Clinical Gastroenterology and Hepatology

Risk of Malignancy in Adenomas Detected During Screening Colonoscopy

--Manuscript Draft--

Manuscript Number:	CGH-D-17-01297R2
Full Title:	Risk of Malignancy in Adenomas Detected During Screening Colonoscopy
Article Type:	Fast Track - Alimentary Tract (Invited)
Section/Category:	Clinical Research (non-trial)
Corresponding Author:	Thomas Rosch, MD University Hospital Hamburg-Eppendorf Hamburg, GERMANY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University Hospital Hamburg-Eppendorf
Corresponding Author's Secondary Institution:	
First Author:	Thomas Rosch, MD
First Author Secondary Information:	
Order of Authors:	Thomas Rosch, MD
	Lutz Altenhofen
	Jens Kretschmann
	Bernd Hagen
	Hermann Brenner
	Christian Pox
	Wolff Schmiegel
	Arno Theilmeier
	Jens Aschenbeck
	Andrea Tannapfel
	Dominik von Stillfried
	Katharina Zimmerman-Fraedrich
	Karl Wegscheider
Order of Authors Secondary Information:	
Abstract:	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 ≤ 0.05). 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.

"Risk of Malignancy in Adenomas Detected During Screening Colonoscopy"
(CGH-D-17-01297R1)

Reply to Editorial Board

1. We agree with the suggestions made by the Reviewer and ask that you revise the paper accordingly.

Reply: See below

2. HGD definition: As previously discussed, this encompasses CIS and intramucosal CA, thus stating HGD/TiS is unnecessary. We suggest defining HGD in the Methods and using "HGD" subsequently throughout the paper.

Reply: The term was cleaned und HGD uniformly used throughout

3. Regarding the lack of central Pathology review and inter-observer variability regarding grading of dysplasia: We appreciate your points in the Reply, but could not locate where this was clearly addressed in the paper. This issue should be mentioned as a Limitation and discussed as you did in the reply.

Reply: Done (p. 4, Methods, and Discussion p. 7/8)

4. Please use sessile serrated polyp (SSP) throughout, instead of SSA.

Reply: Corrected throughout

5. In general, adenoma size in the literature is subdivided into ≤ 5mm, 6-9 mm, and ≥ 10 mm. We believe making this revision would make your findings more directly comparable to other papers, and are unlikely to significantly change the results of the analysis.

Reply: We apologize that in Methods, the precise size categories of the CRF were not given; this is now corrected (p. 4): „Size, with the following categories: < 0.5 cm, 0.5-1 cm, 1-2 cm, > 2cm; for this analysis, the latter two categories were taken together, i.e. > 1 cm.” Therefore, as done in the paper, we had to stick to these categories as was done in Tables and in the Figure. This was mentioned as limitation of the paper and discussed more broadly, with respect to the lack of reliable mesasurements in studies and databases. This fact may reduce the relevance of a slightly different size categorization in our paper (Discussion, p. 8)

6. The definition of distal versus proximal colon: We appreciate that some studies have employed a similar definition, but others have defined proximal colon as proximal to the splenic flexure. We do not view your definition as a limitation, but your study represents a unique opportunity to address in more detail the relation between colon location and HGD. We ask that you present the data according to colon location (cecum, AC, TC, etc), and determine whether changing the definition of proximal (i.e. proximal to splenic flexure) affects your primary findings.

Reply: We fully agree, but, as mentuioned, the CRF only had rthese two categories, so a further subdifferentiation is not possible; again, the question of reliablity/interobserver variance arises here as well.

7. There are some inconsistencies in the data: The unknown site rate is reported as 36.2%, but Table 2 lists that distal+proximal adenomas (hence site unknown) were 35.7%. Please review the paper and Tables, and ensure all the results are consistent.

Reply: we apologize and corrected the errors (which were mostly due to recalculating the figures tot he 2007-2012 instead of 2003-2012 collective).

8. The paper has several syntax and grammar errors. Please consider inviting a native English speaker to review and edit.

Reply: Done

We look forward to receiving your revised paper, and thank you again for your interest in CGH!

"Risk of Malignancy in Adenomas Detected During Screening Colonoscopy"
(CGH-D-17-01297R1)

Reply to Editorial Board

1. We agree with the suggestions made by the Reviewer and ask that you revise the paper accordingly.

Reply: See below

2. HGD definition: As previously discussed, this encompasses CIS and intramucosal CA, thus stating HGD/TiS is unnecessary. We suggest defining HGD in the Methods and using "HGD" subsequently throughout the paper.

Reply: The term was cleaned und HGD uniformly used throughout

3. Regarding the lack of central Pathology review and inter-observer variability regarding grading of dysplasia: We appreciate your points in the Reply, but could not locate where this was clearly addressed in the paper. This issue should be mentioned as a Limitation and discussed as you did in the reply.

Reply: Done (p. 4, Methods, and Discussion p. 7/8)

4. Please use sessile serrated polyp (SSP) throughout, instead of SSA.

Reply: Corrected throughout

5. In general, adenoma size in the literature is subdivided into ≤ 5mm, 6-9 mm, and ≥ 10 mm. We believe making this revision would make your findings more directly comparable to other papers, and are unlikely to significantly change the results of the analysis.

Reply: We apologize that in Methods, the precise size categories of the CRF were not given; this is now corrected (p. 4): „Size, with the following categories: < 0.5 cm, 0.5-1 cm, 1-2 cm, > 2cm; for this analysis, the latter two categories were taken together, i.e. > 1 cm." Therefore, as done in the paper, we had to stick to these categories as was done in Tables and in the Figure. This was mentioned as limitation of the paper and discussed more broadly, with respect to the lack of reliable mesasurements in studies and databases. This fact may reduce the relevance of a slightly different size categorization in our paper (Discussion, p. 8)

6. The definition of distal versus proximal colon: We appreciate that some studies have employed a similar definition, but others have defined proximal colon as proximal to the splenic flexure. We do not view your definition as a limitation, but your study represents a unique opportunity to address in more detail the relation between colon location and HGD. We ask that you present the data according to colon location (cecum, AC, TC, etc), and determine whether changing the definition of proximal (i.e. proximal to splenic flexure) affects your primary findings.

Reply: We fully agree, but, as mentuioned, the CRF only had rthese two categories, so a further subdifferentiation is not possible; again, the question of reliablity/interobserver variance arises here as well.

7. There are some inconsistencies in the data: The unknown site rate is reported as 36.2%, but Table 2 lists that distal+proximal adenomas (hence site unknown) were 35.7%. Please review the paper and Tables, and ensure all the results are consistent.

Reply: we apologize and corrected the errors (which were mostly due to recalculating the figures tot he 2007-2012 instead of 2003-2012 collective).

8. The paper has several syntax and grammar errors. Please consider inviting a native English speaker to review and edit.

Reply: Done

We look forward to receiving your revised paper, and thank you again for your interest in CGH!

Risk of Malignancy in Adenomas Detected During Screening Colonoscopy

Thomas Rösch[1], Lutz Altenhofen[2], Jens Kretschmann[2], Bernd Hagen[2], Hermann Brenner[3], Christian Pox[4], Wolff Schmiegel[4], Arno Theilmeier[5], Jens Aschenbeck[6], Andrea Tannapfel[7], Dominik von Stillfried[2],

Katharina Zimmermann-Fraedrich[1], and Karl Wegscheider[8]

Department of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf, Hamburg[1], Central Research Institute of Ambulatory Health Care, Berlin[2], Division of Clinical Epidemiology and Aging Research and Division of Preventive Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg[3], Department of Medicine, Ruhr University Bochum, Knappschaftskrankenhaus [4], Private Practice Gastroenterology, Mönchengladbach [5], Private Practice Gastroenterology, Berlin[6], Institute of Pathology, Ruhr University Bochum [7], Department of Medical Biometry and Epidemiology , University Hospital Hamburg-Eppendorf, Hamburg, Germany[8]

Correspondence to:
Prof. Thomas Rösch, M.D.
Department of Interdisciplinary Endoscopy

University Hospital Hamburg Eppendorf~~7~~
Martinistr. 52, 20246 Hamburg, Germany
E-mail: t.roesch@uke.de

Author contributions:
T. Rösch, L. Altenhofen, J. Kretschmann, B. Hagen ~~und~~ and K. Wegscheider ~~analysed~~ analyzed the data and wrote the paper, K. Fraedrich helped with literature review, H. Grenner, C. Pox, W. Schmiegel, D. Stillfried, A, Tannapfel, A. Theilmeier and J. Aschenbeck ~~have~~ corrected and amended the paper.

Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)

Conflicts of interest:
There ~~is~~ are no conflicts of interest for any of the authors. No funding was received for the study.

Abstract

BACKGROUND & AIMS: A higher incidence of proximal interval cancers after colonoscopy has been ~~described~~ reported in several follow-up studies. One possible explanation for ~~T~~this might be that proximally located adenomas ~~could be due an increased~~ have greater malignant potential ~~of proximally located adenomas~~. ~~Aim~~ The aim of the present study was to assess the risk of malignancy ~~of~~ in proximal versus distal adenomas in patients included in a large screening colonoscopy database; adenoma ~~form~~shape, and the patients' age and sex distribution were also ~~analys~~analyzed.

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

RESULTS: ~~20.873 adenomas carried~~ HGD histology was noted in 20,873 adenomas (3.5%). Proximal adenoma locations ~~was~~ were not associated with a higher HGD rate. The most significant risk factor for HGD was adenoma size (OR 10.36 ≥ ~~1~~ 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~~ 64 years) and sex (OR 1.15 male vs. female). ~~As~~ In compar~~ed to~~ison with flat adenomas as a reference lesion, sessile lesions had a similar HGD rate (OR 1.02) and ~~,~~ pedunculated adenomas ~~a~~ had a higher rate ~~HGD rate~~ (OR 1.23). All associations were statistically significant (~~at least~~ *P* ≤~~<~~ 0.05).

CONCLUSIONS: In this large screening database, ~~we find~~ 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 ~~CRC~~colorectal cancer. We suggest that certain lesions (flat, serrated lesions) ~~could~~ may be missed in the proximal colon ~~which~~ and may acquire a more aggressive biology over time. ~~Therefore, a~~A combination of ~~endoscopy~~ endoscopy-related factors and biology ~~could~~ may therefore account for higher rates of proximal versus distal interval ~~CRC~~colorectal cancer.

Keywords: Screening colonoscopy, colorectal adenomas, interval cancer rate, side differences

Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: Font: Italic, English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)

Introduction

Screening colonoscopy has been shown to ~~decrease~~ reduce ~~CRC~~ the incidence of and also the ~~as well as~~ mortality associated with colorectal cancers (CRCs)[1-5] by ~~finding~~ identifying cancers at an earlier stage and by detecting and removing adenomas as the precursor lesions. ~~Reduction~~ However, the reduction ~~of~~ in the ~~CRC~~ incidence of CRC ~~by~~ resulting from colonoscopy, including polypectomy, is ~~however~~ only in the ~~magnitude~~ range of 50~~-~~80%[3, 4, 6-8], since interval cancers are reported to occur after a negative colonoscopy or colonoscopic clearance of all detected polyps. The interval cancer rates have repeatedly been shown to be higher in the right colon [7, 9-13]~~.~~, but it is ~~however~~ not known whether this is due to a higher miss rate ~~of~~ for proximal carcinomas and adenomas, different polypectomy success rates, or ~~due to different~~ because the biology of proximal neoplasms differs in relation ~~with regards~~ to the risk of malignancy. Although the overall adenoma detection rate ~~(ADR)~~ ~~was~~ correlate~~d~~s with the occurrence of interval cancers[14-17], possible differences between adenoma locations were not ~~considered~~ taken into account in ~~these~~ the relevant studies. ~~In addition, certain types of adenoma forms , such as flat adenomas, have been are thought to accused to harbour an increased risk of malignancy, [18-27] [18-27] which although this has not been confirmed by in recent Western series[28-33].~~

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

Methods

The German Screening Colonoscopy Registry of the Central Research Institute ~~of~~ for Ambulatory Health Care, Berlin (Zentralinstitut ~~fuer~~ für die Kassenärztliche Versorgung, ZI) is part of a mandatory quality assurance program~~me~~ ~~in~~ for CRC screening. ~~—~~ It includes ~~a~~ compulsory photo documentation ~~of cecal reach~~that the cecum has been reached~~,~~ and ~~electronic~~ standardized electronic documentation of the relevant data. ~~This~~ The data is ~~centrally~~ collected centrally and ~~analys~~analyzed by the ZI. The program~~me~~ and documentation started at the end of 2002, but~~, since polyp location was only documented after 2007, ~~~~ the period 2007~~-~~2012 was

Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)

chosen for analysis, as polyp locations were only documented after 2007. Final ~~data~~ release of the data is usually delayed for at least 2~~–~~3 years ~~due to~~ for monitoring reasons.

Documented data used for this analysis

- Age and sex of the ~~screeneess~~screened patients
-
- Number of all 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 ~~regards to~~details of:
  - Size, with the following categories: ~~<~~< 0.~~5~~5 cm, 0.5~~–~~1.~~0~~ cm, 1~~–~~2 cm, >~~–~~2 cm; for this analysis, the latter two categories were taken together, i.e. ~~>~~> ~~1~~1 cm.
  -
  - ~~Form~~Shape: pedunculated / sessile / flat.
  - Location; categories included distal location (i.e., rectum and sigmoid colon) and proximal location (above the sigmoid colon). The case report form (CRF) contains a third category, namely distal *and* proximal location for patients with multiple polyps ~~also~~, including the index adenoma as well; ~~here, no~~ precise ~~location~~ localization of the index adenoma is not possible in this category (35.7% of ~~cases~~ patients with adenomas), and ~~therefore,~~ this group is therefore analyzed separately.
  - Histology~~, namely~~ : tubular / villous / tubulovillous, and the category of low-grade and ~~high~~ high-grade dysplasia (HGD), with the latter also including ~~also~~ carcinoma in situ (Tis) ~~according to~~ in accordance with the World Health Organization definition. A separate category for serrated adenomas was not included in the CRF. Sessile serrated adenomas/polyps (SSPs) were not a category in the registry. Local histopathologists made the diagnoses, and ~~there is no~~ central uniform ~~histopathology~~ histopathological ~~analysis~~analyses were not carried out.

Outcome parameters~~:~~

The main outcome parameter~~:~~ for the study was the rate of ~~high~~ high-grade ~~intraepithelial neoplasia~~dysplasia (HGD) among all adenomas, calculated as the number of all HGDs/all patients with at least one adenoma. Colorectal cancers were excluded from the analysis. ~~We used t~~The HGD rate was used as a surrogate marker ~~of~~ for the risk of malignancy of adenomas, ~~since~~ as it was found that HGD histology was associated with a~~n~~ 1.8~~–~~6.~~8~~ 8-fold increase in CRCs and advanced adenomas during the follow-up, a higher rate than the villous histology [34]. ~~We~~ It was hypothesized that location ~~was~~ would not be an independent factor for HGD occurrence in a multivariate analysis.

Secondary outcome parameters~~:~~ considered were factors ~~of~~ potentially relevan~~ce for~~t to the ~~occurrence~~ development of HGD: patient age and sex, adenoma size, adenoma ~~form~~ shape and location.

Statistical analysis~~:~~

Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: Font: Not Italic, English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: Font: Not Italic, English (United States)
Formatted: English (United States)
Formatted: English (United States)

All ~~cases~~ patients with HGD were ~~related~~correlated ~~to~~ with the total number of patients with one or more adenomas with fully described polyp size, polyp ~~form~~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 (CIs). Three separate models (flat adenomas, sessile adenomas, pedunculated adenomas) for the occurrence of HGD and polyp cancer were analyzed using the logistic regression approach.

~~We~~ Variables tested included the role of sex, age, loca~~liza~~tion (dichotomized ~~(~~, proximal vs. distal; ranges were used to correct for unclear loca~~liza~~tion in the third group, see above) and polyp size (dichotomized ~~(~~, ~~<~~ ~~10~~ 10 mm vs. ≥ ~~10~~ 10 mm) as independent predictor variables. These variables were simultaneously included in the ~~multivariable~~ multivariate models for theoretical consideration~~s~~ of their potential influence on the detection of the three adenoma subtypes.

~~To~~ For ~~compare~~ comparison of the three models, Nagelkerke's R^2 was calculated, which ~~is~~ indicat~~inges~~ the amount of ~~the~~ variation that is explained by the specific logistic model. All odds ratios ~~were displayed~~ were shown with 95~~-~~% CIs.

All of the statistical ~~computations~~ calculations were performed with~~–~~ IBM SPSS Statistics for Windows, version 19.0 (IBM Corporation, Armonk, New York~~SPSS version 19.0 (SPSS IBM Company~~) or Stata 13.1 (StataCorp LLC, College Station, Texas ~~77845 USA~~). The graph was produced ~~with~~ using the R statistics package (http: //www.r-project.org).

Results

Patient and polyp characteristics

Details of ~~included~~ the patients included and ~~their~~ of the ~~detected~~ adenomas detected are shown in ~~**Table**~~ **Table 1**. ~~About~~ Approximately 2.~~5~~ 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 ~~adenomas~~ cases, ~~were 5 mm or less,~~ and only 19.7% were larger than ~~1~~ 1 cm. HGD was found in 3.5% of all adenoma~~-~~ ~~cases~~ s (n = 20~~-~~,873), with polyp cancers (cancers in adenomas) being diagnosed in 4~~-~~,435 cases.

Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: Font: Italic
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)

~~Overall, it was not possible to identify the location of the index adenoma in there were more than a third of casesthe patients , where the index adenoma location could not be identified (see above), of ; in the remaining cases, more adenomas were localized located distally (**Table ~~**Table 2**~~).~~

Sex distribution

Table 2 also shows the sex distribution of the adenomas~~; despite a~~ . Although the ~~different~~ adenoma detection rate differed ~~ADR~~ between men (29.7%) and women (18.1%), women had more proximal adenomas than men (26.9% vs. 23.6%, *P* < 0.01) and they also had a slightly higher percentage of flat ~~adenomas~~ (15.9% vs. 14.9%, *P* < 0.05) as well as proximally located flat adenomas (4.8% vs. 3.8%, *P* < 0.05). ~~Nevertheless,~~ However, the rate~~s~~ of HGD in proximally located and/or flat adenomas ~~were~~ was ~~overall~~ 3.0% overall and it was nearly identical in both men (3.0%) and women (3.1%)~~ and . The rate was also were lower than in distal flat adenomas (4.0% overall) as shown in ; **Table ~~**Table 2~~**).

Uni~~-~~variate and multivariate analysis of location and other risk factors for HGD in adenomas

~~**Table** ~~**Table 3** shows the percentages of HGD in adenomas ~~of~~ with different location~~s~~, size~~s~~, and morphology (univariate analysis). ~~In line~~ Consistently with the distribution of all adenomas, ~~we~~ it was also found that flat adenomas were ~~more often~~ detected in the distal colon more often than in the proximal colon. **Table 3** also ~~demonstrates~~ shows the distribution of HGD ~~in~~ among all types of adenoma ~~forms~~ (flat, sessile, or pedunculated). It is evident that there are ~~significant~~ differences between the different adenoma shapes ~~exist~~ for polyps ~~<~~ < ~~5~~ 5 mm and 5~~–~~10 10 mm in size~~between the different forms of adenoma~~, all of which are significant (*P* < 0.05) due to the large ~~adenoma~~ numbers of adenomas included.

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

Sensitivity analysis for adenoma location

As mentioned, one limitation of the study was that it was not possible to identify the location of the index adenoma in about ~~a~~ one-third of ~~cases, the~~

Formatted: Font: Italic
Formatted: Font: Italic
Formatted: Font: Italic
Formatted: Font: Not Bold
Formatted: Font: Italic
Formatted: English (United States)

patients ~~the index adenoma location could not be identified~~ (see Methods, above). ~~Of~~ In the remaining ~~2/3 of cases~~two-thirds, proximal locations ~~was~~ were associated with a ~~of~~ lower risk than distal locations (OR 0.75). The group ~~with~~ in whom the ~~unknown~~ location of the index adenoma was unknown had ~~an~~ an OR of 1.10 (~~**Figure**~~ **Figure 1**). In a theoretical model for sensitivity calculation, ~~it was tried~~ an attempt was made to adjust for the influence of this group with unknown locations ~~of~~ for the index adenoma~~,~~. ~~i.e.~~ If *all* the index adenomas in this group were located proximally, the OR would fall to 0~~,~~.72, while if they were *all* ~~of those were~~ located distally, it would rise to 0.96. This means that the risk with a proximal location ~~has a~~ was similar or slightly lower, but there was certainly no higher risk of HGD in the multivariate analysis.

Further analyses

The influence of size ~~in relation~~ relative to polyp location and ~~form~~ shape on the rate of HGD and cancer is also shown in detail in ~~**Table**~~ **Table 4**. In three separate models ~~referring~~ relative to each of the three polyp morphologies, adenoma size appeared ~~as~~ to be the most important factor for the odds of finding HGD or polyp cancer. ~~Localization~~ The location of the neoplasia was of less importance, but distal ~~vs. proximal~~ locations ~~comprises~~ were associated with a higher risk of neoplasia than proximal locations (with statistically significant odds ratios between 1.4 and 1.6 for HGD).

Formatted: English (United States)

Discussion

Interval cancers, defined as ~~a~~ colorectal adenocarcinomas that ~~was~~ are diagnosed between the time of the screening colonoscopy~~,~~ and the scheduled time ~~of~~ for surveillance colonoscopy[17], are the most significant type of failure ~~of~~ that can occur with any screening method. ~~For (screening) colonoscopy,~~ It has been shown that with screening colonoscopy, ~~that~~ 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 could~~ It might be due to ~~be~~ a higher miss rate, or to ~~a~~ different biology ~~of~~ in proximal lesions.~~:~~ ~~A recent stage-adjusted meta-meta-analysis showed that right-sided CRCs have a worse poorer prognosis than left left-sided lesions[35].~~ ~~In~~ tThe present study, based on the very large German screening colonoscopy database, ~~we demonstrated~~ shows that proximal ~~adenoma~~ locations for adenomas ~~was~~ were not associated with an increase in the rate of HGD in adenomas. ~~Thus, a~~Adenoma location per se is thus not associated with the HGD rate and hence ~~possibly~~ the potential cancer risk.

Formatted: English (United States)

Formatted: English (United States)

Formatted: English (United States)

Field Code Changed

Formatted: Check spelling and grammar

The issue of the "biology" of proximal versus distal lesions has been ~~discussed controversially~~a matter of controversy; recent retrospective analyses have ~~demonstrated~~ reported that proximally located adenomas with

HGD were significantly smaller[36] or that proximal location ~~s~~was ~~–~~ were associated with a higher rate of malignancy[37]. However, ~~our~~ the present results are in line with those of other studies showing contradictory evidence: recurrence rates after polypectomy ~~–~~ – a possible indicator ~~of~~ for more aggressive biology ~~–~~ – were equivalent or even lower in the proximal colon[38, 39]. ~~Finally,~~ In addition, the mortality rate from colorectal cancer after polypectomy was not found to be higher ~~on~~ with ~~the~~ right-~~–~~sided adenomas in the Norwegian cancer registry[40]. ~~Thus, lesion biology does not seem to be different in the proximal colon as shown by our and other studies~~. 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, 41]. 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 present study represents the largest database on of colorectal adenomas from a homogeneous screening collective so far published in the literature. We previously confirmed tThe validity of the registry data with regards in relation to adenoma detection was confirmed in a previous study[42]. With such large case numbers, even subtle differences become statistically significant; to avoid overestimation of minor and potentially less relevant effects, clinical judgement assessment of the observed effects should be used for to draw conclusions. We This study also confirmed the well -known risk factors such as adenoma size, and the patient's age and sex for the HGD rates. Furthermore, there was nIn addition, no differences between men and women were observed with regards in relation to the higher rate of proximal interval cancers[9, 41].~~

The use of HGD as a surrogate marker for the risk of cancer ~~development~~ developing from adenomas appears to be established ~~within~~, based on the concept of the adenoma-~~–~~carcinoma sequence[43], although it is not fully known how long HGD persists before it ~~developing~~ develops into carcinoma, ~~and~~ or to ~~which~~ what extent this is related to other factors ~~such as polyp size and the patient's age or personal history~~. There is better evidence for ~~In the upper GI tract,~~ an increased risk of cancer development ~~for~~ from HGD in the upper gastrointestinal tract ~~is better established~~ [44-46]. However, two recent ~~meta~~ meta-~~analysis~~ 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 ~~on~~ at follow-up than other histologic parameters such as villous histology[34, 47].

The role of the shape of adenomas ~~form~~ has also been ~~discussed~~ debated for many years~~, and~~. Flat lesions ~~were~~ have often been thought ~~accused~~ to harbor an increased risk of malignancy[23, 48], although contradictory results ~~were~~ have recently been published ~~from~~ by groups in Italy[32] and Austria[33].

Formatted: Check spelling and grammar
Field Code Changed
Field Code Changed
Formatted: Check spelling and grammar
Formatted: Check spelling and grammar
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed
Field Code Changed
Formatted: Check spelling and grammar
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed
Formatted: Check spelling and grammar

In ~~our~~ the present study, flat adenomas, especially ~~the~~ smaller ones, ~~had~~ 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, ~~taking~~ when HGD is considered as a risk parameter for cancer development, flat lesions do not appear ~~not~~ to be more aggressive per se. However, it is ~~well~~ quite possible that flat lesions ~~are~~ may be ~~missed~~ more readily missed, and this could be the case more often in the right colon (e.g., due to more incomplete colonoscopies, insufficiently cleansed right colon, etc.)~~, and . therefore This may therefore be one of the main major factors of behind right-sided interval cancers~~.

~~There a~~ The present study has some limitations ~~of our study~~, similar to those in other large database analyses: First of all, there was no uniform histopathology analysis or ~~a~~ central histopathology reading, which would be helpful in order to reduce interobserver variance, but this was the case~~. On the other hand, the same situation can be found~~ in nearly all previous large database studies [14, 15, 17, 40, 49-51]. Furthermore, the categories we used for size determination (≤ 5 mm/6-~~–~~10 mm/> ~~10~~ 10 mm and more) are slightly different from those used in other large ~~The same is also true for size determinationmeasurements; the categories we used (≤ 5 mm/6 – 10 mm/> 10 10 mm and more) are slightly different from those used in other large~~ studies ~~(≤ (~~≤ 5 mm, 6-~~–~~9 9 mm, and ~~≥ ~~≥ ~~10~~ 10 mm). However, given the lack of reliable size determination and ~~a~~ substantial interobserver variability in endoscopic size measurements [52-57], these differences may ~~of~~ be of limited relevance. A further limitation of ~~our~~ this study may be that sessile serrated adenomas/polyps (SSPs) [58] were not included as a separate entity in the database. They were not well known and/or recognized ~~as such at the beginning of~~ 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. ~~However, e~~Even if there is a separate pathway from SSP to serrated cancer~~s~~, some studies suggest that the overall risk appears to be similar to that of conventional adenomas [59, 60]~~,~~ while, on the other hand , they could be a marker of concurrent CRC [61]~~;~~. The ~~final~~ ultimate role ~~of~~ played by SSPs in interval cancers (with more aggressive biology or a higher miss rate) is not yet clear. ~~There is~~ However, there is evidence~~,~~ that the rate of SSP-related features is higher in interval cancers [41, 62, 63]. Especially with SSP, uniform histologic assessment would be desirable, but this is not realistic in large population-~~–~~based databases. ~~A further~~Finally, a limitation of this analysis is that ~~there~~ it ~~is~~ only includes data ~~of~~ for one adenoma per patient~~,~~ ~~–~~ namely, the most significant one ~~by means~~ in terms of size or histology~~,~~ ~~which~~ . This may have introduced some bias, especially in patients with multiple polyps, which may have diluted some of the effects seen. ~~We therfore performed a~~A sensitivity analysis was therefore carried out, assuming different ~~probabilities~~probabilities, which showed that the OR varied between 0.72 and 0.96. This means~~,~~ that the HGD rate ~~of~~ for proximal

Formatted: Check spelling and grammar
Field Code Changed
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Field Code Changed
Formatted: English (United States)
Formatted: English (United States)
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed
Formatted: Check spelling and grammar
Field Code Changed

adenomas was at most similar to the HGD rate ~~of~~ for distal adenomas, or ~~could~~ might have been lower to a variable ~~degree~~extent.

In summary, this large study ~~finds~~ shows that adenomas that are detected in the proximal and distal colon at a baseline screening colonoscopy ~~in the proximal and distal colon,~~ have similar rates of HGD, a strong surrogate marker for CRC. This suggests that ~~biology~~ biological 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 ~~the~~ sessile serrated polyps[41, 62, 63], which may be subtle, ~~,~~ and difficult to detect, ~~and~~ with lesions that are difficult to resect completely[10]. ~~We conclude that~~ eEndoscopist factors such as missed lesions or incompletely removed lesions may therefore account for the predominance of proximal interval CRCs.

Formatted: English (United States)

Formatted: English (United States)

Formatted: English (United States)

Formatted: English (United States)

Formatted: English (United States)

Formatted: English (United States)

TABLES

Table 1: Basic data of for screening colonoscopies included in the National Screening Colonoscopy Registry, 2007–2012. Adenomas reported are index adenomas, i.e., those with the most severe histology (see text)

Characteristic		Study population (n=2,532,298)	
Patient age (mean [SD], range)		64.15[7.31]	55—99
Patient sex (male : female in %)		M: 1,175,926; F: 1,356,372) 46.4 : 53.6	
		N	%
Completed colonoscopies (of in all reliably documented cases)		2,495,686	98.6
Colonoscopies with sedation (of in all reliably documented cases)		2,290,006	90.4
Patients with at least one adenoma (ADR) of in all cases		603,838	23.8
Of those, adenomas with size, form shape, and and location reported*		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 formshape	Pedunculated	109,867	18.2
	Sessile	398,768	66.0
	Flat	91,758	15.2
Adenoma Adenoma histology**	Tubular	493,667	81,8
	Tubulovillous	81,395	13,5
	Villous	4,418	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

ADR = , adenoma detection rate. Cases without lacking documentation bot are not included (add to 100%).

* Figures in the following (and % the percentages in the right column) relate to the total adenoma number of , 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).

** Cancer in adenoma (T1), called termed "polyp cancer": n n = = 4 ,435 not included in the table.

Formatted: English (United States)

Table 2: Sex distribution of adenoma location, ~~form~~ 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	
All patients with adenomas 2007–2012**	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%$	82,499	**23.6%**$	68,483	**26.9%**
Of those, HGDs	3,205	2.1%	1,846	**2.2%**	1,359	**2.0%**
Only distal location	228,357	37.8%$	127,796	36.6%$	100,561	39.5%
Of those, HGDs	8,643	3.8%	5,063	4.0%	3,580	3.6%
Adenoma ~~form~~ 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	3,358	3.7%	1,979	**3.9%**	1,379	**3.5%**
Pedunculated	109,046	18.3%	67,231	19.5%	41,815	16.7%
Of those, HGDs	7,657	7.0%	4,948	7.4%	2,709	6.5%
Sessile	394,574	66.4%	225,856	65.6%	168,718	67.4%
Of those, HGDs	9,282	2.4%	5,723	**2.5%**	3,559	**2.1%**
Adenoma ~~form~~ 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%	9,251	2.7%	5,768	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	1,779	1.6%	1,013	**1.7%**	766	**1.5%**
Distal flat	26,504	4.5%	14,754	4.3%	11,750	4.7%
Of those, HGDs	1,047	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	3,913	7.0%	2,311	7.2%	1,602	6.7%
Distal sessile	146,009	24.6%	80,970	23.5%	65,039	26.0%
Of those, HGDs	3,683	2.5%	2,139	**2.6%**	1,544	**2.4%**

SC, screening colonoscopy; ADR, adenoma detection rate.

* Distal = rectum and sigmoid colon, proximal = above the sigmoid colon; for distal and proximal, see text (for multiple polyps).

** Only the most advanced adenoma (defined by size or histology of HGD) is reported per patient, even if multiple adenomas are present (see text).

$ Percentages are related to the total number of adenomas with precise data.

Table 3: Rate of HGD in relation to polyp size and polyp ~~form~~shape (*all* patients with one or more adenomas with complete documentation of parameters, but with the data on the most relevant adenoma per case), univariate analysis~~.~~

Polyp size	Polyp ~~form~~shape						Total no. of adenomas
	Pedunculated		*Sessile*		*Flat*		
	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
< 5 mm	69/5,730	1.20 (0.95—1.52)	1,364/215,590	0.63 (0.60—0.67)	294/36,588	0.80 (0.72—0.90)	257,908
5—10 mm	1,786/52,676	3.39 (3.24—3.55)	3,033/138,848	2.18 (2.11—2.26)	800/32,843	2.44 (2.27—2.61)	224,367
> 10 mm	5,864/51,396	11.41 (11.14—11.69)	5,011/44,112	11.36 (11.07—11.66)	2,294/22,212	10.33 (9.93—10.73)	117,720
All cases	7,719/109,802	7.03 (6.88—7.18)	9,408/398,550	2.36 (2.31—2.41)	3,388/91,643	3.70 (3.58—3.82)	599,995

Formatted Table
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)
Formatted: English (United States)

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	
No. of adenomas	52.047		258.517		71.880	
No. of HGDs	1.811		5.462		4.575	
% of HGDs						
No. of cancers	331		1.042		888	
% of 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						
55–64 years	1.000					
65–74 years	1.117	1.004–1.242	1.205	1.135–1.279	1.164	1.091–1.242
75–84 years	1.521	1.322–1.749	1.450	1.331–1.579	1.163	1.053–1.284
85 years / older	1.398	0.851–2.299	2.024	1.540–2.660	1.222	0.813–1.836
Localization						
Proximal	1.000					
Distal	1.604	1.454–1.769	1.440	1.358–1.526	1.484	1.363–1.616
Polyp size						
< 1 cm	1.000					
≥ 1 cm	8.290	7.491–9.173	10.484	9.923–11.078	3.777	3.527–4.044

LEGENDS TO FIGURES

Figure 1:

Multivariate analysis of patient and adenoma factors ~~with respect~~ relative to the occurrence of HGD.

Formatted: English (United States)

Formatted: English (United States)

Formatted: English (United States)

References

1. Imperiale TF, Glowinski EA, Lin-Cooper C, et al. Five-year risk of colorectal neoplasia after negative screening colonoscopy. N Engl J Med 2008;359:1218-24.
2. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977-81.
3. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687-96.
4. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. Bmj 2014;348:g2467.
5. Lieberman D. Screening for colorectal cancer in individuals at average risk: current methods and emerging issues. JAMA Intern Med 2014;174:10-1.
6. Brenner H, Haug U, Arndt V, et al. Low risk of colorectal cancer and advanced adenomas more than 10 years after negative colonoscopy. Gastroenterology 2010;138:870-6.
7. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150:1-8.
8. Brenner H, Chang-Claude J, Seiler CM, et al. Interval cancers after negative colonoscopy: population-based case-control study. Gut 2012;61:1576-82.
9. Brenner H, Chang-Claude J, Seiler CM, et al. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 2011;154:22-30.
10. Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. Clin Gastroenterol Hepatol 2010;8:858-64.
11. Martinez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology 2009;136:832-41.
12. Singh S, Singh PP, Murad MH, et al. Prevalence, Risk Factors, and Outcomes of Interval Colorectal Cancers: A Systematic Review and Meta-Analysis. Am J Gastroenterol 2014.
13. Brenner H, Hoffmeister M, Arndt V, et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst 2010;102:89-95.
14. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362:1795-803.
15. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298-306.
16. Meester RG, Doubeni CA, Lansdorp-Vogelaar I, et al. Variation in Adenoma Detection Rate and the Lifetime Benefits and Cost of Colorectal Cancer Screening: A Microsimulation Model. Jama 2015;313:2349-58.
17. Kaminski MF, Wieszczy P, Rupinski M, et al. Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death. Gastroenterology 2017;153:98-105.
18. Muto T, Kamiya J, Sawada T, et al. Small "flat adenoma" of the large bowel with special reference to its clinicopathologic features. Dis Colon Rectum 1985;28:847-51.
19. Church JM, Muto T, Appau K. Flat lesions of the colorectal mucosa: differences in recognition between Japanese and American endoscopists. Dis Colon Rectum 2004;47:1462-6.

Formatted: English (United States), Check spelling and grammar

20. Watanabe T, Sawada T, Kubota Y, et al. Malignant potential in flat elevations. Dis Colon Rectum 1993;36:548-53.
21. Kudo S, Kashida H. Flat and depressed lesions of the colorectum. Clin Gastroenterol Hepatol 2005;3:S33-6.
22. Wolber RA, Owen DA. Flat adenomas of the colon. Hum Pathol 1991;22:70-4.
23. Hart AR, Kudo S, Mackay EH, et al. Flat adenomas exist in asymptomatic people: important implications for colorectal cancer screening programmes. Gut 1998;43:229-31.
24. Hurlstone DP, Cross SS, Adam I, et al. A prospective clinicopathological and endoscopic evaluation of flat and depressed colorectal lesions in the United Kingdom. Am J Gastroenterol 2003;98:2543-9.
25. Josifovski J, Pilcevic D, Kocic M, et al. Synchronous and metachronous flat adenomas in colorectal cancer: single institution experience. J buon 2003;8:167-9.
26. Parra-Blanco A, Gimeno-Garcia AZ, Nicolas-Perez D, et al. Risk for high-grade dysplasia or invasive carcinoma in colorectal flat adenomas in a Spanish population. Gastroenterol Hepatol 2006;29:602-9.
27. Soetikno RM, Kaltenbach T, Rouse RV, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. Jama 2008;299:1027-35.
28. Jaramillo E, Watanabe M, Slezak P, et al. Flat neoplastic lesions of the colon and rectum detected by high-resolution video endoscopy and chromoscopy. Gastrointest Endosc 1995;42:114-22.
29. O'Brien M J, Winawer SJ, Zauber AG, et al. Flat adenomas in the National Polyp Study: is there increased risk for high-grade dysplasia initially or during surveillance? Clin Gastroenterol Hepatol 2004;2:905-11.
30. Diebold MD, Samalin E, Merle C, et al. Colonic flat neoplasia: frequency and concordance between endoscopic appearance and histological diagnosis in a French prospective series. Am J Gastroenterol 2004;99:1795-800.
31. Park DH, Kim HS, Kim WH, et al. Clinicopathologic characteristics and malignant potential of colorectal flat neoplasia compared with that of polypoid neoplasia. Dis Colon Rectum 2008;51:43-9; discussion 49.
32. Bianco MA, Cipolletta L, Rotondano G, et al. Prevalence of nonpolypoid colorectal neoplasia: an Italian multicenter observational study. Endoscopy 2010;42:279-85.
33. Reinhart K, Bannert C, Dunkler D, et al. Prevalence of flat lesions in a large screening population and their role in colonoscopy quality improvement. Endoscopy 2013;45:350-6.
34. Calderwood AH, Lasser KE, Roy HK. Colon adenoma features and their impact on risk of future advanced adenomas and colorectal cancer. World J Gastrointest Oncol 2016;8:826-834.
35. Yahagi M, Okabayashi K, Hasegawa H, et al. The Worse Prognosis of Right-Sided Compared with Left-Sided Colon Cancers: a Systematic Review and Meta-analysis. J Gastrointest Surg 2016;20:648-55.
36. Gupta S, Balasubramanian BA, Fu T, et al. Polyps with advanced neoplasia are smaller in the right than in the left colon: implications for colorectal cancer screening. Clin Gastroenterol Hepatol 2012;10:1395-1401.e2.
37. Sawhney MS, Dickstein J, LeClair J, et al. Adenomas with high grade dysplasia and early adenocarcinoma are more likely to be sessile in the proximal colon. Colorectal Dis 2015.
38. Moss A, Williams SJ, Hourigan LF, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal

neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut 2015;64:57-65.
39. Oka S, Tanaka S, Saito Y, et al. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol 2015;110:697-707.
40. Loberg M, Kalager M, Holme O, et al. Long-term colorectal-cancer mortality after adenoma removal. N Engl J Med 2014;371:799-807.
41. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095-105.
42. Adler A, Lieberman D, Aminalai A, et al. Data quality of the German screening colonoscopy registry. Endoscopy 2013;45:813-8.
43. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet 2014;383:1490-502.
44. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology 2001;120:1607-19.
45. O'Connor A, McNamara D, O'Morain CA. Surveillance of gastric intestinal metaplasia for the prevention of gastric cancer. Cochrane Database Syst Rev 2013;9:Cd009322.
46. Sharma P, Montgomery E. Gastrointestinal dysplasia. Pathology 2013;45:273-85.
47. de Jonge V, Sint Nicolaas J, van Leerdam ME, et al. Systematic literature review and pooled analyses of risk factors for finding adenomas at surveillance colonoscopy. Endoscopy 2011;43:560-72.
48. Rembacken BJ, Fujii T, Cairns A, et al. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet 2000;355:1211-4.
49. Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet 2017;389:1299-1311.
50. Anderson JC, Butterly LF, Robinson CM, et al. Risk of Metachronous High-risk Adenomas and Large Serrated Polyps in Individuals With Serrated Polyps on Index Colonoscopy: Data from the New Hampshire Colonoscopy Registry. Gastroenterology 2017.
51. van der Vlugt M, Grobbee EJ, Bossuyt PMM, et al. Interval Colorectal Cancer Incidence Among Subjects Undergoing Multiple Rounds of Fecal Immunochemical Testing. Gastroenterology 2017.
52. Rex DK, Rabinovitz R. Variable interpretation of polyp size by using open forceps by experienced colonoscopists. Gastrointest Endosc 2014;79:402-7.
53. Chaptini L, Chaaya A, Depalma F, et al. Variation in polyp size estimation among endoscopists and impact on surveillance intervals. Gastrointest Endosc 2014;80:652-9.
54. Barancin C, Pickhardt PJ, Kim DH, et al. Prospective blinded comparison of polyp size on computed tomography colonography and endoscopic colonoscopy. Clin Gastroenterol Hepatol 2011;9:443-5.
55. Turner JK, Wright M, Morgan M, et al. A prospective study of the accuracy and concordance between in-situ and postfixation measurements of colorectal polyp size and their potential impact upon surveillance. Eur J Gastroenterol Hepatol 2013;25:562-7.
56. de Vries AH, Bipat S, Dekker E, et al. Polyp measurement based on CT colonography and colonoscopy: variability and systematic differences. Eur Radiol 2010;20:1404-13.
57. Moug SJ, Vernall N, Saldanha J, et al. Endoscopists' estimation of size should not determine surveillance of colonic polyps. Colorectal Dis 2010;12:646-50.
58. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315-29; quiz 1314, 1330.

59. Holme O, Bretthauer M, Eide TJ, et al. Long-term risk of colorectal cancer in individuals with serrated polyps. Gut 2015;64:929-36.
60. Pellise M, Burgess NG, Tutticci N, et al. Endoscopic mucosal resection for large serrated lesions in comparison with adenomas: a prospective multicentre study of 2000 lesions. Gut 2016.
61. Gao Q, Tsoi KK, Hirai HW, et al. Serrated polyps and the risk of synchronous colorectal advanced neoplasia: a systematic review and meta-analysis. Am J Gastroenterol 2015;110:501-9; quiz 510.
62. Arain MA, Sawhney M, Sheikh S, et al. CIMP status of interval colon cancers: another piece to the puzzle. Am J Gastroenterol 2010;105:1189-95.
63. Stoffel EM, Erichsen R, Froslev T, et al. Clinical and Molecular Characteristics of Post-Colonoscopy Colorectal Cancer: A Population-based Study. Gastroenterology 2016;151:870-878.e3.

Formatted: English (United States)

Figure 1

Click here to download Figure Figure 1.tif