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Risk stratification of individuals with low-risk colorectal adenomas using clinical characteristics: a pooled analysis

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Abstract

Objective—For individuals with 1–2 small (<1 cm) low-risk colorectal adenomas, international guidelines range from no surveillance to offering surveillance colonoscopy in 5–10 years. We hypothesised that the risks for metachronous advanced neoplasia (AN) among patients with low-risk adenomas differ based on clinical factors distinct from those currently used.

Design—We pooled data from seven prospective studies to assess the risk of metachronous AN. Two groups with 1–2 small adenomas were defined based on guidelines from the UK (n=4516) or the European Union (EU)/US (n=2477).

Results—Absolute risk of metachronous AN ranged from a low of 2.9% to a high of 12.2%, depending on specific risk factor and guideline used. For the UK group, the highest absolute risks for metachronous AN were found among individuals with a history of prior polyp (12.2%), villous histology (12.2%), age ≥70 years (10.9%), high-grade dysplasia (10.9%), any proximal adenoma (10.2%), distal and proximal adenoma (10.8%) or two adenomas (10.1%). For the EU/US group, the highest absolute risks for metachronous AN were among individuals with a history of prior polyp (11.5%) or the presence of both proximal and distal adenomas (11.0%). In multivariate analyses, strong associations for increasing age and history of prior polyps and odds of metachronous AN were observed, whereas more modest associations were shown for baseline proximal adenomas and those with villous features.

Conclusions—Risks of metachronous AN among individuals with 1–2 small adenomas vary according to readily available clinical characteristics. These characteristics may be considered for recommending colonoscopy surveillance and require further investigation.

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer death worldwide[1] and can be prevented by detection and removal of colorectal polyps.[2–11] Surveillance colonoscopy is often recommended after polypectomy to further reduce the risk of subsequent CRC. Practice guidelines generally base recommendations for surveillance on baseline polyp characteristics, with differing recommendations for low-risk versus high-risk adenomas. Importantly, there are significant variations by geographical region in both the definition of baseline low risk, as well as recommendations for follow-up among individuals with 1–2 small adenomas <1 cm in size[12–15] (table 1). Specifically, for definition of low-risk groups, United States Multisociety Task Force on Colorectal Cancer (USMSTF) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines exclude individuals with high-grade dysplasia or tubulovillous or villous features within adenomas, European Union (EU) guidelines offer the option of excluding individuals with these criteria from the lowest risk group, while the UK National Institute for Health and Care guidelines include these individuals. For follow-up of their respective low-risk groups, USMSTF guidelines recommend offering surveillance colonoscopy in 5–10 years, ESGE guidelines recommend return to screening in 10 years, EU guidelines recommend against routine surveillance colonoscopy, while the UK guidelines recommend consideration of surveillance colonoscopy at 5 years. Few data exist to guide identification of patients with 1–2 small adenomas who might benefit from early (eg, 5 year) surveillance, versus those who might

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either defer surveillance colonoscopy for 10 years, return to routine screening in 10 years or avoid further screening or surveillance altogether.

From both a patient and a societal perspective, the implications of having a colonoscopy in 5 years vs 10 years, or not at all, are substantial with respect to risk exposure, time burden and costs.[16] Therefore, additional evidence on which to base recommendations for individuals meeting current low-risk criteria at baseline colonoscopy is needed.

We hypothesised that risk for metachronous advanced neoplasia (AN) among patients with 1–2 small adenomas differs based on clinical factors beyond those used in current guidelines. Accordingly, we conducted analyses using a large, pooled data set of individuals who received surveillance colonoscopy to determine variation in risk for metachronous AN among individuals with 1–2 small adenomas at baseline across a range of clinical factors.

METHODS

Study participants and data sources

Data from patients with previously resected colorectal adenomas participating in six chemoprevention trials and one cohort study conducted in North America were available for pooling.[17–23] As previously reported,[24] the pooling study protocol required a complete baseline colonoscopy with the removal of one or more adenomas and all visualised lesions, a specified schedule of surveillance follow-up colonoscopies, and availability of end point data about the adenoma features and CRC detected at follow-up. Patients with a history of prior polyps were eligible for inclusion in the chemoprevention trials but not in the Veterans Affairs Study. The studies used self-administered questionnaires to ascertain patient-level characteristics (age, sex, smoking history, history of CRC in first-degree relatives and history of colorectal polyps preceding the baseline colonoscopy). Data on the number, size, location and histological characteristics of baseline adenomas were abstracted from endoscopy and pathology reports. Adenoma size was ascertained from the pathology report and when this was missing, we used size from the endoscopy report. The coordinating centres for each study obtained approval from their respective institutional review boards for the current protocol.

In the seven studies, 4711 patients had 1–2 small adenomas at baseline. Of these, 195 could not be classified as having metachronous AN due to missing data on histology or high-grade dysplasia, resulting in 4516 patients who met the UK criteria for low risk. We recognise that the EU guidelines offer the option of excluding patients with villous component or high-grade dysplasia from the lowest risk group, and in this analysis have assumed that patients with these features were treated as high risk, similar to USMSTF and ESGE guidelines. Therefore, in this paper, the EU/USMSTF/ESGE group (hereafter referred to as the EU/US group) included individuals with adenomas 1 to 2 <1 cm in size, without the presence of high-grade dysplasia or villous features. To arrive at the EU/US patient group, we excluded 540 and 1133 participants with missing histology and high-grade dysplasia data, respectively. We further excluded 366 patients classified as high risk by having adenomas with villous features or high-grade dysplasia from the larger UK group, which resulted in a

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total of 2477 participants in the EU/US group. Details regarding the exclusions are found in the online supplementary table.

Outcome variable and statistical analysis

The outcome variable for this study was AN at 3–5 years after qualifying colonoscopy, defined as the presence of CRC, or the presence of an adenoma containing one or more of the following three features: (1) size ≥1 cm, (2) villous histology and (3) high grade dysplasia. We conducted analyses considering two groups with 1–2 small adenomas defined as those classified as low risk at baseline based on guidelines from the UK (n=4516) or the EU/US (n=2477), as summarised above and in table 1.

The outcome categories for the present analyses were advanced metachronous neoplasia versus no metachronous neoplasia. Results were summarised with two approaches. First, absolute risks and 95% CIs of metachronous AN were calculated to quantify the risk associated with each patient and clinical factor. Second, we employed logistic regression to conduct univariate and multivariate analyses between participant and adenoma characteristics and odds of metachronous AN, expressed as crude and adjusted ORs and 95% CIs. Multivariate modelling was conducted by including all variables that were significant in univariate analysis and all the baseline adenoma characteristics. We provide absolute risks as well as multivariate odds for AN because the two approaches provide complimentary information on risk. Analyses were conducted with STATA V.10.0 (College Station, Texas, USA) and SAS V.9.0 (Cary, North Carolina, USA).

RESULTS

As shown in table 2, demographic and clinical characteristics were similar between the UK and EU/US groups, except for the presence of tubulovillous/villous histology or adenoma with high-grade dysplasia at baseline, which was expected as they were the primary characteristics that differentiate between the UK and the EU/US guidelines for the classification of individuals with 1–2 small adenomas.

Absolute risk of metachronous AN

For all low-risk patients, the absolute risk of metachronous AN was 8.3% for the UK group and 7.6% for the EU/US group. Marked variation in the absolute risk of AN across baseline predictors was noted. For example, for the low-risk group defined by the UK guidelines, the absolute risks of metachronous AN ranged from a low of 3.9% (95% CI 2.5% to 6.0%) for persons under 50 years of age to a high of 12.2% (95% CI 9.3% to 15.9%) for those with a tubulovillous or villous adenoma at baseline, and 12.2% (95% CI 10.5% to 14.1%) for those who reported having polyps prior to the index colonoscopy (table 3 and figure 1). For the low-risk group defined by the EU and US guidelines, the absolute risks of metachronous AN ranged from a low of 2.9% (95% CI 1.4% to 5.9%) for persons under 50 years of age to a high of 11.5% (95% CI 9.3% to 14.3%) for those who reported a history of polyps before the index colonoscopy (table 3 and figure 1). When we restricted the analyses to patients who did not report having a prior polyp, the absolute risks were generally attenuated but the magnitude of the differences persisted (data not shown).

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Multivariate analyses

Table 4 shows crude and multivariate adjusted ORs of the association between patient and adenoma characteristics and odds of AN. Multivariate analyses show general agreement in the relative odds between the UK and the EU/US group (table 4). Strong associations for increasing age and history of prior polyps and odds of metachronous AN were observed in both guideline groups. Statistically significant yet more modest associations for AN were shown for presence of proximal adenomas and those with villous histology at baseline. Although having two adenomas versus one at baseline was significantly associated with metachronous AN, the ORs attenuated and were imprecise in the multivariate model. When we restricted the analysis to patients without a history of polyps, the association for age and metachronous AN continued to be strong and that for baseline proximal lesions was modest but significant; however, the OR for baseline villous histology and AN was attenuated and imprecise (data not shown).

DISCUSSION

Guideline recommendations for surveillance colonoscopy after removal of 1–2 small adenomas vary considerably, ranging from recommendations for performance of surveillance in 5–10 years (USMSTF), no surveillance/return to routine screening in 10 years (EU/ESGE), to consideration of 5-year surveillance (UK, table 1). Guideline variation, in part, may be due to uncertainty regarding risk for metachronous neoplasia among the large, and probably heterogeneous group of individuals with low-risk adenomas at baseline. Indeed, we found substantial variation in risk for metachronous AN across a number of readily available clinical characteristics. For example, according to the presence of various characteristics, absolute risks varied from a low of 3.9% to a high of 12.2% for the UK group, and from a low of 2.9% to a high of 11.5% for the EU/US group. Results from multivariate analyses, which provide data on relative odds of developing metachronous AN, are generally consistent with the results from absolute risk analyses pointing to increasing age, history of previous polyps and presence of proximal adenomas at prior colonoscopy as criteria associated with increased risk.

Our results may have clinical and research implications. Some decision makers may believe that a high threshold should be set for recommending early 5 years or any surveillance at all for individuals with 1–2 small adenomas. In this scenario, it might be noted that none of the clinical characteristics considered in our study was associated with a more than 12% absolute risk of metachronous AN, in which case, our data would support EU guidelines that recommend no surveillance for individuals with low-risk adenomas. Other decision makers may be concerned that current guideline-defined low-risk groups include individuals who might benefit from early surveillance, and note twofold or higher increased odds of metachronous neoplasia, and ≥10% risk of absolute neoplasia were present for individuals with baseline proximal adenoma, age >70 years and history of prior polyp. Of note, even without the ability to confirm histology of prior polyps for all individuals in our analysis, history of prior polyps showed the strongest association with metachronous AN. Our observation of 1.7-fold increased risk for metachronous advanced adenoma among individuals with adenoma containing villous features within the UK group might sway some

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to argue that the EU/US definitions of low risk (which exclude villous histology) are superior to the UK guideline definition. The clinical impact of our observations, if replicated, depends highly on the risk thresholds set to change management, which currently do not exist. For example, in the US, if a 10% or higher threshold of absolute metachronous AN were set to justify special management, patients with low risk adenomas at baseline might be advised to have surveillance colonoscopy in 5 years only if a history of prior polyp or presence of both a distal and proximal adenoma were noted. Such a shift could have significant practice implications by reducing the demand for early, 5-year surveillance colonoscopy. Conversely, if decision makers in the US deemed a 15% risk for metachronous AN (similar to what is observed among individuals with advanced adenoma at baseline[1624]), then guidelines might be changed to advise that no patients with low-risk adenoma receive early 5-year surveillance. To make full use of our observation of substantial variation in metachronous AN risk among individuals with low-risk adenomas at baseline across multiple clinical characteristics, future research is required to replicate our risk findings, and, importantly, determine from patients, providers, and policy makers the optimal risk thresholds that should trigger altered clinical management. Criteria that might be considered for determining the best minimum risk threshold include benefits such as early detection and removal of neoplasia, risks of surveillance colonoscopy, time horizon for benefit (especially relevant for older individuals who may have competing health risks), proportion of individuals requiring specialised surveillance, expected downstream impact of modifying recommendations on colonoscopy resources, baseline risks for AN in a screening population (such as for individuals of similar age) and costs. Overall, our results indicate that considering additional clinical factors, beyond polyp number, size and histology has the potential to contribute to more precise risk stratification and management of individuals with colorectal polyps.

We are not aware of previous reports focused on identifying individuals at increased risk for metachronous AN with only baseline low risk adenomas. Therefore, it is difficult to place our results directly in the context of prior work. In a meta-analysis comparing the risk for metachronous AN among individuals with low-risk adenomas versus normal colonoscopy at baseline, Hassan *et al* reported that the overall risk for metachronous AN was 3.6% for the group with low-risk adenomas versus 1.6% for those with normal colonoscopy.[16] However, an analysis of subgroups of patients who might be at increased risk for AN within either group was not conducted. Our work is consistent with this meta-analysis in confirming that most individuals with low-risk adenomas at baseline have a low risk for metachronous AN, but add to the literature by pointing out several readily available clinical characteristics that may help to identify the subset of patients who might benefit from repeat and/or early colonoscopy surveillance.

Several limitations must be considered in interpreting our results. Our analysis could not consider factors such as type of prior polyp or relationship and age of family members with CRC. In addition, we had incomplete information on variation in bowel preparation across studies, especially those conducted in earlier years. Colonoscopies contributing data were performed between 1984 and 1998. Changes in colonoscopy quality may have occurred over time, such that individuals with only 1–2 small adenomas encountered in clinical practice now might be at even lower risk for metachronous AN than the individuals with 1–2 small

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adenomas included in this study due to increases in awareness of the importance of polyp detection and complete removal. We hypothesise that such a reduction in risk could result from a lower risk of missed lesions, and the potential for higher detection of diminutive lesions of minimal significance with today's high definition colonoscopes. Indeed, our overall rate of metachronous AN for the US/EU group was substantially higher than reported in a recent meta-analysis that included more modern studies[16] (7.6% vs 3.6%). Another limitation is that six of the seven studies contributing to this analysis were from prevention trials, such that the patients contributing data may not be representative of the general population of individuals with 1–2 small adenomas. Furthermore, the primary outcome used was metachronous AN detected at 3–5 years. While metachronous AN is an accepted surrogate marker for CRC risk, the ideal outcome for comparing surveillance intervals would be CRC -related mortality.[25] In practice, it is unclear whether there is a substantial clinical benefit to detecting metachronous AN at 5 vs 10 years among individuals with only 1–2 small adenomas at baseline. We did not have data on sessile serrated adenomas/polyps, which were not commonly recognised during the timeframe studies contributing data were completed.

Our pooled study also has considerable strengths, including the prospective design of studies contributing data, pooling of individual patient-level data and consideration of four different international guidelines for postpolypectomy surveillance of individuals with low-risk adenomas.

In conclusion, substantial variation in the risk of metachronous AN among individuals with 1–2 small adenomas exists according to readily available clinical characteristics. Considering these characteristics for risk stratification might reduce both underuse and overuse of surveillance colonoscopy, and ultimately optimise the risks and benefits of programmatic postpolypectomy surveillance. Additionally, the limitations of currently available predictors for metachronous AN call for research on novel approaches for risk stratification of individuals with colorectal polyps. Specifically, future work should investigate whether additional patient, polyp and/or quality factors (such as the adenoma detection rate of the colonoscopist who performed the polypectomy) can offer more precise post polypectomy risk stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance of this study

What is already known on this subject?

- International recommendations for follow-up surveillance of individuals with 1–2 small colorectal adenomas are highly variable.
- Recommendations range from promoting no surveillance to offering colonoscopy in 5–10 years.
- Data to support current recommendations are sparse.

What are the new findings?

- Absolute risk of metachronous advanced neoplasia (AN) ranged from a low of 2.9% to a high of 12.2%, depending on specific risk factors and guidelines used.
- Multivariate relative risks also confirmed variation in risk for metachronous AN across multiple different clinical characteristics.
- Several factors not consistently used across guidelines (presence of villous histology, presence of high-grade dysplasia and prior polyp history) or currently used within guidelines (presence of proximal adenoma and two adenomas) were associated with an increased risk for metachronous AN.

How might it impact on clinical practice in the foreseeable future?

- Among individuals with 1–2 small adenomas at baseline, characteristics such as presence of proximal adenoma, adenoma with villous or high-grade histology, two adenomas, or history of prior polyp may be considered for recommending colonoscopy surveillance.

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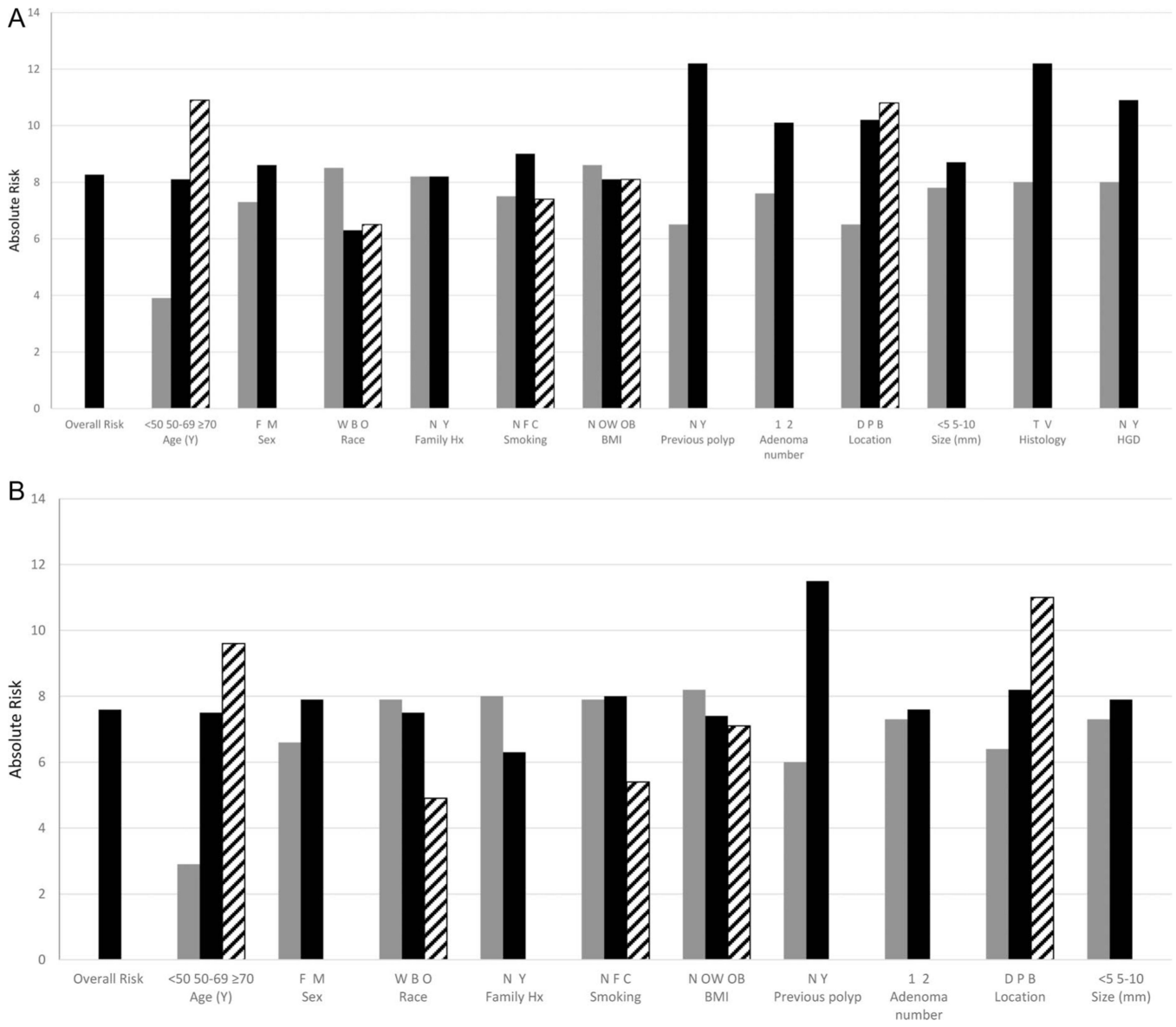

Figure 1.

Absolute risk of advanced neoplasia at follow-up evaluation, according to baseline patient and adenoma characteristics among individuals with low-risk adenomas according to UK guidelines (A) and European Union (EU)/US (B) guidelines. Age groups (years); sex (F=female, M=male); race (W=white, B=black, O=other); family Hx is family history of colorectal cancer (N=no, Y=yes); smoking (N=never, F=former, C=current); BMI is body mass index (N=normal weight BMI <25 kg/m^2; OW=overweight BMI ≥25 kg/m^2 and BMI<30 kg/m^2; OB=obese BMI ≥30 kg/m^2); prev polyp is history of a previous polyp (N=no, Y=yes); number is number of baseline adenomas (<5 mm and ≥5 to <10 mm); histology is histology of baseline adenomas (T=tubular; V=tubulovillous or villous); HGD is high-grade dysplasia in baseline adenomas (N=no, Y=yes).

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Table 1

Guideline definitions of individuals with low-risk baseline adenomas and recommended management

Guideline	Definition of low risk	Recommended management
USMSTF 2012[13]	1–2 adenomas, both smaller than 1 cm, without villous histology or high-grade dysplasia	Offer repeat colonoscopy in 5–10 years
ESGE[15] 2013	1–2 adenomas, both smaller than 1 cm, without villous histology or high-grade dysplasia	Return to screening after 10 years if screening programme available, otherwise repeat colonoscopy in 10 years
EU 2010[12]	1–2 adenomas, both smaller than 1 cm, without villous histology or high-grade dysplasia *	Routine screening (no routine surveillance colonoscopy)
UK National Institute for Health and Care Excellence (NICE) guideline 2011[14]	1 –2 adenomas, both smaller than 1 cm	Consider repeat colonoscopy in 5 years

* European Union guidelines offer the option of including patients with villous histology or high-grade dysplasia in the low-risk group.

ESGE, European Society of Gastrointestinal Endoscopy; EU, European Union; USMSTF, United States Multisociety Task Force on Colorectal Cancer.

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Table 2

Baseline characteristics of individuals with low-risk adenomas as defined by UK and EU/US guidelines

Characteristic	UK definition* n=4516	EU/US definition† n=2477
Age (years, mean±SD)	61.7±9.5	62.3±9.3
Male (n, %)	3205 (71.0)	1825 (73.7)
Race (n, %)		
White	4034 (89.3)	2227 (89.9)
Black	237 (5.3)	147 (5.9)
Other	245 (5.4)	103 (4.2)
Family history of colorectal cancer‡ (n, %)		
Yes	1054 (23.3)	525 (21.2)
No	3174 (70.3)	1875 (75.7)
Unknown	288 (6.4)	77 (3.1)
Cigarette smoking status (n, %)		
Never	1562 (34.6)	814 (32.9)
Former	2241 (49.6)	1261 (50.9)
Current	691 (15.3)	387 (15.6)
Unknown	22 (0.5)	15 (0.6)
Body mass index in kg/m^2 (n, %)§		
<25	1297 (28.7)	679 (27.4)
25 to <30	2049 (45.4)	1145 (46.2)
≥30	1161 (25.7)	650 (26.2)
Previous polyp (n, %)¶		
Yes	1313 (29.1)	641 (25.9)
No	3113 (68.9)	1780 (71.9)
Unknown	90 (2.0)	56 (2.3)
Adenoma characteristics		
Number of adenomas (mean±SD)	1.3±0.4	1.2±0.4
Location of adenomas (n, %)		
Distal/rectal only	2201 (48.7)	1224 (49.4)
Proximal only	1754 (38.8)	982 (39.6)
Proximal and distal	397 (8.8)	218 (8.8)
Unknown	164 (3.6)	53 (2.1)
Size of largest adenoma (mm, mean±SD)	4.8±1.9	4.7±1.9
Adenoma histology (n, %)		
Tubular	3579 (79.3)	2477 (100.0)
Tubulovillous/villous	386 (8.6)	0 (0.0)
Unspecified	551 (12.2)**	0 (0.0)
High-grade dysplasia (%)††		
Yes	119 (2.6)	0 (0.0)
No	3264 (72.4)	2477 (100.0)

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[*] Low-risk adenomas defined by UK guidelines as 1–2 adenomas <1 cm in diameter, regardless of histology or dysplasia grade.

[†] Low-risk adenomas defined by US guidelines as 1–2 tubular adenomas <1 cm in diameter, without villous/tubulovillous histology and without high-grade dysplasia.

[‡] Family history of colorectal cancer in at least one first-degree relative. Participants with familial syndromes such as FAP or Lynch were excluded from the parent studies.

[§] Body mass index (BMI) data not available (n=9).

[¶] History of polyps prior to qualifying exam.

[**] Adenoma histology data not available for a subset of UK group patients; these were included in analysis because histology beyond presence of adenoma is not required to be part of UK low risk category.

[††] HGD data not available (n=1133).

EU, European Union; HGD, high-grade dysplasia.

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Table 3

Absolute risk of advanced* neoplasia at follow-up evaluation, according to baseline patient and adenoma characteristics among individuals with low-risk adenomas according to UK guidelines† and EU/US guidelines‡

	UK guidelines (373/4516)		EU/US guidelines (188/2477)	
	No events/no at risk	**Absolute risk (95% CI)**	**No events/no. at risk**	**Absolute risk (95% CI)**
Age (years)				
<50	19/490	3.9 (2.5 to 6.0)	7/243	2.9 (1.4 to 5.9)
≥50 and <70	241/2991	8.1 (7.1 to 9.1)	122/1620	7.5 (6.3 to 8.9)
≥70	114/1035	10.9 (9.2 to 13.0)	59/614	9.6 (7.5 to 12.2)
Sex				
Female	96/1311	7.3 (6.0 to 8.9)	43/652	6.6 (4.9 to 8.8)
Male	277/3205	8.6 (7.7 to 9.7)	145/1825	7.9 (6.8 to 9.3)
Race				
White	342/4034	8.5 (7.7 to 9.7)	172/2227	7.7 (6.7 to 8.9)
Black	15/237	6.3 (3.8 to 10.3)	11/147	7.5 (4.3 to 13.1)
Other	16/245	6.5 (4.0 to 10.4)	5/103	4.9 (2.0 to 11.3)
Family history of colorectal cancer§				
No	260/3174	8.2 (7.3 to 9.2)	150/1875	8.0 (4.5 to 8.7)
Yes	86/1054	8.2 (6.6 to 10.0)	33/525	6.3 (4.5 to 8.7)
Cigarette smoking status¶				
Never	117/1562	7.5 (6.3 to 8.9)	64/814	7.9 (6.2 to 9.9)
Former	203/2241	9.0 (7.9 to 10.3)	102/1261	8.0 (6.7 to 9.7)
Current	51/691	7.4 (5.6 to 9.6)	21/387	5.4 (3.6 to 8.2)
Body mass index in kg/m^2 **				
<25	111/1297	8.6 (7.2 to 10.2)	56/679	8.2 (6.3 to 10.6)
25 to <30	166/2049	8.1 (7.0 to 9.4)	85/1145	7.4 (6.0 to 9.1)
30+	94/1161	8.1 (6.7 to 9.8)	46/650	7.1 (5.3 to 9.3)
Previous polyp††				
No	202/3113	6.5 (5.7 to 7.4)	107/1780	6.0 (5.0 to 7.2)
Yes	160/1313	12.2 (10.5 to 14.1)	74/641	11.5 (9.3 to 14.3)

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	UK guidelines (373/4516)		EU/US guidelines (188/2477)	
	No events/no at risk	**Absolute risk (95% CI)**	**No events/no. at risk**	**Absolute risk (95% CI)**
Adenoma characteristics				
Adenoma number				
1	257/3369	7.6 (6.8 to 8.6)	137/1887	7.3 (6.2 to 8.5)
2	116/1147	10.1 (8.5 to 12.0)	51/590	8.6 (6.6 to 11.2)
Adenoma locations‡‡				
Distal	143/2201	6.5 (5.5 to 7.6)	79/1224	6.4 (5.2 to 8.0)
Proximal	179/1754	10.2 (8.9 to 11.7)	81/982	8.2 (6.7 to 10.1)
Distal and proximal	43/397	10.8 (8.1 to 14.3)	24/218	11.0 (7.5 to 15.9)
Adenoma size (mm)				
<5	170/2179	7.8 (6.7 to 9.0)	91/1255	7.3 (5.9 to 8.8)
5 to <10	203/2337	8.7 (7.6 to 9.9)	97/1222	7.9 (6.5 to 9.6)
Adenoma histology§§				
Tubular	285/3579	8.0 (7.1 to 8.9)	188/2477	7.6 (6.6 to 8.7)
Tubulovillous/villous	47/386	12.2 (9.3 to 15.9)	0	0
High-grade dysplasia¶¶				
No	263/3264	8.0 (7.1 to 9.0)	188/2477	7.6 (6.6 to 8.7)
Yes	13/119	10.9 (6.4 to 18.0)	0	0

*Adenoma ≥1 cm in size; or containing >25% villous or tubulovillous histology; or the presence of high-grade dysplasia; or colorectal cancer.

†Low-risk adenomas defined by UK guidelines as 1–2 adenomas <1 cm in diameter, regardless of histology or dysplasia grade.

‡Low-risk adenomas defined by US guidelines as 1–2 tubular adenomas <1 cm in diameter, without villous/tubulovillous histology and without high-grade dysplasia.

§Family history data unavailable (n=288).

¶Smoking data unavailable (n=22).

**Body mass index data unavailable (n=9).

††Previous polyp data unavailable (n=90).

‡‡Adenoma location data unavailable (n=164).

§§Histology data unavailable (n=551).

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¶¶High-grade dysplasia data unavailable (n=1133).

EU, European Union.

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Table 4

Risk of advanced[*] neoplasia at follow-up evaluation, according to baseline patient and adenoma characteristics among individuals with low-risk adenomas according to UK guidelines[†] and EU/US guidelines[‡]

	UK guidelines (373/4516)			EU/US guidelines (188/2477)		
	n, %	**Crude OR (95% CI)**	**Adjusted OR[§] (95% CI)**	**n, %**	**Crude OR (95% CI)**	**Adjusted OR[§] (95% CI)**
Age (years)						
<50	19 (3.9)	1.00 (ref)	1.00 (ref)	7 (2.9)	1.00 (ref)	1.00 (ref)
≥50 and <70	241 (8.1)	2.46 (1.52 to 3.99)	2.21 (1.10 to 4.45)	122 (7.5)	3.18(1.46 to 6.94)	2.99 (1.29 to 6.95)
≥70	114 (10.9)	3.78 (2.28 to 6.26)	3.05 (1.47 to 6.30)	59 (9.6)	4.64 (2.07 to 10.38)	4.08 (1.71 to 9.76)
Sex						
Female	96 (7.3)	1.00 (ref)	1.00 (ref)	43 (6.6)	1.00 (ref)	1.00 (ref)
Male	277 (8.6)	1.38 (1.08 to 1.76)	1.37 (0.98 to 1.91)	145 (8.0)	1.42 (0.99 to 2.03)	1.39 (0.95 to 2.03)
Previous polyp						
No	202 (6.5)	1.00 (ref)	1.00 (ref)	107 (6.0)	1.00 (ref)	1.00 (ref)
Yes	160 (12.2)	2.35 (1.88 to 2.95)	2.34 (1.73 to 3.18)	74 (11.5)	2.54 (1.84 to 3.51)	2.25 (1.61 to 3.15)
Race						
White	342 (8.5)	1.00 (ref)		172 (7.7)	1.00 (ref)	
Black	15(6.3)	0.75 (0.43 to 1.29)		11 (7.5)	1.07 (0.56 to 2.06)	
Other	16 (6.5)	0.64 (0.38 to 1.08)		5 (4.9)	0.50 (0.20 to 1.26)	
Family history of colorectal cancer						
No	260 (8.2)	1.00 (ref)		150 (8.0)	1.00 (ref)	
Yes	86 (8.2)	1.04 (0.80 to 1.35)		33 (6.3)	0.89 (0.56 to 1.25)	
Cigarette smoking status						
Never	117 (7.5)	1.00 (ref)		64 (7.9)	1.00 (ref)	
Former	203 (9.1)	1.31 (1.02 to 1.66)		102 (8.1)	1.05 (0.75 to 1.47)	
Current	51 (7.4)	1.01 (0.71 to 1.44)		21 (5.4)	0.67 (0.40 to 1.12)	
Body mass index in kg/m^2						
<25	111 (8.6)	1.00 (ref)		56 (8.3)	1.00 (ref)	
25 to <30	166 (8.1)	1.01 (0.78 to 1.30)		85 (7.4)	0.98 (0.68 to 1.41)	
30+	94 (8.1)	1.01 (0.75 to 1.35)		46 (7.1)	0.91 (0.60 to 1.37)	
Adenoma characteristics						

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	UK guidelines (373/4516)			EU/US guidelines (188/2477)		
	n, %	Crude OR (95% CI)	Adjusted OR[§] (95% CI)	n, %	Crude OR (95% CI)	Adjusted OR[§] (95% CI)
Adenoma number						
1	257 (7.6)	1.00 (ref)	1.00 (ref)	137 (7.3)	1.00 (ref)	1.00 (ref)
2	116 (10.1)	1.66 (1.31 to 2.11)	1.26 (0.85 to 1.87)	51 (8.6)	1.54 (1.09 to 2.19)	1.22 (0.78 to 1.92)
Adenoma location						
Distal	143 (6.5)	1.00 (ref)	1.00 (ref)	79 (6.5)	1.00 (ref)	1.00 (ref)
Proximal	179 (10.2)	1.82 (1.44 to 2.30)	1.60 (1.17 to 2.18)	81 (8.3)	1.46 (1.05 to 2.02)	1.41 (1.00 to 1.99)
Distal and proximal	43 (10.8)	2.26 (1.55 to 3.28)	1.74 (0.97 to 3.13)	24 (11.0)	2.53 (1.53 to 4.21)	1.98 (1.04 to 3.79)
Adenoma size (mm)						
<5	170 (7.8)	1.00 (ref)	1.00 (ref)	91 (7.3)	1.00 (ref)	1.00 (ref)
5 to <10	203 (8.7)	1.12 (0.90 to 1.39)	1.17 (0.87 to 1.58)	97 (7.9)	1.13 (0.83 to 1.53)	1.20 (0.87 to 1.66)
Adenoma histology						
Tubular	285 (8.0)	1.00 (ref)	1.00 (ref)	188 (7.6)	N/A[¶]	N/A
Tubulovillous/villous	47 (12.2)	1.52 (1.08 to 2.13)	1.77 (1.17 to 2.66)	0 (0.0)		
High-grade dysplasia						
No	263 (8.1)	1.00 (ref)	1.00 (ref)	188 (7.6)	N/A	N/A
Yes	13 (10.9)	1.42 (0.77 to 2.62)	0.88 (0.41 to 1.88)	0 (0.0)		

[*] Adenoma >1 cm in size, and/or containing >25% villous or tubulovillous histology, presence of high-grade dysplasia or colorectal cancer.

[†] Low-risk adenomas defined by UK guidelines as 1–2 adenomas <1 cm in diameter, regardless of histology or dysplasia.

[‡] Low-risk adenomas defined by US guidelines as 1–2 tubular adenomas <1 cm in diameter.

[§] Models include simultaneous adjustment for all variables.

[¶] Not applicable given that these characteristics are not part of the guidelines.

EU, European Union.