Predicting Outcome in Colonoscopic High-risk Surveillance

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Abstract. *Aim: Surveillance with colonoscopy in risk groups for colorectal cancer needs to be based on an adequate selection of individuals to examine and a well-devised timing. To stratify the risk of finding neoplasia at colonoscopy, a cohort with increased familial risk of colorectal cancer was studied. Patients and Methods: Based on family history, 1,203 individuals with at least two-fold increased risk of colorectal cancer were offered regular colonoscopies. The impact of different variables in the family history was assessed by logistic regression for the prevalence of adenoma and advanced adenoma. Findings at first colonoscopy were assessed regarding the association with risk of future lesions. Results: The prevalence of advanced lesions, when controlling for age, was associated with the number of first-degree relatives with colorectal cancer, with an age below 50 years for the youngest family member with colorectal cancer, but not with gender. Family history had a low impact on the prevalence of simple adenoma. The risk of future advanced lesions was only associated with the prevalence of advanced lesions at the screening colonoscopy, whereas a finding of subsequent adenoma was associated with advanced lesions, adenomas and hyperplastic polyps. Conclusion: Adenomas and advanced lesions were not associated with the same risk factors. In the present study, the most important risk factors for advanced lesions, including cancer, were the number of first-degree relatives and a young family member with colorectal cancer. Findings of simple adenomas and hyperplastic polyps did not seem to be associated with subsequent advanced lesions.*

Colorectal cancer (CRC) is the third most common cancer worldwide and often a lethal disease (1). Approximately 25% of all CRC cases occur in individuals with a family history of CRC. A monogenic disorder causing the disease is diagnosed in fewer than 5% of the cases (2); the most common are Lynch syndrome, caused by a mutation in one of the mismatch-repair genes, and familial adenomatous polyposis, caused by an adenomatous polyposis coli (*APC*) gene mutation. Besides having an inherited high-risk mutation, the most important risk factors for CRC are number of first-degree relatives (FDRs) with CRC and increasing age. Depending on the number of FDRs, the relative risk is increased two- to eightfold compared with those without family history of CRC (3, 4). In the majority of cases, CRCs arise from adenomas in the adenoma–carcinoma sequence (5). Progression from normal colonic mucosa to invasive carcinoma is usually suggested to occur over a period of 4-10 years (6), except in Lynch syndrome, where the progression is observed to be faster (7). Colonoscopic prevention of CRC is feasible by removal of premalignant lesions, *i.e.* adenomas, which has been shown to reduce both the incidence of and mortality in CRC (8). Thus, colonoscopic surveillance is recommended in moderate-risk groups for CRC (9). On the other hand, colonoscopy is costly and scarce, and therefore it is important to select individuals suitable for prevention and to have a well-selected timing, regarding both surveillance interval and age at initiation of surveillance. In moderate-risk groups, based on different factors in the family history, it would be profitable to identify subgroups that have the highest risk and assign priority of the colonoscopy resources to these.

Besides age and sex, parameters that can be assessed for impact on risk of CRC are the number of FDRs, second-degree relatives (SDRs) and third-degree relatives (TDRs) with CRC (4, 10, 11), the kind of FDR relationship (sibling or parent) (3, 4), and the age of the youngest affected individual in the family (12). Development of colorectal adenoma is an important precursor to the subsequent development of CRC, and therefore adenoma could serve as a marker for subsequent CRC (10, 13). Thus, the detection of polyps, regarding multiplicity and adenoma advancement, has been suggested to have an impact on detection of additional lesions during surveillance (14).

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We have analysed the outcome of a 20-year colonoscopic surveillance programme to test predictors of future adenoma and advanced lesions. Based on their family history of CRC, 1203 individuals with at least twofold increased risk of CRC were included. Factors taken into account were age; sex; number of FDRs, SDRs and TDRs (cousins) with CRC; kind of FDR (sibling or parent/child); and age of the youngest affected individual in the family.

Patients and Methods

Patients. Since 1990, individuals with an at least two-fold increased relative risk of CRC were offered a programme with genetic counselling and surveillance at the Department of Clinical Genetics at the Karolinska University Hospital in Stockholm, Sweden (15). Data for this study were collected until June 2010. Individuals were included if they had two or more FDR, SDR or cousins (TDR) with CRC, or if they had one FDR below the age of 50 years with CRC. Patients with Lynch syndrome and familial adenomatous polyposis were excluded according to the current clinical protocol, using family history of CRC or polyposis, microsatellite instability, *BRAF* mutation, immunohistochemistry on tumours, or mismatch repair gene screening (16). All individuals were offered screening with an ileocolonoscopy every third year. Patients who had cancer before they entered the surveillance programme were not included in the study. All data were anonymized. The study was approved by the Stockholm regional ethical committee (KI 241/02; 2005/566 - 31/1).

Study protocol. The majority of the colonoscopies were performed at a single centre at Karolinska University Hospital, and the remaining endoscopies were performed elsewhere but reported to the study centre. A standard routine video endoscope was used. The quality of the colonoscopy procedure concerning complete colonoscopies, bowel cleansing, pain control and adenoma detection rate was consistent with European guidelines for quality control of CRC screening (17). For all polyps, the localization, size and appearance was recorded and all polyps were removed and sent for histological diagnosis. In the vast majority of cases, polyps were removed endoscopically: snared, taken by cold biopsy or coagulated. The size of the polyp was estimated with the use of open-biopsy forceps. Lesions in or proximal to the splenic flexure were assigned as right-sided and those distal to the flexure as left-sided. The adenomas were classified according to the WHO classification as tubular, tubulo-villous, villous, or serrated adenomas. The dysplasia was graded as high- or low-grade. An advanced lesion was defined as either cancer, or adenoma with an estimated diameter ≥10 mm, a villous component larger than 20%, or high-grade dysplasia. The surveillance period was defined as the time from the first colonoscopy to the last colonoscopy.

A thorough pedigree of each family was constructed, where all FDR, SDR and cousins (TDR) with CRC, as well as the youngest affected individual, were recorded. For FDRs with CRC, it was recorded whether they were siblings or children/parents. By utilising the curves constructed by Butterworth *et al*. (3) of the cumulative absolute risk of developing CRC over 20 years, the absolute risk was estimated, taking into account the age of the individual and the number of FDRs with CRC. Low age (<50 years) of the index-person was not considered for the absolute risk assessment in this study.

Statistical methods. Analyses were undertaken using the statistical software programme Statistica (version 10.0; StatSoft Inc.©, Tulsa, OK, USA. A *p*-value of less than 0.05 was considered to be statistically significant. Logistic regression with the modelled probability of having an advanced lesion or an adenoma during screening or surveillance was used to determine the impact of different risk factors. The age of the individual, of the youngest in the pedigree, and of the youngest FDR, the sex, number of FDR, SDR and TDR, and the kind of FDR relationship (sibling or parent), were considered. When assessing inheritance, only individuals with either parents or siblings, not both, with CRC were analysed. Age at the first lesion (adenoma or advanced lesion) or, when no lesion was detected, the age at the last colonoscopy, was employed in the logistic regression analyses.

Multicolinearity and interaction were considered when fitting the models, and this was the reason why a Cox regression model was not employed. The number of FDRs and the sum of the numbers of SDRs and TDRs were not independent covariates, and therefore two separate models were employed. In validating the multivariate fitted model, the Hosmere Lemeshow "goodness-of-fit" statistic was employed. A large *p*-value (>0.05) indicated that the null hypothesis (lack of fit) could not be rejected, meaning we do not have reason to believe that the model fitted the data at a non-acceptable level. Student's *t*-test was employed for comparing ages in different subgroups. Incidence of adenomas and advanced lesions at surveillance were analysed by χ^2 test, and for the multivariate analysis, a logistic regression model was employed considering age, sex, time in the study and prevalence of hyperplastic polyps (HP), adenomas and advanced lesions at screening. The estimated number of screening cancers in the cohort was calculated by adding the expected number for each age group extracted from the age- and gender-specific incidence in the Swedish population (18).

Results

Descriptive data. The study covered 20 years of colonoscopic examinations (January 1990 to June 2010). There were 1203 individuals, 470 (39%) men, from 521 families included in the study. There were 676 (56%) individuals with one FDR, 299 (25%) with two or more FDR and 228 (19%) with only SDR and TDR with CRC. Five hundred and seventy-one (47%) individuals had a FDR below the age of 50 years with CRC. In the total population, the mean age at the first colonoscopy was 51.9 (range=17-86; SD=11.8) years, and for men it was 51.1 (range=21-86; SD=12.1) years, and for women 52.3 (range=17-84; SD=11.3). In total, 2293 colonoscopies were performed, and 594 (49.4%) individuals had two or more examinations performed. A relatively large cohort was recruited by the end of the study, and therefore 50.6% had only one colonoscopy examination performed. The mean follow-up time for those who participated in surveillance was 55 (SD 32) months.

Colonoscopy findings. There were five individuals (0.4%) with six carcinomas; four were detected at the screening colonoscopy and two during surveillance. The expected number of screening carcinomas in the Swedish population

Table I. *Univariate and bi-variate (controlling for age) logistic regression analysis of family history variables associated with having simple adenoma or advanced lesion (n=1203).*

		Univariate analysis			Controlling for age		
Variable	Level of effect	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Simple adenoma							
Gender	Men (n=470)	1.08	0.94-1.22	0.58	1.10	0.96-1.24	0.50
	Women (n=733)	1.00			1.00		
Horizontal/vertical[1]	Siblings (n=207)	0.98	0.83-1.21	0.44	0.86	0.73-1.04	0.46
	Parent/child (n=568)	1.00			1.00		
Age, youngest in	<50 Years (n=383)	0.85	0.63-1.14	0.29	0.92	0.80-1.06	0.57
family	>50 Years (n=820)	1.00			1.00		
N FDR		1.18	0.99-1.41	0.06	1.11	0.92-1.34	0.28
N SDR		1.09	0.97-1.21	0.17	1.11	0.98-1.26	0.09
N TDR		1.08	0.94-1.23	0.29	1.12	0.96-1.30	0.15
N SDR+TDR		1.08	0.99-1.17	0.10	1.10	1.01-1.19	0.03
Age of individual[2]		1.01	1.00-1.02	0.03			
Advanced adenoma							
Sex	Men (n=470)	1.21	0.80-1.84	0.37	1.28	1.07-1.49	0.26
	Women (n=733)	1.00			1.00		
Horizontal/vertical[1]	Siblings (n=207)	2.10	1.25-3.53	0.004	1.40	0.80-2.47	0.24
	Parent/child (n=568)	1.00			1.00		
Age, youngest in family	<50 Years (n=383)	1.23	0.97-1.68	0.35	1.62	1.19-2.53	0.04
	>50 Years (n=820)	1.00			1.00		
N FDR		1.75	1.50-2.00	<0.0001	1.38	1.10-1.66	0.03
N SDR		0.79	0.63-0.98	0.04	0.85	0.63-1.07	0.16
N TDR		0.87	0.60-1.14	0.32	0.97	0.71-1.23	0.80
N SDR+TDR		0.84	0.68-1.00	0.04	0.91	0.75-1.07	0.26
Age of individual[2]		1.05[3]	1.03-1.07	<0.0001			

[1]Only those with horizontal (siblings) or vertical (parent/child) inheritance were included (n=775). [2]Age at finding of simple adenoma or advanced adenoma, otherwise age at last colonoscopy. [3]OR per year increase. OR: Odds ratio, CI: confidence interval, FDR: first-degree relatives, SDR: second-degree relatives, TDR: third-degree relatives. N: number of patients.

matched for age and gender (18) was calculated to be 0.8 compared to the four that were found ($p<0.001$).

At least one simple adenoma was found in 228 (19%) of the individuals and 94 (8%) had at least one advanced adenoma, or cancer as the most advanced lesion. HP was encountered as the most advanced lesion in 208 (17%) persons. In 672 (56%) of the individuals, no polyps were recorded.

Risk factors in family history. Table I shows data for univariate and bivariate (controlling for age) analyses, and Table II shows the multivariate logistic regression analysis for the outcome of having adenomas and advanced lesions during screening or surveillance. Increased age was the strongest risk factor for both adenoma and advanced lesions. A difference was that the risk of adenomas was weakly associated with the sum of SDRs and of TDRs, while the risk of advanced lesions was associated with the number of FDRs. There was also an association with early age at onset in the family (<50 years) with having advanced lesions but not with having adenoma. There was no difference between men and women regarding the risk of adenoma or advanced lesions. Likewise, there was no difference in the risk related to the kind of FDR relationship, except for the univariate analysis for advanced lesions, where a strong association for siblings was seen, although this association was lost when controlling for age in the bivariate analysis.

The absolute risk of developing cancer over 20 years, as estimated from Butterworth *et al*. (3), correlated significantly both with having a simple adenoma [odds ratio (OR)=1.09, $p=0.0005$] and with having an advanced lesion (OR=1.24, $p<0.0001$). Due to the fact that this absolute risk was based both on age and on the number of FDRs with CRC, it was not possible to introduce this as a variable in a multivariate analysis because of multicolinearity.

Findings at screening colonoscopy as risk factors. Table III and IV summarize the univariate and multivariate analyses regarding the association between colonoscopic findings at screening and findings during surveillance. The univariate analysis revealed that prevalence of HP and adenoma, as well as advanced lesions, at screening were associated with

Table II. *Multivariate logistic regression analysis of family history variables associated with having a simple adenoma or an advanced lesion (n=1203).*

		Model 1			Model 2		
Variable	Level of effect	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Simple adenoma		#	##				
Gender	Male *vs*. female	1.10	0.84-1.45	0.50	1.07	0.81-1.42	0.62
Age of individual[1]		1.01[2]	1.00-1.02	0.16	1.02	1.00-1.03	0.01
Age youngest <50	Yes *vs*. no	0.90	0.66-1.22	0.49	0.91	0.70-1.23	0.53
N FDR		1.12	0.93-1.36	0.16			
N SDR+TDR					1.10	1.01-1.21	0.04
Advanced lesion		###	####				
Gender	Male *vs*. female	1.28	0.83-1.96	0.26	1.26	0.82-1.94	0.29
Age of individual[1]		1.04	1.02-1.06	0.0001	1.05	1.03-1.07	<0.0001
Age youngest <50 years	Yes *vs*. no	1.53	0.97-2.42	0.07	1.7	1.00-2.47	0.05
N FDR		1.34	1.01-1.77	0.04			
N SDR+TDR					0.91	0.76-1.07	0.24

[1]Age at finding of simple adenoma or advanced adenoma, otherwise age at last colonoscopy. [2]OR per year increase. Hosmere Lemeshow goodness-of-fit statistic (HL): #*p*=0.30; ##*p*=0.34; ###*p*=0.60; ####*p*=0.90. N: number of; FDR: first-degree relatives; SDR: second-degree relatives; TDR: third-degree relatives; OR: odds ratio; CI: confidence interval.

findings of adenoma during surveillance. On the other hand, only an advanced lesion at screening was associated with a higher incidence of advanced adenoma during surveillance. These results were re-affirmed in the multivariate analysis, where in cases of advanced lesions, time in the study and increasing age were associated with increased risk of these.

Discussion

Surveillance by colonoscopy is commonly recommended for individuals with increased risk of CRC due to family history, but recommendations for the interval between the examinations and the age at initiation of screening are not unanimous. Our key issue was whether some of the known risk factors were more powerful than others in predicting risk of developing CRC during surveillance. Therefore, 1,203 individuals with family history of CRC, who participated in a colonoscopy prevention programme, were studied regarding family history and the role of findings at the screening colonoscopy and of subsequent findings during surveillance. Due to the circumstance that very few cases of cancer were detected, the prevalence of advanced lesions was used instead of CRC as end-point when assessing the risks for CRC.

Our results regarding age were in line with other studies. Increased age is a well-recognised risk factor for CRC and adenoma in the context of sporadic cases, as well as in cases with family history of CRC (19, 20).

One important aim was to explore whether having more distant relatives than FDRs with CRC had an impact on the prevalence of adenoma and advanced lesions. We noticed that the risk of advanced lesions increased with the number of FDRs with CRC in univariate as well as multivariate analysis (OR=1.3, *p*=0.04). This phenomenon was not noted for risk of adenomas, but on the other hand, the sum of SDRs and

Table III. *Univariate analysis of correlation of colonoscopy findings at screening and during follow-up (n=594).*

Variable	N	N with adenoma (%)	χ^2	*p*-Value
Adenoma incidence during follow-up				
HP at screening				
Yes	174	53 (30.5)	11.06	0.0008
No	420	76 (18.1)		
Adenoma at screening				
Yes	149	63 (42.3)	49.48	<0.0001
No	445	66 (14.8)		
Advanced lesion at screening				
Yes	55	20 (36.4)	7.65	0.006
No	539	109 (20.2)		
Advanced lesion incidence during follow-up				
HP at screening				
Yes	174	11 (6.3)	0.29	0.86
No	420	25 (6.0)		
Adenoma at screening				
Yes	149	12 (8.1)	1.38	0.24
No	445	24 (5.4)		
Advanced lesion at screening				
Yes	55	11 (20.0)	20.68	<0.0001
No	539	25 (4.6)		

N: Number of individuals; χ^2: Chi-square; HP: hyperplastic polyp.

Table IV. *Multivariate logistic regression analysis of status at screening colonoscopy associated with having a simple adenoma or an advanced lesion during follow-up (n=594).*

Variable	Level of effect	OR	95% CI	*p*-Value
Simple adenoma	#			
Gender	Male *vs*. female	1.25	0.80-1.96	0.32
Age		1.02	1.00-1.04	0.08
Time in study (years)		1.19	1.11-1.29	<0.0001
HP Yes/no		1.64	1.05-2.58	0.03
Ad Yes/no		4.29	2.73-6.73	<0.0001
AAd Yes/no		2.74	1.41-5.35	0.003
Advanced adenoma	##			
Gender	Male *vs*. female	0.91	0.44-1.89	0.80
Age		1.051	1.02-1.09	0.004
Time in study (years)		1.16	1.04-1.29	0.009
HP Yes/no		0.89	0.41-1.92	0.76
Ad Yes/no		1.25	0.59-2.67	0.56
AAd Yes/no		5.22	2.30-11.84	<0.0001

[1]OR per year increase. #HL p=0.99. ##HL p=0.32. OR: Odds ratio, CI: confidence interval; HP: Hyperplastic polyp; Ad: simple adenoma; Aad: advanced adenoma (including cancer); HL: Hosmere Lemeshow goodness-of-fit statistic.

TDRs seemed to have a weak influence on the prevalence of adenoma but not on that of advanced lesions. Our results were in line with a recent study which did not find a direct relationship between number or closeness of affected relatives and frequency of adenoma (21). On the other hand, as shown in a meta-analysis by Wilschut *et al*. (22), for the risk of developing adenoma the existence of family history (defined as at least one FDR with CRC) seemed to be more important than the exact number of FDRs with CRC. In our study, only 25% of the individuals had more than one FDR with CRC, so for the most part we evaluated the effect of having one FDR compared to having no FDR with CRC. Furthermore, in a large population-based study by Taylor *et al*. (23) it was stressed that family history *per se*, irrespective of age, is not a strong predictor of exactly which individuals will acquire CRC in the next 20 years. Interestingly, the estimates by Butterworth *et al*. (3) of the absolute risks of CRC, based on number of FDR and age, correlated very well both with prevalence of advanced lesions and adenoma in our study. Altogether, this might support the notion that the bi-variate OR, correct ORs for age, could be a fair estimation of the risk contribution of each individual variable, since the bivariate ORs did not differ substantially from the multivariate ones (Tables I and II).

Furthermore, Taylor noted when exploring different constellations of FDR, SDRs and TDRs, that a sole positive SDR family history was associated with increased risk of CRC, but this risk was smaller than that of having a positive FDR family history. Our results indicate that history of SDRs and TDRs only contribute to a weakly-increased risk of adenoma and hardly to any risk increase for advanced lesions, on the other hand, we have not explored different constellations of affected FDRs, SDRs and TDRs, mainly due to limitations in the size of our study.

Having a family member afflicted by CRC before the age of 50 years was of importance for the risk of developing an advanced lesion but not of developing adenoma. If equating advanced lesions and CRC, our results were in line with Butterworth *et al*. (3). Taylor *et al*. also reported an increased risk of CRC if there was a FDR below the age of 50 years but also when there was an SDR with early onset of CRC (11). In fact, weincluded FDRs, SDRs and TDRs with CRC below the age of 50 years in our analysis, and having a relative with CRC at early age increased the risk of advanced lesions.

The observation that the risk of having adenomas did not depend on CRC at an early age in the family could suggest that even if adenomas are precursors of advanced adenomas, most will never develop into cancer and thus the risk of CRC does not depend much on the findings of a small adenoma (24).

In the present study, the risk of advanced adenoma was higher for siblings compared to children or parents of the affected relative in the univariate analysis, but when adjusting for age, the difference in risk was lost. Our results after adjusting for age were in contrast to many studies, which have observed that siblings of affected individuals have higher risk than parents (3, 4, 25), although Boardman *et al*. (25) studied relatives of probands with CRC below the age of 50 years. A higher risk in siblings might indicate an autosomal recessive inheritance pattern. On the other hand, our results were in line with other studies, one on adenomas (10) and one on cancer (11). This might be interpreted as reflecting aging of the family members accompanied by more siblings being afflicted by CRC, rather than a true correlation. Moreover, in the univariate analysis in an Italian study, an increased risk of colorectal neoplasia was observed in siblings compared to offspring but was not observed in the multivariate analysis (26).

In contrast to most studies, we did not observe a gender difference regarding the risk of adenoma or advanced adenoma in our study (27), although a Japanese study reported the same observation as ours (27). The absence of gender difference might partly be explained by the fact that in most endoscopies, dyeing with indigo carmine was employed, facilitating a higher a higher detection rate of flat adenomas in the right colon of women. However, it may also be possible that other factors (*e.g*. hormones) could play a more important role in the sporadic cases than in the familial cases.

This study also addressed risks associated with the findings at the screening colonoscopy and with the findings at the surveillance colonoscopies. A correlation between prevalence of HP and adenoma has been reported in previous studies (28, 29). In the present study, HP at the screening colonoscopy seemed to correlate with simple adenoma but not with advanced lesions at surveillance. The lack of correlation between advanced lesions and HP might indicate that HP is not a marker for risk of development of CRC. Simple adenomas at the first colonoscopy correlated with adenomas but not with advanced lesions during surveillance in the univariate analysis, as well as in the multivariate analysis. Indeed, Lieberman *et al*. concluded that one or two small tubular adenomas at baseline colonoscopy represented a low-risk group, and multiple or advanced adenomas represented a high-risk group for advanced neoplasia at follow-up (30). Lieberman *et al*. also suggested that there is a strong association between results of baseline screening colonoscopy and rate of serious incident lesions during 5.5 years of surveillance.

One of the drawbacks of our study was that only half of the population participated in surveillance and that the follow-up time among these was relatively short, on average 55 months. A reason for this was that a relatively large cohort was recruited by the end of the study.

In summary, our data indicate that the influence of different risk factors on the prevalence of adenoma and of advanced lesions diverge, possibly reflecting the fact that simple and advanced adenomas constitute different biological entities. Focusing on advanced lesions, this study indicated that high age of the patient, high prevalence of FDR with CRC, having a close relative younger than 50 years with CRC and findings of advanced lesions at the screening colonoscopy were risk factors of importance for subsequent advanced lesions during follow-up. Findings of simple adenomas and HPs did not seem to predict for subsequent advanced lesions. These results may have implications when designing colonoscopy surveillance programmes for individuals with a family history of CRC.

Conflicts of Interest

None of the Authors has any conflicts of interest to declare with regard to this study.

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