



Adenoma detection rate and risk of colorectal cancer

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ABSTRACT

Goals: The aim of this paper was to discuss association between adenoma detection rate (ADR) and interval colorectal cancer risk.**Background:** Adenoma detection rate is being used as a benchmark quality measure for colonoscopy. There are three studies showing inverse association between ADR and interval colorectal cancer risk. One recent study reports significant impact of increased ADR on decreasing interval colorectal cancer risk.**Study:** We discussed evidence for using ADR as a quality measure in colonoscopy and flexible sigmoidoscopy. We revised three studies (Kaminski et al., N Engl J Med 2010; Corley et al., N Engl J Med 2014 and Rogal et al., Clin Gastroenterol Hepatol, 2013) analyzing association between ADR and interval colorectal cancer. We collated strengths and weaknesses of these studies with the perspective of clinical impact of their results.**Results:** Kaminski et al. and Corley et al. reported inverse association between ADR at colonoscopy and interval colorectal cancer. Kaminski et al. showed that patients examined by endoscopists with ADR of less than 20% had over 10 times greater risk of interval colorectal cancer during the follow-up time than those examined by endoscopists with ADR $\geq 20\%$. Additionally, Corley et al. showed that ADR $\geq 28\%$ resulted in a significantly lower risk of colorectal cancer death than ADR of less than 19%. In parallel, Rogal et al. reported similar association for flexible sigmoidoscopy, with 2.4 higher odds of interval colorectal cancer diagnosis during follow-up time in patients examined by endoscopists with distal ADR $< 7.2\%$ than those with distal ADR $\geq 7.2\%$.

Apart from inevitable clinical importance of the studies, they are not without disadvantages. In Kaminski et al. study cohort and study endpoint are well defined, but there is lack of statistical power to provide more robust results. In Rogal et al. study cohort is well defined, but approximation of the study endpoint was used. Finally, Corley et al. study has both poorly defined study cohort and study endpoint, but has the highest statistical power of all three to detect the differences for both interval colorectal cancer and colorectal cancer death.

Conclusion: Both, inverse relationship between ADR and ADR improvement and colorectal cancer risk and death reaffirm ADR as a crucial quality control parameter.

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1. Introduction

Adenoma detection rate (ADR) is a benchmark quality measure for colonoscopy. It is defined as proportion of patients with at least one colorectal adenoma detected among all patients examined by an endoscopist [1]. Both, the European Society of Gastrointestinal

Endoscopy [1] and the American Society for Gastrointestinal Endoscopy jointly with the American College of Gastroenterology [2] in their current guidelines recommend for screening colonoscopy setting a minimum endoscopist's ADR cut-off of 25% (in a male/female population aged 50 or more). It is believed that this standard assures sufficient colorectal mucosa inspection to consider time to surveillance colonoscopy safe.

The aim of this paper is to discuss the available evidence supporting the use of ADR as a quality measure for colonoscopy with special emphasis on its association with interval colorectal cancer

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(iCRC) risk.

2. ADR variation

ADR by its definition is highly correlated with adenoma prevalence in a specific cohort. It has been shown that ADR varies between males and females, increases with patients' age [3–12] and differs among geographical regions [4,8,11,13]. ADR depends on indication for colonoscopy with significantly higher values in diagnostic and secondary screening (colonoscopy following positive guaiac fecal occult blood test (gFOBT) or fecal immunochemical test (FIT)) than in primary screening [6,14–16].

Even if the above factors explain the ADR variability between populations, still high variability among endoscopists within one population is observed. Indeed, endoscopist has been shown to be the most powerful predictor of ADR [17]. The studies using primary colonoscopy screening show that ADR ranges between 7% and 44% [5,17–23] with some studies reporting ADR of more than 50% [24,25]. At the same time, polyp miss rate estimated based on tandem colonoscopies varies between 2.1% for adenomas ≥ 10 mm and 26% for adenomas 1–5 mm [26].

Another study shows that in FIT positive population ADR of 45% is equivalent to ADR of 20% in primary colonoscopy screening and that there is a significant positive correlation between ADR in primary and secondary (following FIT positive) colonoscopy screening (Pearson's coefficient 0.716, $P < 0.001$) [16]. Reported median ADR after positive FIT among subjects aged 50–69 was 55% (range 21%–83%) [16], whereas mean ADR after positive FOBT among subjects aged 60–92 was 46.5% (range 21.9%–59.8%) [14].

It has been suggested that in colorectal cancer (CRC) screening setting endoscopists' ADR does not need to be adjusted for the case mix [14]. However, if ADR is planned to be calculated for endoscopic units providing services only for selected profile of patients the case-mix adjustment would be needed. Currently, this process is not clear yet and needs further studies [27].

With the adenomas being CRC precursors, both low ADR and high adenoma miss rate may have major clinical consequences.

3. ADR vs. colorectal cancer risk

Two studies reported inverse association between ADR and iCRC risk for colonoscopy (Kaminski et al. [28] and Corley et al. [29]) and one study reported inverse association between distal ADR and distal iCRC risk for flexible sigmoidoscopy (Rogal et al. [30]). Below, similarities and differences of these studies are presented.

3.1. Study design

Two of the studies (Kaminski et al. and Rogal et al.) used screening programs' databases for the analysis. In the first study it was an opportunistic colonoscopy screening, in the second study it was a randomized controlled trial comparing sigmoidoscopy screening with the usual care. In the study of Corley et al., integrated databases of insurance companies were used. They covered screening (18.3%), surveillance (24.3%) and diagnostic (57.4%) colonoscopies.

3.2. Study endpoints

Only in Kaminski et al. study final diagnosis of the primary colonoscopy for all subjects were given. This enabled authors to make a fair differentiation between screen detected CRC and iCRC for CRC reported at the beginning of the follow-up time. In this study iCRC was defined as CRC diagnosed between the date of index colonoscopy to the date of scheduled surveillance. Scheduled

surveillance was 3 years in subjects with high-risk adenoma removed (adenoma with ≥ 10 mm in diameter or high-grade dysplasia or villous/tubule-villous or ≥ 3 adenomas) and 5 years in subjects with low-risk adenoma removed (1–2 tubular adenomas < 10 mm in diameter with low-grade dysplasia). Follow-up time for subjects with no adenomas was censored after 5 years of observation.

In the two other studies, the final diagnosis of the primary colonoscopy was not known and distinguish between CRC diagnosed in the index exam and iCRC had to be approximated. In the Corley et al. study, iCRC was defined as CRC diagnosed between 6 months and 10 years after index colonoscopy. All CRCs diagnosed up to 6 months from index colonoscopy were considered to be detected in the index exam. In the Rogal et al. study, iCRC was defined as CRC stage I or II diagnosed between 1 year and 30 months after negative sigmoidoscopy or CRC stage III or IV diagnosed between 1 year and 48 months after negative sigmoidoscopy. All CRC diagnosed after this period of time were considered to be undetectable at the index exam.

In Kaminski et al. and Corley et al. studies data on iCRC were obtained from the cancer registries, whereas in Rogal et al. study iCRC was identified through the annually mailed questionnaire (overall response rate was 93.8%). Corley et al. was the only study where risk of iCRC death was analyzed. Data on causes of death were obtained from cancer registry and state mortality files.

3.3. Inclusion criteria

In Kaminski et al. study only subjects with adequate bowel preparation, with removal of all detected polyps and no detection of CRC at screening were included. In Rogal et al. study all subject that were diagnosed with iCRC and for whom index sigmoidoscopy was found to be low-quality (i.e. with inadequate bowel preparation or inadequate depth of insertion), with delayed follow-up colonoscopy or lesion missed at subsequent colonoscopy were excluded. Moreover, only subjects not undergoing cancer treatment (apart from skin cancer), no history of prostate, lung, colorectal or ovarian cancer and no colonoscopy, sigmoidoscopy or barium enema during last 3 years were eligible to have index colonoscopy (this requirement was not fulfilled during the first 2 years of enrollment period). No data on quality of bowel preparation or depth of insertion were given in Corley et al. study.

Minimum follow up time was 6 months in Corley et al. study, 12 months in Rogal et al. study and was not prespecified in Kaminski et al. study. Minimum number of screening exams performed by endoscopists to be included into the analysis was 30 in Kaminski et al. study, 75 in Corley et al. study and 100 in Rogal et al. study. Additionally, in Corley et al. study endoscopists were also required to perform at least 300 diagnostic exams.

3.4. Study population

Age range and proportion of male sex in the studies population was 40–66 years (55 on average) and 35.7% in Kaminski et al., 50–72 years (64 on average) and 47.7% in Corley et al. and 55–74 years (approx. 62 on average) 52% in Rogal et al. 20% of subjects had 1⁰ family history of CRC in Kaminski et al. study and 9.9% had 1⁰ family history of CRC in Rogal et al. study. Family history of CRC among subjects in Corley study was not available.

3.5. Adenoma detection rate

Total number of endoscopists was 186 in Kaminski et al. study, 136 in Corley et al. study and 93 in Rogal et al. study. Median non-adjusted ADR in Kaminski et al. study was 12.2% with an interquartile range

from 8.4% to 16.6%. In Corley et al. study median non-adjusted ADR was approx. 26.1% (obtained by taking the midpoint between 40th and 60th percentile) with a range from 7.35% to 52.5%. In Rogal et al. study median non-adjusted ADR was 9.1% and distal ADR was 6.9% (ranges were not reported). Rogal et al. study was the only one where adjusted point estimates of ADR and distal ADR were used for the analysis. Subject's age, sex and completion of subsequent colonoscopic follow-up were used for adjustment. Median adjusted ADR was 12.1% (range 3.6–24.5), median adjusted distal ADR was 9.2% (range 2.0–15.8).

In the study of Kaminski et al. predefined cut-off values of ADR were used to define ADR category, whereas in Rogal et al. and Corley et al. study quartiles and quintiles of ADR were used, respectively. Additionally, Corley et al. reported on linear relationship between ADR and the outcomes.

3.6. Results

Kaminski et al. showed that patients examined by endoscopists with ADR of less than 20% had over 10 times greater risk of CRC during the follow-up time than those examined by endoscopists with ADR $\geq 20\%$ with the hazard ratio (HR) for the lowest ADR category of 12.50 (95%CI 1.51–103.43, $P = 0.02$). These results were adjusted only for subjects' age, but family history of CRC, sex and endoscopists characteristics, such as cecal intubation rate, age, sex and specialty were tested for inclusion into a multivariable model.

Similarly, Corley et al. reported that ADR $\geq 28\%$ resulted in a significantly lower risk of CRC death than ADR of less than 19% with HR for the highest ADR category of 0.52 (95%CI 0.39–0.69), what translates to HR 1.92 for highest ADR category being a reference. Moreover, 1% increase in ADR was associated with 3% reduction in CRC risk (HR 0.97, 95%CI 0.96–0.98). These models included age, Charlson comorbidity score, sex and indication for colonoscopy as confounders.

In parallel, the comparable association was reported by Rogal et al. for flexible sigmoidoscopy, where odds of distal CRC diagnosis during follow-up time were 2.4 higher among patients examined by endoscopists with distal ADR $\leq 7.2\%$ than those with distal ADR $> 7.2\%$ (OR 2.4, 95%CI 1.1–5.0). Additionally, it was shown that overall ADR $\leq 9.3\%$ was almost statistically significantly associated with higher odds of distal CRC than overall ADR $> 9.3\%$ (OR 2.0, 95%CI 0.98–4.0, $P = 0.06$).

3.7. Strengths and weaknesses

Main advantage of Kaminski et al. study is the fact that this it was set in purely primary colonoscopy screening and detailed information on screening exam was given. This enabled to define the cohort well (only high-quality colonoscopy) and distinguish between CRC detected during index exam and iCRC. Follow-up period in this study was censored at scheduled colonoscopy surveillance, so the final results are not driven by the results of surveillance findings. Nevertheless, actual time and diagnosis of surveillance colonoscopy was not known and some patient may undergone the exam before the scheduled time.

Similarly, in Rogal et al. study the cohort is well defined, but data on quality of the colonoscopy were taken into account only if iCRC was diagnosed. Both, Rogal et al. and Corley et al. use a predefined time span after which they considered CRC to be iCRC. In consequence, some CRC that were diagnosed within this time span may actually be iCRCs and the other way round. What is more, in Corley et al. study there is no information about the quality of index exam and surveillance procedures. In consequence, observed effect of ADR may be a cumulative effect of low-quality exams (incomplete adenoma removal or inadequate bowel preparation) and

imbalanced surveillance. It should be also pointed out, that Rogal et al. used mailed survey for endpoint identification, what may lead to data collection bias.

Much higher ADR estimates were observed in Corley et al. study than in Kaminski et al. study. This may be an effect of the older study population (64 vs. 55 on average), higher proportion of males (47.7% vs. 35.7%), latter data collection period (1998–2010 vs. 2000–2004), inclusion of surveillance and diagnostic colonoscopies (81.7% of all exams) and higher population CRC risk in US than in Poland (age-standardized rate per 100,000 in 2000 was 30 vs. 20 among women and 40 vs. 30 among men [31]). Moreover, in Corley et al. study there was a linear relationship between ADR and iCRC whereas in Kaminski et al. study the non-linear relationship was observed. This may suggest that all adenomas are of clinical importance and even diminutive or small adenomas will eventually become cancer. Such a result, may be a consequence of different time of follow up, which in Kaminski et al. study was censored after 3 or 5 years and in Corley et al. study was censored after 10 years. It is rather unlikely that missing diminutive adenoma will lead to iCRC before the time of surveillance, but it could be a case in a longer perspective.

Even though, study cohort and study endpoints are rather poorly defined in Corley et al. study, still this is the only study with sufficient statistical power to provide with robust estimates for both iCRC risk and death. Summary of the studies characteristics can be found in Table 1.

4. Improved ADR vs. colorectal cancer risk

Results of association between ADR and CRC risk are of high clinical importance. With no doubts, they raised awareness of importance of the quality of the exams and contributed to increase of ADR over the years [32,33]. Still, little was known until now about impact of ADR improvement on CRC risk and death.

In a recent paper, Kaminski MF and Wieszczy P et al. [34] showed that ADR improvement (reaching higher quintile ADR category or maintaining the highest category) was associated with significant decrease in iCRC risk and death (HR 0.63, 95%CI 0.45–0.88 and 0.50, 95%CI 0.27–0.95, respectively). Moreover, reaching or maintaining the highest quintile ADR category ($> 24.56\%$) significantly decreased CRC risk as compared with no improvement (HR 0.27, 95%CI 0.12–0.63 and 0.18, 95%CI 0.06–0.56, respectively).

5. ADR vs. other detection measures

ADR is considered a surrogate for careful inspection of colorectal mucosa on colonoscope withdrawal [35]. However, ADR by definition is prone to 'one-and-done' effect, where detection of one, even minuscule and likely innocent adenoma is sufficient to count the patient as adenoma bearer. Therefore, there has been call for a more robust quality indicator.

More resistant to manipulation measures of colonoscopy quality are advanced adenoma (i.e. adenoma ≥ 10 mm or with villous component or high-grade dysplasia) detection rate (AADR), number of adenomas per colonoscopy (nADR or APC) or number of adenomas per positive colonoscopies (nADR+). There is a strong correlation of ADR and nADR (correlation coefficient 0.85, $p < 0.001$) and fair correlation between ADR and nADR+ (correlation coefficient 0.54, $p < 0.001$) [14], but no correlation between ADR and AADR (correlation coefficient -0.42 , $p = 0.13$) [36]. Undeniably these parameters provide additional information on colonoscopy quality. However, little is known about their association with CRC and death with only one study suggesting noninferiority of polyp detection rate (PDR) and nADR as compared to ADR [37].

Table 1
Characteristics of the studies.

	Kaminski et al.	Corley et al.	Rogal et al.
Design			
Exam	Colonoscopy	Colonoscopy	Sigmoidoscopy
Type of analysis	Registry based	Registry based	Registry based
Setting	Screening	Screening, surveillance & diagnostic	Screening
No. of endoscopists	186	136	93
No. of subjects	45,026	223,842	46,835
No. of exams	45,026	264,972	66,711
Data collection period	2000–2004	1998–2010	1993–2001
Follow-up period	2000–2008	1998–2010	1994–2002
Inclusion criteria	Only exams with adequate bowel preparation, all polyps removed and no CRC at screening	–	If CRC in follow-up, then only exams with adequate bowel preparation, cecum intubation and no CRC at screening
Primary endpoint	CRC diagnosed between colonoscopy and scheduled surveillance (3 or 5 years) ^a	CRC diagnosed 6 months to 10 years after colonoscopy	Distal CRC stage I or II found within 30 months or stage III or IV found within 48 months after negative sigmoidoscopy ^b
Secondary endpoint	–	CRC death diagnosed 6 months to 10 years after colonoscopy	–
Endpoint identification	Registry	Registry	Survey
Subjects			
Age (range)	40–66	50 ^d	55–74
Male sex	35.7%	47.7%	52%
1 ^o family history of CRC	20%	–	9.9%
ADR			
Estimate	Crude	Crude	Age, sex and diagnostic follow-up rate adjusted ^d
Median	12.2	c.a. 26.1	12.2 (9.2)
P20-P80	–	19.1–33.5	–
P25-P75	8.4–16.6	–	9.4–14.4 (7.3–11.2)
Minimum-maximum	–	7.4–52.5	3.6–24.5 (2.0–15.8)
Results			
Follow-up [months], median (IQR)	52.1 (41.3–60)	35 (19–59)	≥30 months for 98.9%, ≥40 months for 97.3% of subjects
Follow-up time [person-years]	188,788	927,523	–
CRC, N (per 10,000 person-years)	42 (2.2)	712 (7.7)	32 ^c
CRC death, N	–	147	–
Models' results for primary endpoint			
1 st ADR category	≥20% HR = 1.00 (ref)	33.51–52.51% HR = 0.52 [1.00 ^e] 95%CI 0.39–0.69	–
2 nd ADR category	15.0–19.9% HR = 10.94 95%CI 1.37–87.01	28.41–33.50% HR = 0.70 [1.34 ^e] 95%CI 0.54–0.91	7.3–15.8% ^c OR = 1.00 (ref)
3 rd ADR category	11.0–14.9% HR = 10.75 95%CI 1.36–85.06	23.86–28.40% HR = 0.85 [1.63 ^e] 95%CI 0.68–1.06	–
4 th ADR category	< 11.0% HR = 12.50 95%CI 1.51–103.43	19.06–23.85% HR = 0.93 [1.79 ^e] 95%CI 0.70–1.23	2.0–7.2% ^c OR = 2.4 95%CI 1.1–5.0
5 th ADR category	–	7.35–19.05% HR = 1.00 [1.92 ^e] (ref)	–

^a Scheduled surveillance was 3 years in subjects with high-risk adenoma removed (adenoma with ≥10 mm in diameter or high-grade dysplasia or villous/tubule-villous or ≥3 adenomas) and 5 years in subjects with low-risk adenoma removed (1–2 tubular adenomas <10 mm in diameter with low-grade dysplasia). Follow-up time for subjects with no adenomas was censored after 5 years of observation.

^b Negative sigmoidoscopy was defined as an exam with no polyps or masses detected.

^c Distal CRC and distal ADR.

^d Values in brackets applies to distal ADR.

^e Values in brackets are point estimates for 1st ADR category being a reference. HR = hazard ratio, OR = odds ratio, CI = confidence interval, P = percentile.

Growing recognition of sessile serrated polyps as colorectal cancer precursors [38], leads to another measure of colonoscopy quality defined as sessile serrated polyps detection rate (SSP-DR). SSP-DR was shown to associate with ADR [39], however data on its relationship with CRC risk is lacking.

Since ADR measurement requires merging histopathological databases with endoscopic ones, there is also call for a more feasible quality indicator that can be used as ADR surrogate. It has been shown, that PDR may be used to estimate ADR [40,41]. PDR is easy to calculate and monitor, however it is prone to gaming, because lymphoid nodules or even protrusions of normal mucosa could be mistakenly taken for polyps. Although association

between PDR and interval cancer risk has been demonstrated in one study [37], it should be used with caution.

6. Open issues

Beneficial impact of recommended colonoscopy surveillance may be observed if and only if high-quality baseline exam is delivered. Since, ADR is considered a surrogate of meticulous mucosa inspection and prerequisite for iCRC risk, it should have non-negligible impact on surveillance recommendations. Although the high ADR stands for lower iCRC risk, it results in more adenomas detected and ironically leads to shorter surveillance intervals.

Studies on relation between ADR and optimal surveillance are warranted.

With no doubts, data on association between ADR improvement and iCRC risk and death is of great clinical importance. However, optimal ADR cut-off and estimates of its upper limits are lacking. Still, nothing is known on ADR value above which there is a plateau in iCRC incidence and mortality.

Finally, wide recognition of FOBT and FIT based CRC screening programs reveal an urgent need for studies on association between ADR and iCRC risk and death in this screening setting. Even though, positive association between ADR in primary and secondary colonoscopy screening is highly expected, robust measure of the clinical effect is lacking.

7. Summary

Both, inverse relationship between ADR and ADR improvement and CRC risk and death reaffirm ADR as a crucial quality control parameter. These results are an important framework to clinical application of devices and programs aiming to increase ADR.

Practice points

- Adenoma detection rate (ADR) is widely recognized colonoscopy quality measure
- Inverse association between both ADR and ADR improvement and interval colorectal cancer and death has been shown
- These results are an important framework to clinical application of devices and programs aiming to increase adenoma detection rate

Research agenda

- There is a striking lack of evidence for optimal ADR cut-off and estimate of its upper limits
- Association between ADR and optimal surveillance needs to be quantified
- Studies on association between ADR and interval colorectal cancer risk and death in screening with guaiac fecal occult blood test or fecal immunochemical test are warranted

Conflicts of interest statement

PW has no competing interests. MFK is on the advisory board of Alfa Wasserman and has spoken and taught for Olympus Poland. JR is on the advisory boards of Alfa Wasserman, Ipsen Pharma, Polpharma, and Takeda and has a travel grant from Abbvie.

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