Colorectal screening and surveillance have been very effective tools in the fight against colorectal cancer (CRC). Colonoscopy is more than a cancer screening test; it also can prevent CRC by detecting and removing precancerous lesions. Despite this potential, there has been increasing concern about CRCs that occur after a previous colonoscopy and before the next screening/surveillance examination (interval CRCs). The etiology of interval CRC is thought to be caused mostly by missed or incompletely resected lesions on index colonoscopy with some contribution of rapidly progressive new lesions. If this is true, many interval cancers should be preventable by improving colonoscopy technique. There are a variety of strategies to decrease interval CRC rates including use of a split-dosed bowel preparation, optimizing withdrawal technique, ensuring complete polypectomy, and careful pathologic examination of the tissue removed. Furthermore, there should be an increased emphasis on how endoscopists are trained to cultivate high-quality technique throughout their careers. It is important to inform patients that even high-quality colonoscopy is not perfectly sensitive for the detection of advanced neoplasia. Improving colonoscopy quality can decrease interval CRC rates and further decrease CRC incidence and mortality.

Keywords: Colonoscopy; Advanced Neoplasia; Interval Cancer.

Colorectal cancer (CRC) incidence and mortality rates have been decreasing steadily in the United States for the past quarter century, in part owing to increasing use of effective screening strategies (Figure 1). Although these decreases started before widespread population screening via colonoscopy, conservative estimates suggest that more than half of the trend can be attributed to screening. Nonetheless, CRC remains the third most common malignancy and the second leading cause of cancer-related death in the United States. An average-risk individual has an approximately 5% lifetime risk of developing CRC and a 2% to 3% risk of death from the disease.
Risk of Interval Colorectal Cancer

Recent data have highlighted a significant rate of CRC despite previous colonoscopy. Rabeneck and Paszat 10 have suggested using the term postcolonoscopy CRC for any CRC found after a colonoscopy. In this review, we use the term interval CRC for CRC found at or before the next recommended screening/surveillance colonoscopy. A similar definition can be used for interval advanced adenomas (defined as any adenoma ≥ 1 cm in size or with high-grade dysplasia or villous/tubulovillous architecture). Although the finding of an advanced adenoma during normal screening/surveillance should not be considered a failure of screening, the risk factors for interval cancers and interval advanced adenomas are similar, and examining them both provides insight into the process.

Frequency and Risk Factors for Interval Colorectal Cancer

Large retrospective studies from Canada11,12 and the United States13 have used administrative databases to estimate the percentage of CRCs that occur 6 to 36 months after a colonoscopy as a proxy for interval CRCs (the assumptions are that a CRC suspected at colonoscopy would have been diagnosed within 6 months, and 36 months is the usual shortest surveillance interval after polypectomy). By using this definition, 7.2% to 9% of CRCs met the definition of interval CRCs (Table 1). There was a significantly higher likelihood of interval cancers occurring in the proximal compared with the distal colon (9.9%–12.4% vs 4.5%–6.8%) in all these studies (Table 1). Similarly, a follow-up study of patients after a negative colonoscopy14 and a German case-control study15 found that interval cancers were about twice as likely to occur in the proximal colon than the distal colon when compared with noninterval CRCs. These studies (Table 2) also suggested that lower interval CRC rates are found after colonoscopies performed by gastroenterologists/colorectal surgeons than by other types of endoscopists and by endoscopists with higher completion and polypectomy rates (based on billing data) as well as for endoscopies performed in the hospital setting. It is not clear from these studies if age, sex, or the number of comorbidities are related to interval CRC rates (Table 2). Taken together, these data suggest that interval CRCs are related, in large part, to the quality of the index examination.

Interval Advanced Neoplasia After Colonoscopic Polypectomy

Numerous individual studies16–34 as well as a meta-analysis35 have reported that features that currently are used for recommending a shorter surveillance interval (adenoma number, advanced histologic features, and adenoma size) generally are associated with higher rates of interval advanced neoplasia. A pooled analysis36 of 8 prospective studies of 9167 patients reported an 11.2% rate of interval advanced adenoma and a 0.6% interval CRC rate after a mean follow-up period of 4 years. On multivariate analysis, age (for the age group 60–69 y: odds ratio [OR], 1.39; 95% confidence interval [CI],

Table 1. Frequency and Location of Interval CRCs

<table>
<thead>
<tr>
<th>Study</th>
<th>Data source</th>
<th>Total detected cancers, n</th>
<th>Interval cancers</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter et al,12</td>
<td>Ontario Cancer Registry (2000–2005)</td>
<td>34,312</td>
<td>1260 (9.0)</td>
<td>676 (12.4)</td>
<td>584 (6.8)</td>
</tr>
<tr>
<td>Singh et al,11,14</td>
<td>Manitoba Cancer Registry (1992–2008)</td>
<td>4883</td>
<td>388 (7.9)</td>
<td>225 (11.3)</td>
<td>147 (5.3)</td>
</tr>
<tr>
<td>Cooper et al,13</td>
<td>SEER-Medicare Database (1994–2005)</td>
<td>57,839</td>
<td>4192 (7.2)</td>
<td>2851 (9.9)</td>
<td>1253 (4.5)</td>
</tr>
</tbody>
</table>

SEER, Surveillance, Epidemiology and End Results.
1.16–1.68), male sex (OR, 1.40; 95% CI, 1.19–1.65), history of polyps before baseline examination (OR, 1.76; 95% CI, 1.48–2.09), and findings at baseline including number of adenomas (for ≥5 adenomas: OR, 3.87; 95% CI, 2.76–5.42), size of largest adenoma (for ≥20 mm: OR, 2.99; 95% CI, 2.24–4.00), and the presence of proximal adenoma (OR, 1.68; 95% CI, 1.43–1.96) were risk factors for interval advanced neoplasia. There was only a minimally increased risk for those with baseline villous histology (OR, 1.28; 95% CI, 1.07–1.52) and no increased risk based on race, family history, cigarette smoking, obesity, or baseline high-grade dysplasia. Thus, polyp characteristics at baseline are strong but are not the only predictors of interval advanced neoplasia.

### Table 2. Risk Factors and Protective Factors for Interval CRCs

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk factors</th>
<th>Protective factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter et al(^\text{12})</td>
<td>Age Every 10-year increase: 1.18 (1.08–1.28)(^a) 3+ comorbidities 2.02 (1.34–3.03)(^o) 2.78 (1.78–4.35)(^a) Nongastroenterologist/nonsurgeon 1.87 (1.34–2.66)(^a) 1.67 (1.13–2.46)(^a) Nonhospital setting 1.88 (1.2–2.92)(^a) 1.67 (1.13–2.46)(^a)</td>
<td>Male sex 0.79 (0.66–0.93)(^a) &gt;95% Colonoscopy completion rate 0.72 (0.53–0.97)(^a) 0.73 (0.54–0.97)(^a) Endoscopist polypectomy rate &gt;30% 0.61 (0.42–0.89)(^a)</td>
</tr>
<tr>
<td>Singh et al(^\text{11})</td>
<td>Zero comorbidities 1.59 (1.06–2.37) Prior colonoscopy With polypectomy: 4.33 (3.14–5.92) With biopsy: 2.97 (1.91–4.5) No intervention: 2.42 (1.58–3.61) Endoscopist specialty Family practice: 1.59 (1.01–2.47)</td>
<td></td>
</tr>
</tbody>
</table>
Etiology of Interval Colorectal Cancers

Four plausible reasons (missed polyps, incompletely resected polyps, rapid progression of new polyps, and failure of biopsy to diagnose a CRC that was present) have been proposed to explain interval CRCs. Pabby et al\(^2\) and Robertson et al\(^3\) used adjudication algorithms to estimate the frequency of these causes of interval cancer. They concluded that 50% to 75% of interval CRCs were likely the result of missed or incompletely resected lesions and less than 30% were the result of rapidly progressing lesions. Pohl and Robertson\(^4\) using a mathematical model, also concluded that most interval cancers likely resulted from missed rather than new lesions. These estimates suggest that interval CRCs could be reduced substantially by better colonoscopic technique.

Missed Lesions

There is now ample evidence that colonoscopy is highly operator-dependent, that significant miss rates occur for even advanced neoplasia, and that there is substantial variation in adenoma detection rates (ADRs). In one study of expert endoscopists\(^5\) the ADR varied almost 3-fold (range, 17%–47%) and there was even higher variability in detection rates of serrated polyps (range, 1%–18%). A systematic review of tandem colonoscopy studies by van Rijn et al\(^6\) combined results from 6 studies to include a total of 1650 polyps and found an overall adenoma miss rate of 22%, but the miss rate for adenomas of 10 mm or greater was only 2%. In contrast, a well-performed study of colonoscopy performed in tandem with computed tomography colonography found that 12% of lesions 10 mm or greater were missed with colonoscopy.\(^7\) There is little doubt that missed lesions occur commonly and contribute meaningfully to interval CRC risk.

Incomplete Polypectomy

Incomplete removal of adenomas is a second important cause of interval CRCs. There are now data that incomplete polypectomy is not only common but varies substantially among endoscopists. Pohl et al\(^8\) reported an overall incomplete resection rate (IRR) of 10.1% with a 3.4-fold difference among endoscopists (range, 6.5%–22.7%). IRRs were significantly higher for larger polyps (5.8% for 5- to 7-mm polyps vs 23.3% for 15- to 20-mm polyps; OR, 3.21; 95% CI, 1.41–7.31) and for sessile serrated polyps in comparison with adenomas (31% vs 7.2%; OR, 3.74; 95% CI, 2.04–6.84). Although alarming, it is not surprising that larger and serrated lesions have higher IRRs.

Rapid Progression

The contribution of new rapidly progressing lesions to the interval cancer rate is the most difficult to determine because the rates of missed and incompletely resected lesions may well be underestimates. It is not known how much variability there is in the time-course of the sporadic adenoma-carcinoma progression, but the finding that it is shorter in Lynch syndrome is proof of principle that it can vary. Interval CRCs appear to have a different molecular profile than noninterval CRCs (Table 3): they are more likely to be microsatellite unstable,\(^3\) have the CpG island methylator phenotype,\(^9\) and have lower rates of \(KRAS\)\(^1\) mutations than noninterval CRCs. These molecular features are characteristic of the serrated polyp pathway to CRC and support the concept that this pathway contributes disproportionately to interval CRCs.

It is unknown whether interval cancers with these molecular characteristics arise as a result of more rapidly progressive tumors that were not present on the index examination, or whether these molecular characteristics contribute to factors that increase the risk of missed or incompletely resected lesions. For instance, sessile serrated polyps\(^1\) are known to be more common in the right colon, to be missed more frequently during endoscopy,\(^1\) and to have a higher rate of incomplete resection than conventional adenomas.\(^1\)

How Should Clinicians Proceed?

It is critically important that patients and referring providers understand that colonoscopic screening/surveillance will not prevent all CRCs. It is prudent to incorporate the risk of and reasons for interval CRCs into the informed consent process.

Table 3. Molecular Characteristics of Interval CRCs

<table>
<thead>
<tr>
<th>Study</th>
<th>Interval CRC rate</th>
<th>Molecular characteristic</th>
<th>Interval CRCs</th>
<th>Noninterval CRCs</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sawhney et al(^1)</td>
<td>5.1% (61/993)</td>
<td>MSI</td>
<td>30.4% (14/46)</td>
<td>10.3% (10/97)</td>
<td>3.70 (1.50–9.10)</td>
</tr>
<tr>
<td>Arain et al(^1)</td>
<td>4.8% (63/1323)</td>
<td>CIMP</td>
<td>57.0% (31/54)</td>
<td>33.0% (33/100)</td>
<td>2.41 (1.20–4.90)</td>
</tr>
<tr>
<td>Shaukat et al(^2)</td>
<td>4.8% (63/1323)</td>
<td>(BRAF)</td>
<td>28.0% (15/54)</td>
<td>19.0% (21/110)</td>
<td>0.93 (0.36–2.38)</td>
</tr>
<tr>
<td>Shaukat et al(^2)</td>
<td>4.8% (63/1323)</td>
<td>(KRAS)</td>
<td>12.9% (7/54)</td>
<td>28.9% (31/107)</td>
<td>0.36 (0.15–0.90)</td>
</tr>
</tbody>
</table>

CIMP, CpG island methylator phenotype; MSI, microsatellite instability.

\(^*\)Interval CRC was defined as CRC within 5 years of a complete colonoscopy.

\(^1\)Matched 1:2 by age and sex to patients with interval cancers.

\(^2\)Analyses were performed on the same case series.
What Can Be Done to Prevent Interval Colorectal Cancers?

Rapidly progressing lesions. Although aggressive biology is not modifiable at this time, it may be possible to identify patients who are predisposed to the development of biologically aggressive neoplasia on the basis of their family history or perhaps by histologic and/or molecular analysis of their initial adenomas. For example, patients with a strong family history of CRC should have earlier and more frequent colonoscopic screening/surveillance. Similarly, patients with more than 10 adenomas and those with multiple large sessile serrated adenomas and particularly those with cytologic dysplasia should have early surveillance (within 1–3 y).

Missed and incompletely resected lesions. It should be possible to decrease the proportion of missed and incompletely resected lesions by improving the quality of colonoscopy. The first step to improving colonoscopy quality is to be able to measure it reliably; this requires an infrastructure for continuous monitoring of colonoscopy quality. Although monitoring interval CRC rates would be a direct measure of screening/surveillance colonoscopy quality, it is not feasible in most clinical settings and we currently rely on surrogates of quality such as cecal intubation rates and ADRs. In the only study to date comparing ADRs with interval CRC rates, Kaminski et al showed that endoscopists with ADRs less than 20% had more than a 10-fold higher rate of interval CRCs than those with higher ADRs. Some experts have argued that measuring ADR is not as robust as other measures such as adenomas per colonoscopy, advanced ADRs, right-sided ADRs, or serrated polyp detection rates, whereas other experts have argued that measuring ADRs is too cumbersome and proposed simpler measures such as polypectomy rates. Currently, ADR is the best evidence-based surrogate for quality of mucosal inspection during colonoscopy.

Variability in ADR likely results from multiple factors but distills down to inadequate mucosal inspection. One critically important factor affecting mucosal inspection is the quality of bowel preparation. Quality of bowel preparation has been shown to worsen with longer intervals between completion of the preparation and the start of colonoscopy and there has been significant improvement in mucosal visualization with the emergence of a split-dose bowel preparation. A meta-analysis of 9 studies concluded that split-dosed bowel preparation resulted in superior bowel preparation with an OR for excellent or good bowel preparation quality of 3.46, compared with other methods (95% CI, 2.45–4.89; P < .01). To maximize preparation quality, the goal should be to start the colonoscopy within 3–5 hours of the last dose of preparation.

The amount of time taken to visualize the mucosa also affects the quality of mucosal inspection. Colonscopic withdrawal times traditionally have been used as a marker of time spent examining mucosa and withdrawal times have been shown to correlate with ADRs in some but not all studies; direct measurement of ADRs is a better quality monitor. Variations in skills and withdrawal technique likely are responsible for much of the remaining variability in ADRs.

To maximize their effectiveness, endoscopists must be well trained to perform complete colonoscopy, to identify and completely remove colonic polyps of all types, and to actively look for flat lesions, especially in the right colon. Careful inspection behind folds and flexures, washing away residual stool with lavage, and attention to subtle mucosal abnormalities such as interruptions in vascular patterns, mucosal deformities, or friability are important examination techniques. Some experts have advocated looking at the right colon twice in an attempt to decrease the miss rate.

It is reasonable to expect that endoscopy centers dedicate quality assurance resources to identify underperforming endoscopists who can be targeted for additional training. Interventions designed to improve colonoscopy quality, however, have had mixed results. Efforts to mandate or incentivize longer withdrawal times do not seem to increase ADRs; similarly, merely informing endoscopists of their ADRs does not appear to substantially change ADRs. In contrast, endoscopic quality improvement programs that included general education along with specific recommended inspection techniques and training have had success in increasing ADRs, even among experienced endoscopists.

In addition to specific training protocols, a variety of technologic advances have been developed to try to improve detection of difficult-to-find lesions. Cap-assisted colonoscopy (CAC), which allows the endoscopist to splay colonic folds and potentially improve visualization behind folds, is perhaps the most promising of these technologies. Two meta-analyses of CAC vs standard colonoscopy have found somewhat disparate results, with one reporting that CAC improved ADRs and the other reporting a marginal increase of overall polyp detection but no effect on ADR. It appears that CAC can increase diminutive adenoma detection, but it is not yet clear if CAC increases detection of advanced adenomas or decreases the development of interval CRCs. Narrow band imaging (NBI) highlights mucosal patterns and facilitates the endoscopic detection of polyp histology, but NBI does not appear to significantly decrease adenoma miss rates. Other emerging technologies such as wide-angle colonoscopes and retrograde viewing devices show promise in improving lesion detection but there is, as yet, insufficient data to promote their widespread use.

Much less attention has been given to IRRs than to ADRs as a colonoscopy quality measure and none of the currently recommended quality monitors address the issue of IRRs. Endoscopic guidelines call for complete removal of all colonic polyps if technically possible with the exception of numerous small, hyperplastic-appearing polyps in the rectosigmoid that can be sampled. Failure to completely remove proximal polyps...
called hyperplastic by the pathologist could contribute to the higher risk of right-sided interval CRCs. It seems clear that a substantial portion (15%–20%) of these larger (>5 mm) and right-sided lesions that were classified as hyperplastic polyps would now be recognized as sessile serrated polyps, lesions that are thought to be important precursors to a subset of CRCs.

There is evidence, as detailed earlier, that incomplete polyp resection is common, it is in part predictable, and it varies substantially among endoscopists. There are some data supporting the use of high-magnification endoscopy to assess polypectomy completion and for coagulation at polyp edges of large polyps if complete resection is in doubt. Similarly, data support the guideline that patients with high-risk lesions (those >2 cm, those removed piecemeal) should return for a repeat endoscopy with biopsy of the scar to assess the polypectomy site in 3 to 6 months. Although recommendations to remove small polyps with cold snares, being careful to include a margin of normal tissue and to use NBI, chromoendoscopy, or submucosal injection with dye such as methylene blue to define polyp borders more accurately, seem reasonable, these approaches have not been evaluated or compared properly.

Collaboration with a good gastrointestinal pathologist is another important, but frequently neglected, tool for the detection of incompletely resected polyps. Many pathologists in the United States no longer routinely comment on the resection margins of polypectomy specimens whereas reporting of the completeness of polyp resection specifically is included as a quality measure for pathologists in the European guidelines. If there is doubt about the completion of a polypectomy, the pathologist should be asked to assess whether the polypectomy margins are involved, but this will not be possible for polypectomies performed piecemeal or with biopsy forceps resulting in multiple biopsy fragments. A high-quality polypectomy technique will make the assessment of polyp margins easier by removing polyps in a single piece whenever possible and including a visible margin of normal tissue. Overall, there is a great need for studies addressing how endoscopists can maximize and monitor completeness of polyp resection.

Recommendation of evidence-based colonoscopy surveillance intervals are a recognized component of a high-quality colonoscopy, but failure to follow guidelines is unlikely to contribute greatly to interval CRCs because endoscopists tend to bring patients back earlier rather than later than guidelines recommend. It is not clear if testing between surveillance colonoscopies with fecal occult blood or stool DNA would decrease interval CRC rates, and this approach is not currently recommended.

### Endoscopist Training

Given that one of the most predictive factors of ADRs or IRRs is the individual endoscopist, a focus on colonoscopy training is essential. Variability in practice likely originates largely from variability in training and early acquisition of endoscopic skills and habits. Multiple studies consistently have shown lower adenoma miss rates among gastroenterologists and colorectal surgeons than among endoscopists with less training. More focused efforts on endoscopy education and standard measurement of endoscopy quality during training are needed. At the present time, the multisociety Gastroenterology Fellowship Core Curriculum and the Accreditation Council of Graduate Medical Education require that gastroenterology trainees perform at least 140 colonoscopies before competence can be assessed, whereas the Accreditation Council of Graduate Medical Education and the American Academy of Family Physicians only require that general surgery trainees and family medicine trainees, respectively, perform 50 colonoscopies before assessment of competence. Recent data suggest that it may take between 175 and 400 (average, 275) colonoscopies for learners to achieve minimal competence. At present, there is little guidance regarding who is qualified to assess competence, what competence measures should entail, and how to implement endoscopy curricula to foster high-quality examinations and ongoing quality assessment. Training programs will need to move from a volume threshold to a more thorough competency assessment that mirrors the quality measures expected of practicing endoscopists.

### Conclusions

Colonoscopic screening and surveillance has contributed substantively to the recent steady decrease in cancer incidence and mortality in the United States (Figure 1). Nonetheless, clinicians must measure their colonoscopic quality and acknowledge that colonoscopy, even in the best of hands, does not prevent all interval CRCs. Endoscopists should discuss the risk of interval CRC with patients and include it in the informed consent process. Although interval CRCs may be partially caused by aggressive biology, they are more likely caused by missed or incompletely resected lesions. There are multiple ways clinicians can improve colonoscopy quality including routine use of split-dose bowel preparations, careful visualization of the entire mucosa using the best techniques and tools, and proper resection technique followed by close collaboration with the pathologist to assure complete polypectomy. There may be emerging technologies to assist with these tasks, however, the most important factors in improving colonoscopy quality are unlikely to hinge on a single technology, but rather will rely on well-trained, vigilant endoscopists. Despite its limitations, colonoscopy will remain a powerful tool in the fight against colon cancer both as a primary screening test and as the final pathway for other screening modalities. Thus, the practice of high-quality colonoscopy is critically important to the success of any CRC screening/prevention program.
References


Reprint requests
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Conflicts of interest
The authors disclose no conflicts.

1. The lifetime risk of developing colon cancer in an average risk person is
   a. 12%
   b. 1%
   c. 5%
   d. 15%

2. Interventions that have been shown to consistently increase adenoma detection rates include
   a. cap colonoscopy
   b. NBI endoscopy
   c. General education on specific endoscopic recommended inspection techniques
   d. Mandating a prolonged withdrawal time

3. The average number of colonoscopies needed to achieve minimal competence is
   a. 145
   b. 50
   c. 500
   d. 275

True or False

4. The most common cause of interval cancers is the development of rapidly progressive new lesions not present during the prior colonoscopy

5. Interval colon cancers tend to have a molecular profile that is different from non-interval colon cancers, suggesting a serrated polyp pathway to cancer in these interval cancers

6. Adenoma detection rate is currently the best surrogate grading the quality of mucosal inspection during colonoscopy