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Incidence of Interval Colorectal Cancer Attributable to an Endoscopist in Clinical Practice

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Abstract

Background and Aims—Endoscopists who encounter an interval colorectal cancer (I-CRC) may be concerned about the implications because I-CRCs may represent a lapse in colonoscopy quality and a missed opportunity for prevention. To determine the I-CRC rate per colonoscopy examination and to examine the effect of colonoscopy volume and adenoma detection rate (ADR) on the number of I-CRCs attributable to an endoscopist.

Methods—We determined the rate of I-CRC diagnosis per outpatient colonoscopy examination by measuring the incidence of CRC diagnosis in practice and by assessing, via literature review, the percentage of cancers that are interval. We also estimated the number of attributable I-CRCs as a function of ADR and colonoscopy volume.

Results—Among 93,562 colonoscopies performed in 2013 to 2015 by 120 physicians in 4 diverse U.S. medical centers, 526 CRCs were diagnosed (0.6%). Of 149,556 CRCs in the published literature, 7,958 were I-CRCs (5.25% $\pm$ 0.94). With rates of 0.6% (CRC per colonoscopy) and 5.25% (I-CRC per CRC) the rate of I-CRC is 1 per 3,174 colonoscopies (95% CI, 1 per 2,710–1 per 3,875). An endoscopist at the median of colonoscopy volume (316/year), in the lowest ADR quintile of detection (7%–19%) would have an I-CRC attributed every 8.2 years, or 4.2 I-CRCs in a 35-year career, versus every 16.7 years, or 2.0 I-CRCs in a 35-year career, for an endoscopist in the highest ADR quintile (33%–52%).

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Conclusions—An average-volume endoscopist will have 2 to 4 attributable I-CRCs in a 35-year career, but the frequency will vary depending on colonoscopy volume and ADR.

Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer death in the United States¹. Screening for CRC with flexible sigmoidoscopy^{2,3} and colonoscopy^{4,5} reduces CRC incidence, presumably through the removal of adenomatous and sessile serrated polyps, precursor lesions that have the potential to evolve to CRC. Endoscopic screening with colonoscopy is the most common means of CRC screening in the United States,⁵ but the efficacy of colonoscopy depends on the quality of the examination. An endoscopist's adenoma detection rate (ADR), or the prevalence of adenomas detected on colonoscopy, is inversely associated with that endoscopist's patients' risk of developing a subsequent cancer. Patients of practitioners with a lower ADR at colonoscopy^{6,7} or at flexible sigmoidoscopy⁸ have higher subsequent rates of CRC. From a pathophysiologic perspective, the presumption is that patients of practitioners who leave behind significant numbers of precursor lesions are at greater risk for one of those lesions to subsequently evolve into CRC.

CRCs that occur subsequent to testing have been classified as interval colorectal cancers (I-CRC) and are defined as cancers “diagnosed after a screening or surveillance examination in which no cancer is detected, and before the date of the next recommended examination.”⁹ I-CRC are a focus of attention because they may represent a missed opportunity to prevent a subsequent cancer. Among practitioners in the Kaiser Northern California healthcare system in the highest quintile of ADR, there was a 50% lower incidence of interval cancer compared to practitioners in the lowest quintile of ADR detection⁷. Although a higher ADR was associated with a significantly lower rate of I-CRC, interval cancers did occur even in the highest ADR performance quintile.

Though I-CRC may seem like an appealing quality metric, I-CRCs are rare in an endoscopist's practice¹⁰. I-CRCs are also difficult to measure due to the long risk period after a patient's last colonoscopy, and a fragmented healthcare system in the United States that may lead to CRC diagnosis and treatment at a different facility, without the knowledge of the original endoscopist. The aim of our investigation is to determine the expected rate of an I-CRC in outpatient clinical practice and to examine the effect of an endoscopist's colonoscopy volume and ADR on the number of I-CRC's attributable to that endoscopist, in order to provide context for endoscopists regarding an I-CRC they might encounter in routine clinical practice.

Methods

Overview

We determined the frequency of CRC diagnosis in clinical practice by analyzing CRC diagnoses in a sample of 93,562 outpatient colonoscopy examinations in 4 clinical sites. Using literature review, we determined the percentage of CRCs that are I-CRC. Using the rate of CRC diagnosis in clinical practice and the average percentage of I-CRC among all

CRCs, we calculated the rate of I-CRC diagnosis per outpatient colonoscopy examination. Because the rate of I-CRC for an individual endoscopist will vary by colonoscopy volume, we assessed colonoscopy volumes of individual endoscopists in our clinical practice sample. To estimate the effect of ADR on the rate of I-CRC attributable to an endoscopist, we applied the unadjusted relative risk of interval cancer as a function of ADR reported by Corley et al⁷. I-CRCs may be diagnosed by an endoscopist who is different from the one who performed the initial examination. We have used the term “attributable” to reflect the overall expected incidence after initial examinations by a given practitioner, but this does not necessarily reflect the I-CRCs diagnosed personally by that particular practitioner.

I-CRC rate among reported CRCs

To estimate the percentage of CRCs that are I-CRCs, we conducted a literature search on PubMed and Cochrane databases with search terms including “Interval Colorectal Cancer,” “Post-colonoscopy interval Cancer,” and “Post-colonoscopy Colorectal Cancer.” Searches were limited to the English language and to within the years January 2006 to January 2017. Studies that reported the incidence of I-CRCs among total number of CRCs were included and were used to calculate the average percentage of I-CRC among all CRCs. Studies that reported I-CRC rates based on person-year observation were excluded (Supplementary Table 1).

CRC Diagnosis in Clinical Practice

To determine the frequency of CRC diagnoses in contemporary endoscopic practice, we examined a large cross-sectional sample of outpatient colonoscopy examinations from October 1st 2013 to September 30th 2015 using a previously validated natural language processing system.^{11–14} Four health systems were studied including a staff model health maintenance organization (Kaiser Permanente Washington (KPW)) in Seattle, Washington (16 physicians), a private practice (Central Illinois Endoscopy (CIE)) in Peoria, Illinois (11 physicians), an academic medical center (University of North Carolina (UNC)) in Chapel Hill, North Carolina (23 physicians), and a mixed academic-community health system (University of Pittsburgh Medical Center (UPMC)) in Western Pennsylvania (70 physicians). This study was approved by the Institutional Review Board at the University of Pittsburgh.

We restricted the analysis to endoscopists performing at least 200 colonoscopy examinations over 2 years to exclude part-time physicians or those for whom colonoscopy was a small component of clinical practice. Inpatient colonoscopies, procedures for adults age less than 40 years old, and patients with inflammatory bowel disease were excluded. All pathology reports that contained text including the words “Carcinoma,” “Carcinoma in-situ,” or “Cancer” were reviewed manually to confirm the diagnosis of invasive CRC. We assessed the rate of CRC by colonoscopy indication (screening vs not) and calculated colonoscopy volumes per endoscopist.

Frequency of CRC Diagnosis by Specialty and Colonoscopy Volume

We also examined whether the frequency of CRC diagnosis in clinical practice differed by endoscopist specialty (gastroenterology vs non-gastroenterology) and by colonoscopy volume – low volume (below median) versus high (above median).

I-CRC Diagnosis in Clinical Practice

Based on the incidence of CRC per colonoscopy, and the fraction of CRCs that are I-CRCs, we determined the number of colonoscopy examinations to diagnose an I-CRC. We then examined the time to reach this number of colonoscopy examinations depending on the colonoscopy volume of an individual endoscopist.

I-CRCs Attributable as a Function of ADR

The ADR of an endoscopist is inversely related to the incidence of I-CRC¹⁵. We used the unadjusted relative risk of I-CRC by quintile of adenoma detection⁷ and applied the proportionate risk to the expected incidence of I-CRC. ADR quintiles and their respective unadjusted risk of I-CRC⁷ are as follows: quintile 1 (ADR: 7.35% – 19.05%), 2.04; quintile 2 (ADR: 19.06%–23.85%), 1.79; quintile 3 (ADR: 23.86%–28.4%), 1.66; quintile 4 (ADR: 28.41%–33.50%), 1.45; quintile 5 (ADR: 33.51%–52.51%), 1.0.

Sensitivity Analysis

In our study cohort, endoscopists for some health systems such as UPMC perform procedures in facilities or ambulatory centers that are not part of the system; hence, determination of colonoscopy volume may be an underestimate. As a sensitivity analysis, we examined the colonoscopy volumes among practitioners in CIE, the private practice group in our study sample, for whom capture of outpatient endoscopic activity was necessarily complete because they performed all of their outpatient examinations in a single center.

Results

I-CRC rate among reported CRCs

Of 149,556 CRC cases reported in 17 eligible U.S. and international studies since 2006, 7,958 cases were interpreted as I-CRC (Table 1). The average percent of CRCs that were I-CRC was $5.25\% \pm 0.94$ (95% CI, 4.31% – 6.16 %).

CRC Diagnosis in Clinical Practice

The demographic characteristics of the patients in our clinical sample of 93,562 outpatient colonoscopy examinations from 4 geographically dispersed U.S. clinical practices are presented in Table 2. The most common indications for colonoscopy included screening without family history (36.0%), surveillance (30.9%), diagnostic (20.9%), and screening with a family history of colon cancer (9.9%). The sample included 120 physicians.

The incidence of CRC diagnosis was 0.6% (565/93,562) across all colonoscopies (Table 2). The rate of CRC diagnosis was consistent across the 4 clinical sites, ranging from 0.5% to 0.7%. Non-screening colonoscopy had a greater than 2-fold higher rate of CRC diagnosis (0.8%) compared with screening colonoscopy (0.3%).

Frequency of CRC Diagnosis by Specialty and Colonoscopy Volume

Among 120 endoscopists, 13 physicians were not gastroenterologists (non-GI). Average CRC diagnosis rate for non-GI physicians ($0.58\% \pm 0.5$) was not significantly different than

for GI endoscopists ($1.02 \% \pm 0.85$; $p = 0.89$). Below-median-volume endoscopists (<316 /year) compared with higher-volume endoscopists (>316 /year) had a higher rate of CRC diagnosis ($0.7 \% \pm 0.72$) versus ($0.56 \% \pm 0.33$; $p=0.04$).

I-CRC Diagnosis in Clinical Practice

With a rate of CRC per colonoscopy of 0.6% and of I-CRC per CRC of 5.25%, the rate of I-CRC in clinical practice is 1 per 3,174 colonoscopies (95% CI, 1 per 2,710–1 per 3,875). The time to reach this number of examinations for an individual endoscopist would depend on colonoscopy volume. In our outpatient practice sample, the median number of colonoscopy examinations per year per endoscopist was 316; the 25th percentile was 172 colonoscopies per year and 75th percentile was 551 colonoscopies per year. Based on these volumes, an endoscopist in the 50th percentile of volume (316/year) would be expected to have one I-CRC every 10 years (Figure 1), and an endoscopist in the 75th would have one I-CRC every 5.8 years (Figure 1).

I-CRCs Attributable as a Function of ADR

Figure 1 depicts the number of years in practice to attribute one I-CRC to an endoscopist based on colonoscopy volume (25, 50 & 75th percentile) and by ADR quintile. For an endoscopist at the 50th percentile of colonoscopy volume, one I-CRC would be attributable every 8.2 versus every 16.7 years at the lowest versus the highest ADR detection quintile (Figure 1). For an endoscopist at the 75th percentile of colonoscopy volume, one I-CRC would be attributable every 4.7 years versus every 9.6 years at the lowest versus highest ADR detection quintiles (Figure 1).

The number of I-CRCs attributable to an endoscopist over a 35-year career based on colonoscopy volumes and ADR is presented in Table 3. For an endoscopist in the 50th percentile of colonoscopy volume, the rate of I-CRC attributable in a 35-year career would vary between 2.0 and 4.2 cases per 35 years.

Sensitivity Analysis

As a sensitivity analysis, we examined the endoscopy volume from the private practice group (CIE) that performed all of its outpatient examinations in a single center. In this subsample, for endoscopists in the 25th (332/year), 50th (593/year), and 75th (721/year) percentiles of colonoscopy volume, an I-CRC would be expected every 9.5, 5.3 and 4.4 years, respectively. For endoscopists in the 50th percentile of colonoscopy volume, one I-CRC would be attributable to an individual endoscopist every 4.3 years versus every 8.8 years at the lowest versus highest ADR detection quintiles.

Discussion

An I-CRC diagnosis raises concern because it may represent a lapse in colonoscopy quality and a missed opportunity to have prevented a subsequent cancer. It is difficult for endoscopists to put an I-CRC diagnosis in context because of uncertainty about what their expected frequency should be. By review of over 93,000 outpatient colonoscopy examinations, and based on the proportion of CRCs that are expected to be an I-CRC, we

estimate that an I-CRC occurs every 3,174 colonoscopy examinations (95% CI, 2,710 – 3,875). The rate attributable to an individual endoscopist will be modulated by colonoscopy volume and ADR. For example, an endoscopist in our sample in the 75th percentile of colonoscopy volume (N=551/year) with an ADR of 30% (which meets the recommended ADR target by guidelines¹⁶) would have an I-CRC every 6.6 years, or about 5 I-CRCs in a 35-year career. When the higher volume of practice estimate derived from the private practice group in our sample is used (721/year for the 75th percentile), an I-CRC would be every 5 years for an endoscopist in the same ADR quintile, or 7 I-CRCs in a 35-year career. For an average endoscopist within the 50th percentile of colonoscopy volume (316/year), an I-CRC would be attributable every 8.2 versus 16.7 years with the lowest versus the highest ADR quintile.

Even among practitioners performing in the highest ADR quintile of detection, some I-CRCs can be considered as an expected outcome. Thus, I-CRCs are somewhat akin to colonoscopy adverse events such as perforation, which can be expected to occur several times within a clinician's lifetime of practice. Coincidentally, the rate of I-CRC is about the same as the rate of perforation, which is also about 1 out of 3000 examinations¹⁷. These estimates do not excuse nor endorse I-CRCs as a necessary outcome. Studies investigating the etiology of I-CRC have shown that preventable causes, such as incompletely resected lesions and missed lesions, account for over 50% of I-CRCs^{18–20}. In addition, increasing the ADR has been shown to reduce the subsequent I-CRC rate^{15,20–21}. However, I-CRCs have been observed even among practitioners in the highest quintile of ADR. Efforts to diminish I-CRC rates remain a high priority and should be pursued¹⁰.

The low absolute rate of I-CRC per endoscopist, the time delay to the event, and the complexity in ensuring accurate feedback to the endoscopist who performed the initial procedure pose formidable challenges to using I-CRC as a quality measure at the level of the endoscopist. There is a distinction between encountering an I-CRC during a colonoscopy examination in practice and having an I-CRC attributable to an endoscopist. Endoscopists in practice do not always have long-term longitudinal contact with their patients. An I-CRC could be diagnosed at a different facility from where the index examination was done, and the initial endoscopist may be unaware of the outcome. Hence, intermediate or surrogate measures of colonoscopy quality such as ADR may be the only practical alternative for measuring colonoscopy quality in clinical practice.

Several limitations of our analysis should be acknowledged. First, our estimates assume a constant rate of CRC and I-CRC as a function of time. But, I-CRCs may not be distributed uniformly across practitioners with similar colonoscopy volume and ADR, just as not every practitioner has a perforation rate of 1 out of 3,000. Second, although there is now a consensus definition of I-CRC in the literature⁹, not all studies assessing the incidence of I-CRC have used the same definition. Our estimate that, on average, 5.25% of all CRCs are interval is a best approximation and is consistent with the estimation of the I-CRC rate by meta-analysis¹⁹. Even when accounting for variable definitions, as in a previous investigation which reported an I-CRC rate ranging from 2.5% to 7.7%²², our estimate of 5.25% appears representative. We also explored a range (4.31% – 6.16 %) represented by a 95% confidence interval (Fig. 1). Third, because of limited access to data before 2013, we

cannot determine prior endoscopic testing, and thus cannot characterize which patients had an interval cancer nor why an interval cancer might have occurred. Fourth, our colonoscopy volumes were based only on outpatient examinations with exclusions by patient age, IBD and a minimal colonoscopy volume per practitioner of 200 per 2 years. For some of the health systems in our sample, endoscopists were performing procedures in facilities or ambulatory centers that were not part of the system, hence our determination of colonoscopy practice volume may be an underestimate. In the CIE health system, procedure volume was higher, and higher practice volumes would lead to a shorter time interval to an I-CRC. However, the incidence of CRC per colonoscopy was similar across all the health systems, hence our determination of the expected frequency of an I-CRC did not vary by clinical practice or geographic location. Finally, because I-CRCs are rare events, it is likely that absolute rates per career will vary across practitioners. Nevertheless, our estimates are informative and provide important context.

In conclusion, interval cancers are estimated to occur approximately every 3,174 colonoscopy examinations. The rate attributable to an individual endoscopist will vary by colonoscopy volume and ADR quintile of detection. Approximately 2 to 4 I-CRCs can be attributed to average-volume endoscopists during a 35-year career, depending on their ADR. Even an endoscopist in the highest quintile of adenoma detection and with the most thorough lesion resection technique may have attributable I-CRCs. Initiatives to further reduce the I-CRC rate are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

I-CRC	interval colorectal cancer
ADR	adenoma detection rate
95% CI	95% confidence interval
KPW	Kaiser Permanente Washington
CIE	Central Illinois Endoscopy

UNC	University of North Carolina
UPMC	University of Pittsburgh Medical Center
non-GI	non-gastroenterologist

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Figure 1.

Estimated number of years in practice for one I-CRC to be attributable to an endoscopist by annual colonoscopy volumes (25th, 50th, 75th percentiles) and quintile of ADR detection. Error bars are based on the 95% confidence interval of I-CRC rates from literature review ($5.25\% \pm 0.94$ [95% CI, 4.31 – 6.16]) (Table 1). The unadjusted risk for I-CRCs by ADR quintile are based on Corley et al.⁷

Table 1

Literature Reported I-CRC rates, 2006 to 2017

Study	Country	Year	Total CRC cases	I -CRC cases	I-CRC rates (%)	I-CRC definition
Nayor et al	USA	2016	5,345	245	4.6	6 –60 months
NBCSP	Australia	2016	4,327	265	6.1	<24 months
Gotfried et al	USA	2015	1,147	45	3.9	6 –36 months
Richter et al	USA	2015	2,509	77	3	< 60 months
Corley et al	USA	2014	8,730	712	8.1	6 –120 months
Samadder et al	USA	2014	2,659	159	6.0	6 –60 months
le Clercq et al	Netherlands	2014	5,107	147	2.9	< 60 months
Erichsen et al	Denmark	2013	38,064	982	2.6	12 – 60 months
Atkinson et al	New Zealand	2012	1,299	49	3.8	<36 months
Brenner et al	Germany	2012	1,945	78	4.0	12 –120 months
Baxter et al	Canada	2011	676	54	9.0	7–36 months
Cooper et al	USA	2011	57,839	4,192	7.2	6 –36 months
Arain et al	USA	2010	1,323	63	4.8	< 60 months
Singh et al	Canada	2010	4,883	388	7.9	6 –36 months
Ferrandez et al	Spain	2010	386	27	6.7	< 36 months
Bressler et al	Canada	2007	12,487	430	3.4	6 –36 months
Farrar et al	USA	2006	830	45	5.4	< 60 months
Total	Number of studies = 17		149,556	7,958	5.25 (CI 4.31–6.16)	

Patient demographics and colonoscopy examinations from 4 diverse clinical sites including an academic medical center (UNC), a mixed academic-community health system (UPMC), a private practice (CIE), and a staff-model health maintenance organization (KPW).

Table 2

Sites	All sites combined	UPMC (%)	UNC (%)	CIE (%)	KPW (%)
Total Patients	93,562	58,447 (62.5)	12,959 (13.9)	11,829 (12.6)	10,327 (11.0)
Number of endoscopists	120	70	23	11	16
Sex					
Male	42,775 (45.7)	27,165 (46.5)	5,686 (43.9)	5,059 (42.8)	4,865 (47.1)
Female	49,678 (53.1)	31,282 (53.5)	7,272 (56.1)	5,662 (47.9)	5,462 (52.9)
Missing	1,109 (1.2)	-	-	1,108 (9.4)	-
Age					
40–49	7,548 (8.1)	5,009 (8.6)	1,195 (9.2)	583 (4.9)	761 (7.4)
50–59	34,175 (36.5)	21,696 (37.1)	5,013 (38.7)	4,215 (35.6)	3,251 (31.5)
60–69	31,609 (33.8)	19,093 (32.7)	4,415 (34.1)	4,052 (34.3)	4,049 (39.2)
70 and over	20,229 (21.6)	12,649 (21.6)	2,335 (18.0)	2,979 (25.2)	2,266 (21.9)
Race					
White	55,233 (59.0)	51,222 (87.6)	4,011 (31.0)	-	-
Black	7,046 (7.5)	5,470 (9.4)	1,576 (12.2)	-	-
Other	5,320 (5.7)	482 (0.8)	4,838 (37.3)	-	-
Missing	25,963 (27.8)	1,273 (2.2)	2,534 (19.6)	11,829 (100.0)	10,327 (100.0)
Indication					
Screening, no family history	33,703 (36.0)	21,197 (36.3)	5,217 (40.3)	5,177 (43.8)	2,112 (20.5)
Screening, with family history	9,292 (9.9)	6,076 (10.4)	1,170 (9.0)	794 (6.7)	1,252 (12.1)
Surveillance	28,900 (30.9)	17,170 (29.4)	4,591 (35.4)	3,286 (27.8)	3,853 (37.3)
Diagnostic	19,549 (20.9)	12,534 (21.5)	1,730 (13.4)	2,315 (19.6)	2,970 (28.8)
Missing	2,118 (2.3)	1,470 (2.5)	251 (1.9)	257 (2.2)	140 (1.4)
Carcinoma detected					
All colonoscopies	526 (0.6)	298 (0.5)	83 (0.6)	76 (0.6)	69 (0.7)
Non-screening colonoscopies	408 (0.8)	230 (0.7)	66 (1.0)	52 (0.9)	60 (0.9)
Only screening colonoscopies	118 (0.3)	68 (0.3)	17 (0.3)	24 (0.4)	9 (0.3)

Table 3

The number of I-CRCs attributable to an endoscopist over a 35-year career based on colonoscopy volume and ADR quintile*.

Colonoscopy Volume	Low ADR (7.35% – 19.05%)	Median ADR (23.86%–28.4%)	High ADR (33.51%–52.51%)
10 th Percentile (N=115 CSE/year)	1.5	1.2	0.7
25 th Percentile (N=172 CSE/year)	2.3	1.8	1.1
50 th Percentile (N=316 CSE/year)	4.2	3.4	2.0
75 th Percentile (N=551 CSE/year)	7.4	6.0	3.6
90 th Percentile (N=789 CSE/year)	10.6	8.6	5.2

* Low ADR is quintile 1, median ADR is quintile 3, and high ADR is quintile 5 from the analysis by Corley et al⁷.