.2, 26.7)	17.9 (12.5, 24.5)

SD, Standard deviation; *Q1*, first quartile; *Q3*, third quartile; *SDR*, serrated polyp detection rate.

SUPPLEMENTARY TABLE 2. Sensitivity analysis

Characteristic	Hazard Ratio	95% CI	*P* value
Polyp size			
No polyp	—	—	
<10 mm	1.17	.87-1.56	.30
10-20 mm	4.40	2.71-7.12	<.001
>20 mm	19.3	11.91-31.35	<.001
Dysplasia grade			
None	—	—	
Low-grade	1.16	.87-1.56	.29
High-grade	7.10	3.57-14.13	<.001

Multivariable hazard ratios with 95% CIs are presented for polyp size and grade of dysplasia. Because surveillance colonoscopy alters subsequent colorectal cancer risk, patients were censored at follow-up colonoscopy. Categories are given of patients diagnosed with at least one polyp <10 mm, 10 to 20 mm or >20 mm, at least one with low grade or high-grade dysplasia, adjusted for patient sex and age.
CI, Confidence interval.

SUPPLEMENTARY TABLE 3. Resection technique according to polyp size at polypectomy

Resection technique	Polyps <10 mm (n = 116,813)	Polyps 10-20 mm (n = 8392)	Polyps >20 mm (n = 3192)	Overall (N = 128,397)
Cold snare	21,082 (18.0%)	2703 (32.2%)	597 (18.7%)	24,407 (7.7%)
Hot snare	12,285 (10.5%)	4128 (49.2%)	1084 (34.0%)	17,510 (5.5%)
Unknown	83,446 (71.4%)	1561 (18.6%)	1511 (47.3%)	274,084 (86.7%)