Gastroenterology 2015;149:952–957

Longer Withdrawal Time Is Associated With a Reduced Incidence of Interval Cancer After Screening Colonoscopy

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CLINICAL AT

This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this exam, successful learners will be able to (1) assess the association of withdrawal time and risk of interval colorectal cancers, (2) discuss the association of adenoma detection rate (ADR) and withdrawal time, and (3) identify risk factors for interval colorectal cancers.

See Covering the Cover synopsis on page 827.

BACKGROUND & AIMS: Withdrawal times and adenoma detection rates are widely used quality indicators for screening colonoscopy. More rapid withdrawal times have been associated with undetected adenomas, which can increase risk for interval colorectal cancer. **METHODS:** We analyzed records of 76,810 screening colonoscopies performed between 2004 and 2009, by 51 gastroenterologists practicing in Minneapolis and St Paul, MN. Colonoscopy records were linked electronically to the state cancer registry (Minnesota Cancer Surveillance System) to identify incident interval cancers that were diagnosed within 5.5 years after the screening examination. **RESULTS:** The physicians' mean ± SD withdrawal time was 8.6 ± 1.7 minutes and adenoma detection rates were 25% ± 9%. Longer mean withdrawal times were associated with higher adenoma detection rates (3.6% per minute; 95% confidence interval: 2.4% to 4.8%; $P < .0001$). We identified 78 cancers during 410,687 person-years of follow-up, for an annual rate of 0.19/1000 person-years. Physicians' mean annual withdrawal times were inversely associated with cancer incidence ($P < .0001$). Compared with withdrawal times ≥6 minutes, the adjusted incidence rate ratio for withdrawal times of <6 minutes was 2.3 (95% confidence interval: 1.5−3.4; $P < .0001$). **CONCLUSIONS:** Shorter mean annual withdrawal times during screening colonoscopies were independently associated with lower adenoma detection rates and increased risk of interval colorectal cancer.

Keywords: IRR; CRC; Colon Cancer; Early Detection.

Colonoscopy is an important screening modality that allows for detection and removal of asymptomatic adenomas.[1,2] However, there is considerable variability in performance of colonoscopy,[3,4] and suboptimal examinations can fail to detect significant lesions.[5–7] As a result, various quality indicators have been proposed, including adenoma detection rate (ADR), with a benchmark of 25% (30% for men and 20% for women), and withdrawal time of at least 6 minutes.[8,9] Physicians with a lower ADR or short withdrawal time might be failing to detect advanced adenomas and cancers. Incident colorectal cancer (CRC) that occurs within 5 years of a clearing colonoscopy might represent a lesion that was present but not detected at the time of the initial examination or was incompletely removed, and can broadly be defined as an interval CRC. Kaminski et al[10] found that an ADR of <20% was associated with higher rates of interval CRC in 45,026 Polish subjects undergoing screening colonoscopy.[10] Corley et al[11] found a progressive decrease in the risk of interval CRC as the ADR increased and, compared with the lowest quintile of ADR (≤19%), the hazard was significantly reduced when ADR were >28%. However, their ADR were not restricted to screening cases and the majority of colonoscopies were done for surveillance and diagnostic purposes. Also, neither study collected information on withdrawal times. Barclay et al[12] found that withdrawal time of >6 minutes is associated with higher ADR. Whether withdrawal time is associated with interval CRC is not known. Our study aims were to study the relationships between withdrawal time, ADR, and the incidence of subsequent CRC in a community gastroenterology practice.

Methods

We retrospectively collected detailed information on all colonoscopy examinations performed between January 2004 and December 2009 by Minnesota Gastroenterology P.A., the

Abbreviations used in this paper: ADR, adenoma detection rate; CRC, colorectal cancer; CI, confidence interval; IRR, incidence rate ratio; MCSS, Minnesota Cancer Surveillance System.

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0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.06.044

largest community practice in Minnesota. All colonoscopies were performed by 51 gastroenterologists at ambulatory endoscopy centers serving the metropolitan areas of Minneapolis and St Paul, Minnesota. Information, including patient demographics and colonoscopy data points, were extracted electronically from the electronic medical record (NextGen System). The colonoscopy reporting software is customized within the NextGen product and has templated fields for the colonoscopy, such as indications, preparation quality, extent of the examination, polyps removed, polyp size, location of the polyps, and pathology results. An SQL query was written to extract the colonoscopy and pathology data points for each of the cases. The pathology results for each case, each polyp, and any histology of adenomatous tissue were exported into a single file by information technology support staff at Minnesota Gastroenterology, P.A. and assigned a unique, blind study record ID to each set of deidentified clinical records. These data files were transmitted to the University of Minnesota using secure encrypted transmission methods. The University staff, under supervision of the principal investigator, identified cases of interest based on inclusion and exclusion criteria. Information technology staff at Minnesota Gastroenterology, P.A. transmitted a limited electronic file of cases of interest, with identifiable information (ie, full name, social security number, date of birth, sex, address) and the unique blind study record ID to the Minnesota Cancer Surveillance System (MCSS). MCSS performed record linkage to incident CRCs and transmitted the electronic file to the University devoid of personal identifiers containing the unique blind study record ID number that was used for analysis. This ensured that no party had identifiable information that they were not authorized to receive. For the purpose of the study, we restricted the analysis to individuals aged 50 years and older who underwent a colonoscopy for the primary indication of screening. Endoscopists had previously signed a partnership agreement that acknowledged the results of their procedures would be monitored for quality purposes. Patients underwent standard bowel preparation using one of several oral lavage regimens. Colonoscopy was considered complete if cecal landmarks or surgical anastomosis were reached and described. Colonoscopies were included if the preparation was rated fair, good, or excellent, if the colonoscopy was complete, or any examination where an adenoma was detected and removed, regardless of preparation quality. The data included the patient's age, sex, completion of the procedure, total procedure time, withdrawal time for negative examinations, time of the day (morning vs afternoon), day of the week when the colonoscopy was performed, and whether one or more histologically confirmed adenomatous polyps (adenoma) was found during the examination. Physicians who had performed a minimum of 100 colonoscopies during the 6-year study period were included in the analysis. They were blinded to the incident cancer data, and were not directly involved in the analysis of the data. To ensure patient privacy, the researchers were blinded to personal identifiable information for both patients and endoscopists.

Withdrawal Times and Adenoma Detection Rates

Both withdrawal times and ADRs were calculated from screening colonoscopies only to exclude the effects of surveillance and diagnostic colonoscopies. Mean withdrawal time for a physician was measured from the time the endoscopist announced he or she was starting to withdraw until removal of the colonoscope from the patient in examinations where no polyps were found. Withdrawal time documentation was available from January 2007 onward. Mean withdrawal times were calculated for each physician for each calendar year. The physician's 2007 mean withdrawal time was assigned to earlier procedures. We defined the annual ADR for a physician as the proportion of annual (calendar year) screening colonoscopies where at least 1 adenoma (adenomatous polyp) was found. We averaged the withdrawal times and ADR for 1 year at a time because they tended to increase during the period of study. This approach is more commensurate with use as quality indicators for screening colonoscopies. Data were extracted electronically. Checks on the quality of electronically extracted data were done by randomly selecting 1% of all database records and performing manual chart review of the colonoscopy and pathology reports. Agreement between extracted data and information in the chart was 99%.

Interval Colorectal Cancer

We obtained information on incident CRC between January 2004 and February 2014 from the state's cancer registry, MCSS. Linkage to the MCSS has been used for a variety of studies to track incident cancers and is a reliable and nearly complete source of all cancers of Minnesota residents diagnosed or treated in the state.[13] Cancer information on Minnesota residents from hospitals in bordering towns and cities of neighboring states (ie, North Dakota, South Dakota, and Wisconsin) was captured as well. MCSS data for 1 year are usually finalized 12 to 24 months after the end of a year and encompass 99.9% of microscopically confirmed cases. For the current analyses, follow-up time was time from index colonoscopy to cancer diagnosis, 5.5 years or February 11, 2014, whichever came first. Interval CRC, for the purposes of the study, was any adenocarcinoma discovered between 3 months after the index examination and within 5.5 years, allowing for a lag in the diagnosis (eg, a 5-year surveillance examination being performed months after the 5-year anniversary of the earlier examination) and assuming the later cases would have been present within 5 years. The pathology department, as required by the state, has an electronic reporting relationship with the state cancer registry to submit pathology reports on all cancers diagnosed by the practice. We used the same mechanism to send information on records of interest. The cancer registry performs extensive quality control through audits of medical records and has reported a coding agreement of 97.1% for CRC.[13]

Statistical Analyses

The person-year incidence of interval CRC was calculated and related to the physicians' mean annual withdrawal times and annual ADR, and patient, physician, and procedure characteristics using Poisson regression. To allow for the possibility of curvilinear relationships, withdrawal times and ADR were fitted as using restricted cubic splines with knots at the 10^{th}, 50^{th}, and 90^{th} percentiles of their distributions.[14] The likelihood ratio test was used to determine significance of unadjusted associations. Wald statistics were used to test for associations controlling for the patient's age and sex and

the quality of the colonoscopy preparation. The withdrawal times and ADRs were also analyzed in categories (>6 and <6 minutes for withdrawal time and >25% and <25% for ADRs) based on recent published guidelines.[8] The overall association between the physicians' mean annual withdrawal times and their annual ADRs was estimated using random-effects generalized least squares regression, including their patients' mean ages and male fraction and mean quality of the patient's preparation for colonoscopy during each year. Robust standard errors were calculated for all regression analyses to account for the clustering of patients within physicians. Stata software, version 12.1 (2012, StataCorp LP, College Station, TX) was used for all analyses. The study was approved by the Institutional Review Boards at the University of Minnesota.

Results

During the study time period, 76,810 colonoscopies performed by 51 endoscopists met the criteria for this analysis. As summarized in Table 1, the patients' mean age was 58 years (range, 50−95 years) and 39,238 (51%) were women. The quality of the colonoscopy preparation was rated good or excellent in 95% of cases. An adenoma was detected in 25% of all the screening colonoscopies. Mean ± SD withdrawal time was 8.3 ± 2.8 minutes with a range from 3.9 to 14.4 minutes. Mean withdrawal time increased by a minute from 2007 to 2008 and 2009 (Table 1). The physicians' annual ADRs averaged 25% ± 9%. The physicians' mean annual withdrawal time was 8.6 ± 1.7 minutes. The physicians' annual withdrawal times and ADRs were positively related (3.6% increase in ADR per minute increase in withdrawal time, 95% confidence interval [CI]: 2.4−4.8; $P < .0001$) (Figure 1). A similar relationship was seen when the regression analysis was restricted to examinations performed in 2007 and later, when withdrawal times were consistently recorded (2.0% increase in ADR per minute increase in withdrawal time, 95% CI: 1.15−2.9; $P < .0001$).

We identified 78 incident cancers during the 410,687 person-years in the follow-up period, for an overall incidence rate of 0.19 per 1000 person-years (95% CI: 0.15−0.24 per 1000 years). As summarized in Table 2, the interval cancers were diagnosed 3.5 ± 1.3 years (range, 0.25−5.4) after the screening examination. The majority (54%) of the cancers were located in the proximal colon. The minimum follow-up time among those without an incident cancer was 4.1 years and averaged 5.3 ± 0.3 years. The mean withdrawal times were significantly ($P < .0001$) related to the incidence of incident CRCs, as illustrated in Figure 2. Starting at a withdrawal time of approximately 8.0 minutes, the incident CRC incidence rate increased as the physician's withdrawal time decreased. The incidence rate ratio (IRR) comparing the physicians' mean withdrawal times <6 to >6 minutes was 2.3 (95% CI: 1.5−3.4; $P < .0001$) adjusted for patients age, sex, and for quality of preparation for colonoscopy. This relationship was unchanged when adjusted for ADR in addition to patient age, sex, and preparation quality. A similar IRR was observed when this comparison was restricted to examinations performed in 2007 and later, when withdrawal times were consistently recorded, adjusting for patient age, sex, and preparation quality (IRR = 2.0; 95% CI: 1.0−3.9; $P = .04$).

Table 1. Description of Patients, Procedures, and Providers

Patients (n = 76,810)	Data
Age, *y*, mean ± SD	58 ± 7.8
Male, %	49
Colonoscopy	
Prep, %	
Fair	5
Good	42
Excellent	53
Afternoon vs morning	39
Monday	21
Tuesday	19
Wednesday	19
Thursday	20
Friday	21
2004	12
2005	18
2006	18
2007	18
2008	19
2009	16
Withdrawal times,[a] *min*, mean ± SD	
2007 (n = 5,113)	7.5 ± 2.9
2008 (n = 9,986)	8.5 ± 2.7
2009 (n = 8,032)	8.6 ± 2.7
Overall (n = 23,131)	8.3 ± 2.8
Physicians (n = 51)	
Age, *y*, mean ± SD	51 ± 10
Male, %	82
Annual number of exams, mean ± SD	283 ± 135
Annual withdrawal times,[a] mean ± SD	8.6 ± 1.7
Annual adenoma detection rate, %, mean ± SD	25 ± 9

[a]Averaged over all examinations where no was adenoma detected; available beginning in 2007.

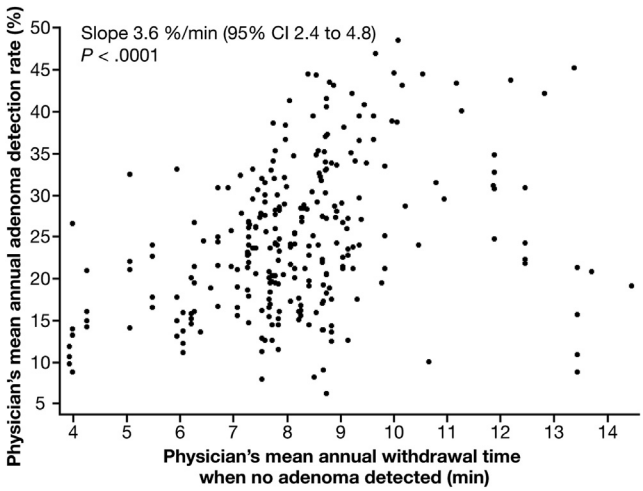

Figure 1. Relationship between physicians' annual withdrawal times and adenoma detection rates (ADRs).

Table 2. Comparisons of Interval Cancer Incidence Rates Within Risk Groups

Risk factor	Interval cancers	Person-years	Incidence rate per 1000 person-years, % (95% CI)	Incidence rate ratio (95% CI)[a]
Overall	78	410,687	0.19 (0.15–0.24)	—
Age				
<60 y	24	263,082	0.09 (0.06–0.14)	Reference
60–69 y	28	102,966	0.27 (0.19–0.39)	2.9 (1.7–5.2)
70 y	26	44,640	0.58 (0.40–0.86)	6.2 (3.7–10.3)
Adenoma found				
No	38	309,284	0.12 (0.09–0.17)	Reference
Yes	40	101,403	0.39 (0.29–0.54)	3.0 (1.8–4.8)
Mean withdrawal time[b]				
>6.0 min	59	363,833	0.16 (0.12–0.21)	Reference
<6.0 min	19	46,854	0.41 (0.26–0.64)	2.3 (1.5–3.4)
Adenoma detection rate[c]				
<25%	49	225,713	0.21 (0.16–0.28)	Reference
≥ 25%	29	184,974	0.15 (0.10–0.22)	0.7 (0.5–1.1)

[a]Adjusted for patient's age (except for age), sex, and quality of the colonoscopy preparation via Poisson regression clustered by physician to obtain CIs based on robust SEs.
[b]Calculated annually for each physician using cases when no adenoma detected.
[c]Calculated annually for each physician using all cases that were screened.

The physician's annual ADR were associated with the risk of interval CRC, but the relationship did not reach statistical significance ($P = .41$) (Figure 3). Similarly, in adjusted models compared with examinations by physicians with ADR <25%, those with ADR ≥25% were associated with a lower incidence rate of interval cancer (IRR = 0.7; 95% CI: 0.5–1.1; $P = .19$), but the relationship did not achieve statistical significance (Table 2). The incidence of interval cancers increased with patient age. Compared with individuals aged <60 years, the IRR for interval cancers was 2.9 (95% CI: 1.7–5.2) for individuals aged 60–69 years and 6.2 (95% CI: 3.7–10.3) for those aged ≥70 years (Table 2). Individuals with one or more adenoma detected during colonoscopy were at increased risk of interval cancer (IRR = 3.0; 95% CI, 1.8–3.8; $P = .006$) (Table 2). The incidence of interval cancer was not associated with patient sex, time of day, day of week, year of colonoscopy, or with physician age, sex, or years of experience.

Discussion

When physicians had a shorter mean annual withdrawal time, the incidence of interval CRC was significantly increased. The continuous relationship of the physicians' mean annual withdrawal times to the incidence of interval CRC appeared to be nonlinear; there was no obvious cut point for defining poor quality for screening colonoscopies. Our analyses suggest that the incidence of interval CRC was lowest and relatively constant when a physician's annual mean withdrawal time was ≥8 minutes. These results

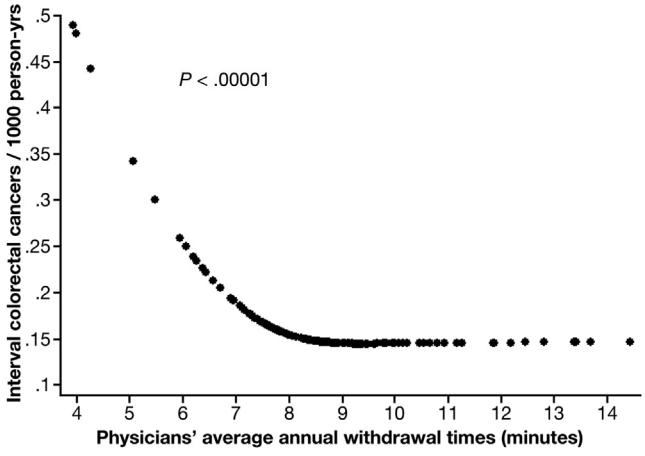

Figure 2. Nonlinear Poisson regression model of the relationship between incidence of interval cancer and physicians' mean annual withdrawal times. The *dots* represent the expected incidence rates for each observed average annual withdrawal time as estimated from the fitted curve.

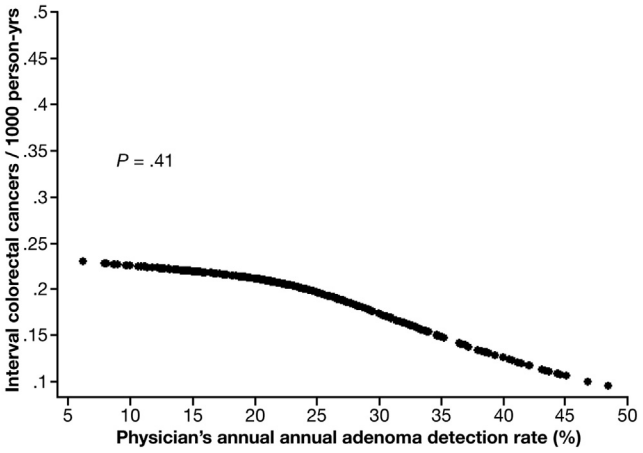

Figure 3. Nonlinear Poisson regression model of the relationship between incidence of interval cancer and physicians' adenoma detection rates (ADRs). The *dots* represent the fitted curve as the estimated incidence rates for each observed annual ADR.

support the use of withdrawal times as a quality indicator for screening colonoscopy,[12,15] and suggest that focusing quality-improvement efforts on withdrawal time <6 minutes would likely have the most impact. This relationship should be examined by additional studies before setting a quality threshold. Withdrawal times are easier to record and measure than ADRs, and can be modified with certain interventions,[11,12] which has potential for improving the efficacy of CRC screening and reducing interval cancers. Although the exact mechanism by which withdrawal time impacts risk of interval cancer is not known, we hypothesize that it is (albeit imperfect) a surrogate of careful colonic mucosal inspection. However, given the low overall incidence of interval cancer in this community practice, the impact of increasing withdrawal times might be small.

Similar to other published reports,[12,15,16] we found an association between the physicians annual withdrawal time and ADR. These measures are presumably related, as both are physician-level factors and indicators of careful inspection of the colonic mucosa. However, the relationship between withdrawal time and interval cancer was unchanged when ADR was added to the model, suggesting ADR was not the primary mediator of the relationship. We could not confirm previous studies that reported physicians' annual detection rates were inversely associated with the incidence of interval cancers.[7,8] We did observe a decreasing trend in the incidence of interval CRC beginning at an annual detection rate of about 25%. However, an inverse relationship between ADR and interval CRC is confounded by the increased risk of interval CRC among those that have an adenoma, as we and others have found.[17] Individuals that harbor an adenoma are usually under closer surveillance and are therefore more likely to have an asymptomatic cancer detected at colonoscopy.[18] Another explanation for this finding is that we restricted the analysis to screening colonoscopies, and other published reports[11] have included surveillance and diagnostic colonoscopies, during which adenomas and advanced neoplasia are more likely to be found. Finally, there were very few physicians in our study with ADRs <20%, and the number of intervals cancers might be too small to reach statistical significance. We found that patient's age was also positively associated with an increased incidence of interval cancer. This finding is consistent with other reports that show increasing prevalence of adenoma and cancer with age.[19] The incidence rate of 0.19 per 1000 person years for interval cancers after screening colonoscopies in our study is comparable with rates reported by others,[10,20] although the methods of case identification and follow-up are different and should be taken into account. Specifically, our follow-up time was 5.5 years, and we are unable to exclude individuals that moved out of state or died during the follow-up period. In this regard, our incidence rates might be an underestimation of the true incidence rates.

Our study has a number of limitations. First, there was lack of documentation of withdrawal times before 2007. We used withdrawal times from 2007 for the years before 2007. The physician's withdrawal times increased from 2007 to 2009, especially from 2007 to 2008, when they began to be recorded. Our analyses might have overestimated the actual withdrawal times in 2004 to 2006. Although this simple imputation reduces the variation in withdrawal times, we were still able to detect a relationship to interval cancers even when the analysis was restricted to data from 2007 to 2009. Second, we might be missing incident cancers that were diagnosed and treated in other states. Also, we do not know if the incident cancers were diagnosed on surveillance colonoscopy or were prompted by symptoms. However, the missing diagnostic information would most likely not be related to withdrawal times and ADRs and bias our results. Third, the study was performed on gastroenterologists practicing in one community, so we are unable to generalize the results to other types of providers or practices.[5,21]

The strengths of our study include having data from a large community-based practice with records linked to a comprehensive state cancer registry. The patients seen in this practice represent asymptomatic community-dwelling individuals, which is the target population for all screening programs. In addition, both withdrawal time and ADR were systematically collected from 2007 onward.

In conclusion, shorter withdrawal times were associated with a small increase in risk of interval CRC.

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Received February 27, 2015. Accepted June 25, 2015.

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Conflicts of interest
The authors disclose no conflicts.

Funding
This work was funded by a Veterans Affairs Career Development program (CDA-2) (A.S.) and Center for Chronic Disease Outcomes Research, a VA HSR&D Center of Innovation (CIN 13-406).