Risk of Malignancy in Adenomas Detected During Screening Colonoscopy

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BACKGROUND & AIMS: **A higher incidence of proximal interval cancers after colonoscopy has been reported in several follow-up studies. One possible explanation for this might be that proximally located adenomas have greater malignant potential. The aim of the present study was to assess the risk of malignancy in proximal versus distal adenomas in patients included in a large screening colonoscopy database; adenoma shape and the patients' age and sex distribution were also analyzed.**

METHODS: **Data for 2007–2012 from the German National Screening Colonoscopy Registry, including 594,614 adenomas identified during 2,532,298 screening colonoscopies, were analyzed retrospectively. The main outcome measure was the rate of high-grade dysplasia (HGD) in adenomas, used as a surrogate marker for the risk of malignancy. Odds ratios (ORs) for the rate of HGD found in adenomas were analyzed in relation to patient- and adenoma-related factors using multivariate analysis.**

RESULTS: **HGD histology was noted in 20,873 adenomas (3.5%). Proximal adenoma locations were not associated with a higher HGD rate. The most significant risk factor for HGD was adenoma size (OR 10.36 ≥1 cm vs <1 cm), followed by patient age (OR 1.26 and 1.46 for age groups 65–74 and 75–84 vs 55–64 years) and sex (OR 1.15 male vs female). In comparison with flat adenomas as a reference lesion, sessile lesions had a similar HGD rate (OR 1.02) and pedunculated adenomas had a higher rate (OR 1.23). All associations were statistically significant ($P \leq .05$).**

CONCLUSIONS: **In this large screening database, it was found that the rates of adenomas with HGD are similar in the proximal and distal colon. The presence of HGD as a risk marker alone does not explain higher rates of proximal interval colorectal cancer. We suggest that certain lesions (flat, serrated lesions) may be missed in the proximal colon and may acquire a more aggressive biology over time. A combination of endoscopy-related factors and biology may therefore account for higher rates of proximal versus distal interval colorectal cancer.**

Keywords: Screening Colonoscopy; Colorectal Adenomas; Interval Cancer Rate; Side Differences.

See editorial on page 1705.

Screening colonoscopy has been shown to reduce the incidence of and the mortality associated with colorectal cancers (CRCs)[1–5] by identifying cancers at an earlier stage and by detecting and removing adenomas as the precursor lesions. However, the reduction in the incidence of CRC resulting from colonoscopy, including polypectomy, is only in the range of 50%–80%,[3,4,6–8] because interval cancers are reported to occur after a negative colonoscopy or colonoscopic clearance of all

Abbreviations used in this paper: **CRC, colorectal cancer; HGD, high-grade dysplasia; OR, odds ratio; SSP, sessile serrated adenomas/polyps.**

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detected polyps. The interval cancer rates have repeatedly been shown to be higher in the right colon,[7,9–13] but it is not known whether this is because of a higher miss rate for proximal carcinomas and adenomas, different polypectomy success rates, or because the biology of proximal neoplasms differs in relation to the risk of malignancy. Although the overall adenoma detection rate correlates with the occurrence of interval cancers,[14–17] possible differences between adenoma locations were not considered in the relevant studies.

The present paper examines the question of why interval cancers tend to be more common in the proximal colon. It might be caused by biologic or endoscopic factors. If adenomas progress to high-grade dysplasia (HGD) differently in the proximal and distal colon, there might be a biologic explanation for the higher rates of interval proximal CRC. The primary hypothesis was that HGD rates do not differ between proximal and distal adenomas. If this is correct, then endoscopist-related factors (missed lesions, incomplete removal of neoplasia), rather than biology, are more likely to account for interval cancers in the proximal colon.

Methods

The German Screening Colonoscopy Registry of the Central Research Institute for Ambulatory Health Care, Berlin (Zentralinstitut für die Kassenärztliche Versorgung) is part of a mandatory quality assurance program for CRC screening. It includes compulsory photo documentation that the cecum has been reached and standardized electronic documentation of the relevant data. The data are collected centrally and analyzed by the Central Research Institute. The program and documentation started at the end of 2002, but the period 2007–2012 was chosen for analysis, because polyp locations were only documented after 2007. Final release of the data is usually delayed for at least 2–3 years for monitoring reasons.

Documented Data Used for This Analysis

Age and sex of the screened patients. Number of polyps found in categories (1/2–4/>4); details are only recorded for the most relevant polyp; in case of multiple adenomas, the largest adenoma or the adenoma with the most advanced histology (HGD) is documented as the index adenoma, with details of size, with the following categories: <0.5 cm, 0.5–1.0 cm, 1–2 cm, >2 cm. For this analysis, the latter 2 categories were taken together (ie, >1 cm).

Shape. Pedunculated/sessile/flat.

Location. Categories included distal location (ie, rectum and sigmoid colon) and proximal location (above the sigmoid colon). The case report form contains a third category, namely distal and proximal location for patients with multiple polyps, including the index adenoma; precise localization of the index adenoma is not possible in this category (35.7% of patients with adenomas), and this group is therefore analyzed separately.

Histology. Tubular/villous/tubulovillous, and the category of low-grade dysplasia and HGD, with the latter also including carcinoma in situ in accordance with the World Health Organization definition. Sessile serrated adenomas/polyps (SSPs) were not a separate category in the registry. Local histopathologists made the diagnoses, and central uniform histopathologic analyses were not carried out.

Outcome Parameters

The main outcome parameter for the study was the rate of HGD among all adenomas, calculated as the number of all HGDs/all patients with at least 1 adenoma. CRCs were excluded from the analysis. The HGD rate was used as a surrogate marker for the risk of malignancy of adenomas, because it was found that HGD histology was associated with a 1.8- to 6.8-fold increase in CRCs and advanced adenomas during the follow-up, a higher rate than the villous histology.[18] It was hypothesized that location would not be an independent factor for HGD occurrence in a multivariate analysis.

Secondary outcome parameters considered were factors potentially relevant to the development of HGD: patient age and sex, adenoma size, adenoma shape, and shape.

Statistical Analysis

All patients with HGD were correlated with the total number of patients with 1 or more adenomas with fully described polyp size, polyp shape, and polyp location. Descriptive variables are presented as means and standard deviations for continuous variables, and proportions for categorical variables.

To control for potential confounding between predictor variables, multivariate logistic regression was performed to calculate odds ratios (ORs) with 95% confidence intervals. Three separate models (flat adenomas, sessile adenomas, pedunculated adenomas) for the occurrence of HGD and polyp cancer were analyzed using the logistic regression approach.

Variables tested included the role of sex, age, location (dichotomized, proximal vs distal; ranges were used to correct for unclear location in the third group [discussed previously]), and polyp size (dichotomized, <10 mm vs ≥10 mm) as independent predictor variables. These variables were simultaneously included in the multivariate models for theoretical consideration of their potential influence on the detection of the 3 adenoma subtypes.

For comparison of the 3 models, Nagelkerke's R^2 was calculated, which indicates the amount of variation that is explained by the specific logistic model. All ORs were shown with 95% confidence intervals.

Table 1. Basic data for screening colonoscopies included in the National Screening Colonoscopy Registry, 2007–2012

Characteristic	Study population (N = 2,532,298)	
Patient age, mean (SD), range	64.15 (7.31)	55–99
Patient sex, male:female, %	M: 1,175,926; F: 1,356,372 46.4:53.6	
	n	%
Completed colonoscopies (in all reliably documented cases)	2,495,686	98.6
Colonoscopies with sedation (in all reliably documented cases)	2,290,006	90.4
Patients with at least 1 adenoma (ADR) in all cases	603,838	23.8
Of those, adenomas with size, shape,and location reported[a]	594,614	98.5
Adenoma size		
<5 mm	258,034	42.7
5–10 mm	224,496	37.2
>10 mm	118,014	19.7
Adenoma shape		
Pedunculated	109,867	18.2
Sessile	398,768	66.0
Flat	91,758	15.2
Adenoma histology[b]		
Tubular	493,667	81.8
Tubulovillous	81,395	13.5
Villous	4418	0.7
HGD	20,873	3.5
Adenoma location		
Distal	228,674	37.9
Proximal	151,159	25.0
Distal and proximal	215,542	35.7

NOTE. Adenomas reported are index adenomas (ie, those with the most severe histology; see text). Cases lacking documentation are not included in ADR.
ADR, adenoma detection rate; HGD, high-grade dysplasia; SD, standard deviation.
[a]Figures in the following (and the percentages in the right column) relate to the total adenoma number, 594,614; only the most advanced adenoma (defined by the size or histology of the HGD) is reported per patient, even if multiple adenomas are present (see text).
[b]Cancer in adenoma (T1), termed "polyp cancer": n = 4435 not included in the table.

All of the statistical calculations were performed with SPSS Statistics for Windows, version 19.0 (IBM Corporation, Armonk, NY) or Stata version 13.1 (StataCorp LLC, College Station, TX). The graph was produced using the R statistics package (http://www.r-project.org).

Results

Patient and Polyp Characteristics

Details of the patients included and of the adenomas detected are shown in Table 1. Approximately 2.5 million colonoscopies were documented, including a total of more than 600,000 adenoma carriers. The adenomas were 5 mm or less in size in 42.7% of cases, and only 19.7% were larger than 1 cm. HGD was found in 3.5% of all adenomas (n = 20,873), with polyp cancers (cancers in adenomas) being diagnosed in 4435 cases (not included).

Sex Distribution

Table 2 shows the sex distribution of the adenomas. Although the adenoma detection rate differed between men (29.7%) and women (18.1%), women had more proximal adenomas than men (26.9% vs 23.6%; $P < .01$) and they also had a slightly higher percentage of flat (15.9% vs 14.9%; $P < .05$) and proximally located flat adenomas (4.8% vs 3.8%; $P < .05$). However, the rate of HGD in proximally located and/or flat adenomas was 3.0% overall and it was nearly identical in men (3.0%) and women (3.1%).

Univariate and Multivariate Analysis of Location and Other Risk Factors for High-Grade Dysplasia in Adenomas

Table 3 shows the percentages of HGD in adenomas with different locations, sizes, and morphology (univariate analysis). Consistently with the distribution of all adenomas, it was also found that flat adenomas were detected in the distal colon more often than in the proximal colon. Table 3 also shows the distribution of HGD among all types of adenoma (flat, sessile, or pedunculated). It is evident that there are differences between the different adenoma shapes for polyps <5 mm and 5–10 mm in size, all of which are significant ($P < .05$) because of the large numbers of adenomas included.

A multivariate analysis of factors responsible for the rate of HGD in adenomas is shown in Figure 1. Previously established factors, such as patient age, sex, and adenoma size, play an important role, the latter most prominently (OR, 10.36; range, 9.94–10.76 ≥1 cm vs <1 cm; for other comparisons, see Figure 1).

Sensitivity Analysis for Adenoma Location

A limitation of the study was that it was not possible to identify the location of the index adenoma in about one-third of the patients (see Methods section). In the remaining two-thirds, proximal locations were associated with a lower risk than distal locations (OR, 0.75). The group in whom the location of the index adenoma was unknown had an OR of 1.10 (Figure 1). In a theoretical model for sensitivity calculation, an attempt was made to adjust for the influence of this group with unknown locations for the index adenoma. If all the index adenomas in this group were located proximally, the OR would fall to 0.72, whereas if they were all located distally, it would rise to 0.96. This means that the risk with a proximal location was similar or slightly lower,

Table 2. Sex Distribution of Adenoma Location, Shape and Histology

	All cases (mean age, 64.1 y)		Men (mean age, 64.4 y)		Women (mean age, 64.0 y)	
All screening colonoscopies 2007–2012	2,532,298		1,175,926		1,356,372	
	n	%	n	%	n	%
All patients with adenomas 2007–2012[a]	603,838	23.8	349,575	29.7	254,263	18.1
Adenoma location						
Of those, with data						
Only proximal location	150,982	25.0[b]	82,499	23.6[b]	68,483	26.9[b]
Of those, HGDs	3205	2.1	1846	2.2	1359	2.0
Only distal location	228,357	37.8[b]	127,796	36.6[b]	100,561	39.5[b]
Of those, HGDs	8643	3.8	5063	4.0	3580	3.6
Adenoma shape						
Data available	594,614	100	344,327	100	250,287	100
Flat	90,994	15.3	51,240	14.9	39,754	15.9
Of those, HGDs	3358	3.7	1979	3.9	1379	3.5
Pedunculated	109,046	18.3	67,231	19.5	41,815	16.7
Of those, HGDs	7657	7.0	4948	7.4	2709	6.5
Sessile	394,574	66.4	225,856	65.6	168,718	67.4
Of those, HGDs	9282	2.4	5723	2.5	3559	2.1
Adenoma shape and location						
Proximal flat	25,093	4.2	13,042	3.8	12,051	4.8
Of those, HGDs	764	3.0	388	3.0	376	3.1
Proximal pedunculated	15,019	2.5	9251	2.7	5768	2.3
Of those, HGDs	662	4.4	445	4.8	217	3.8
Proximal sessile	110,870	18.6	60,206	17.5	50,664	20.2
Of those, HGDs	1779	1.6	1013	1.7	766	1.5
Distal flat	26,504	4.5	14,754	4.3	11,750	4.7
Of those, HGDs	1047	4.0	613	4.2	434	3.7
Distal pedunculated	55,844	9.4	32,072	9.3	23,772	9.5
Of those, HGDs	3913	7.0	2311	7.2	1602	6.7
Distal sessile	146,009	24.6	80,970	23.5	65,039	26.0
Of those, HGDs	3683	2.5	2139	2.6	1544	2.4

HGD, high-grade dysplasia.
NOTE. Distal = rectum and sigmoid colon; proximal = above the sigmoid colon; for distal and proximal, see text (for multiple polyps).
[a]Only the most advanced adenoma (defined by size or histology of HGD) is reported per patient, even if multiple adenomas are present (see text).
[b]Percentages are related to the total number of adenomas with precise data.

but there was certainly no higher risk of HGD in the multivariate analysis.

Further Analyses

The influence of size relative to polyp location and shape on the rate of HGD and cancer is shown in detail in Table 4. In 3 separate models relative to each of the 3 polyp morphologies, adenoma size seemed to be the most important factor for the odds of finding HGD or polyp cancer. The location of the neoplasia was of less importance, but distal locations were associated with a higher risk of neoplasia than proximal locations (with statistically significant ORs between 1.4 and 1.6 for HGD).

Table 3. Rate of HGD in Relation to Polyp Size and Polyp Shape (All Patients With 1 or More Adenomas With Complete Documentation of Parameters, But With the Data on the Most Relevant Adenoma Per Case), Univariate Analysis

Polyp size	Polyp shape						Adenoma total, n
	Pedunculated		Sessile		Flat		
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
<5 mm	69/5730	1.20 (0.95–1.52)	1364/215,590	0.63 (0.60–0.67)	294/36,588	0.80 (0.72–0.90)	257,908
5–10 mm	1786/52,676	3.39 (3.24–3.55)	3033/138,848	2.18 (2.11–2.26)	800/32,843	2.44 (2.27–2.61)	224,367
>10 mm	5864/51,396	11.41 (11.14–11.69)	5011/44,112	11.36 (11.07–11.66)	2294/22,212	10.33 (9.93–10.73)	117,720
All cases	7719/109,802	7.03 (6.88–7.18)	9408/398,550	2.36 (2.31–2.41)	3388/91,643	3.70 (3.58–3.82)	599,995

CI, confidence interval; HGD, high-grade dysplasia.

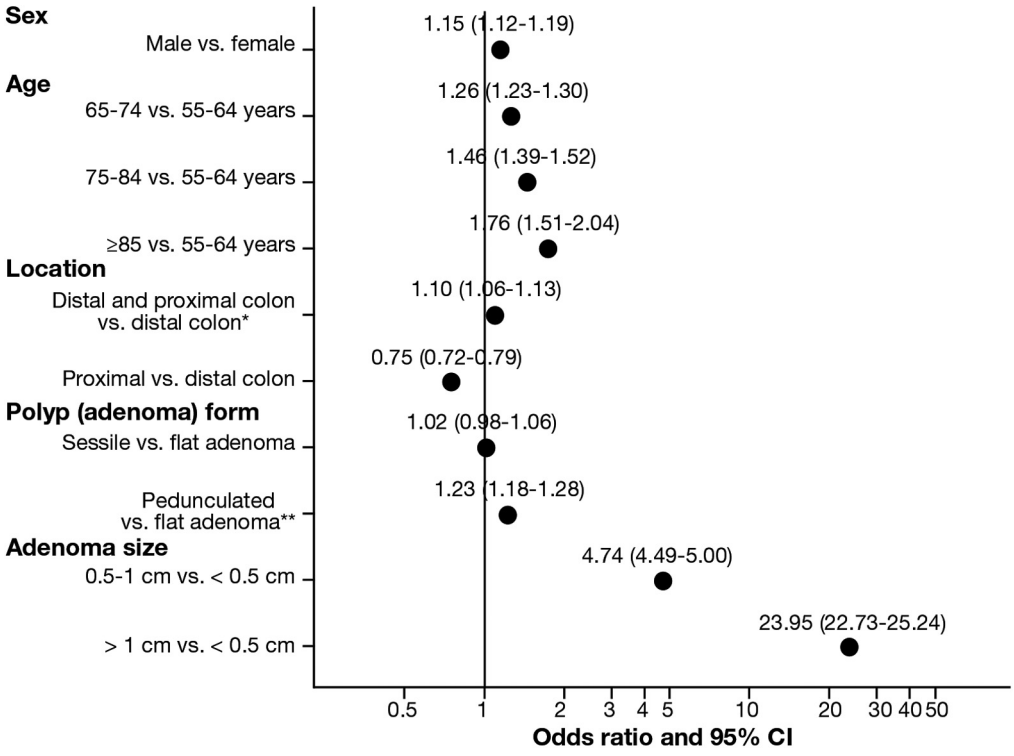

Figure 1. Multivariate analysis of patient and adenoma factors relative to the occurrence of HGD. CI, confidence interval.

Discussion

Interval cancers, defined as colorectal adenocarcinomas that are diagnosed between the time of the screening colonoscopy and the scheduled time for surveillance colonoscopy,[17] are the most significant type of failure that can occur with any screening method. It has been shown that with screening colonoscopy, these interval cancers are more frequently found in the proximal colon. The reason for this higher rate of proximal interval cancers copy is still unknown. It might be caused by a higher miss rate, or by different biology in proximal lesions. The present study, based on a very large German screening colonoscopy database, shows that proximal locations for adenomas were not associated with an increase in the rate of HGD in adenomas. Adenoma location per se is thus not associated with the HGD rate and hence the potential cancer risk.

The issue of the "biology" of proximal versus distal lesions has been a matter of controversy; recent retrospective analyses have reported that proximally located adenomas with HGD were significantly smaller[19] or that proximal locations were associated with a higher rate of malignancy.[20] However, the present results are in line with those of other studies showing contradictory evidence: recurrence rates after polypectomy (a possible indicator for more aggressive biology) were equivalent or even lower in the proximal colon.[21,22] In addition, the mortality rate from CRC after polypectomy was not found to be higher with right-sided adenomas in the Norwegian cancer registry.[23] This study also confirmed well-known risk factors, such as adenoma size and the patient's age and sex for the HGD rates. In addition, no differences between men and women were observed.[9,24] In general, with such large case numbers, even subtle differences become statistically significant; to avoid overestimation of less relevant (minor) differences, clinical assessment of the observed effects should be used to draw conclusions.

The use of HGD as a surrogate marker for the risk of cancer developing from adenomas seems to be established, based on the concept of the adenoma-carcinoma sequence,[25] although it is not fully known how long HGD persists before it develops into carcinoma, or to what extent this is related to other factors. There is better evidence for an increased risk of cancer development from HGD in the upper gastrointestinal tract.[26–28] However, 2 recent meta-analyses that analyzed the risk of recurrence in relation to histologic parameters in the colon found that HGD had a higher risk of advanced neoplasia at follow-up than other histologic parameters, such as villous histology.[18,29]

The role of the shape of adenomas has also been debated for many years. Flat lesions have often been thought to harbor an increased risk of malignancy,[30,31] although contradictory results have recently been published by groups in Italy[32] and Austria.[33] In the present study, flat adenomas, especially smaller ones, were associated with a lower HGD rate than pedunculated ones and were similar in terms of risk to sessile lesions. They were also equally distributed in the proximal and distal colon, and HGD rates in proximal flat adenomas were even lower than in distal ones. Thus, when HGD is considered as a risk parameter for cancer development,

Table 4. Multivariate Analysis of Occurrence of HGDs Relative to Established Risk Factors for Separate Adenoma Morphology Types (Logistic Regression)

	Model 1: flat adenomas		Model 2: sessile adenomas		Model 3: pedunculated adenomas	
Adenomas, n	52,047		258,517		71,880	
HGDs, n	1811		5462		4575	
HGDs, %						
Cancers, n	331		1042		888	
Cancers, %						
HGD rate of adenomas						
Nagelkerke variance, R^2	0.138		0.135		0.067	
Odds ratios and 95% CI						
Sex						
Female	1.000					
Male	1.078	0.978–1.187	1.065	1.008–1.126	1.078	1.013–1.147
Age, *y*						
55–64	1.000					
65–74	1.117	1.004–1.242	1.205	1.135–1.279	1.164	1.091–1.242
75–84	1.521	1.322–1.749	1.450	1.331–1.579	1.163	1.053–1.284
≥85	1.398	0.851–2.299	2.024	1.540–2.660	1.222	0.813–1.836
Location						
Proximal	1.000					
Distal	1.604	1.454–1.769	1.440	1.358–1.526	1.484	1.363–1.616
Polyp size, *cm*						
<1	1.000					
≥1	8.290	7.491–9.173	10.484	9.923–11.078	3.777	3.527–4.044

CI, confidence interval; HGD, high-grade dysplasia.

flat lesions do not seem to be more aggressive per se. However, it is quite possible that flat lesions may be more readily missed, and this could be the case more often in the right colon (eg, because of more incomplete colonoscopies, insufficiently cleansed right colon).

The present study has some limitations, similar to those in other large database analyses. First, there was no uniform histopathology analysis or central histopathology reading, which would be helpful to reduce interobserver variance, but this was the case in nearly all previous large database studies.[14,15,17,23,34–36] Furthermore, the categories we used for size determination (≤5 mm/6–10 mm/>10 mm and more) are slightly different from those used in other large studies (≤5 mm, 6–9 mm, and ≥10 mm). However, given the lack of reliable size determination and substantial interobserver variability in endoscopic size measurements,[37–42] these differences may be of limited relevance. A further limitation of this study may be that SSPs[43] were not included as a separate entity in the database. They were not well known and/or recognized when the registry started recording these data, and later on were probably mostly included in the adenoma category. There is considerable discussion and speculation about the role of SSPs in missed or interval cancers. Even if there is a separate pathway from SSP to serrated cancer, some studies suggest that the overall risk seems to be similar to that of conventional adenomas,[44,45] whereas they could be a marker of concurrent CRC.[46] The ultimate role played by SSPs in interval cancers (with more aggressive biology or a higher miss rate) is not yet clear. However, there is evidence that the rate of SSP-related features is higher in interval cancers.[24,47,48] Especially with SSP, uniform histologic assessment is desirable, but this is not realistic in large population-based databases. Finally, a limitation of this analysis is that it only includes data for 1 adenoma per patient, namely, the most significant one in terms of size or histology. This may have introduced some bias, especially in patients with multiple polyps, which may have diluted some of the effects seen. A sensitivity analysis was therefore carried out, assuming different probabilities, which showed that the OR varied between 0.72 and 0.96. This means that the HGD rate for proximal adenomas was at most similar to the HGD rate for distal adenomas, or might have been lower to a variable extent.

In summary, this large study shows that adenomas that are detected in the proximal and distal colon at a baseline screening colonoscopy have similar rates of HGD, a strong surrogate marker for CRC. This suggests that biologic factors alone are unlikely to explain the higher rates of interval cancer in the proximal colon. Many of these proximal interval cancers have characteristics of sessile serrated polyps,[24,47,48] which may be subtle and difficult to detect, with lesions that are difficult to resect completely.[10] Endoscopist factors, such as missed lesions or incompletely removed lesions, may therefore account for the predominance of proximal interval CRCs.

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Conflicts of interest
The authors disclose no conflicts.