International Journal of Colorectal Disease (2019) 34:123–140
https://doi.org/10.1007/s00384-018-3182-8

ORIGINAL ARTICLE

The contribution of endoscopy quality measures to the development of interval colorectal cancers in the screening population: a systematic review

Deirdre M. Nally[1] · Athena Wright Ballester[1] · Gintare Valentelyte[2] · Dara O. Kavanagh[1]

Accepted: 22 October 2018 / Published online: 29 October 2018

Abstract

Background Colon cancer is the second most common cause of cancer-related death and an important cause of morbidity. The natural history of carcinogenesis, via the adenoma-carcinoma sequence, permits screening, which reduces the relative risk of mortality by up to 16%. The efficacy of a screening programme is limited by the growth of interval colorectal cancers between screening examinations. Quantifying the rate of interval cancers and delineating contributing endoscopic factors are crucial to maximise the benefit of a screening program.

Methods A systematic review was performed in accordance with PRISMA principles. Electronic databases were interrogated with a considered search strategy, and reference lists of retrieved papers were surveyed. For inclusion, studies included the rate of interval cancer (stated or calculated) and reported at least one of a predefined list of endoscopy characteristics. The primary outcome was to establish the rate of interval cancers. The secondary outcome was to determine the association between endoscopy quality measures and interval cancers.

Results The search yielded 2067 papers. Seventy-six full text papers were reviewed. Fifteen papers met the inclusion criteria. In total, there were 117,793 colon cancers, 7281 of which were interval lesions, giving an overall rate of 6.2%. The adenoma detection rate (ADR) of the endoscopist performing the index operation was the most consistent endoscopy factor associated with development of interval cancers. The impact of setting, volume and bowel preparation varied between papers.

Conclusion Interval cancers reduce the efficacy of colorectal screening programmes. Ensuring the quality of the endoscopy process, specifically by increasing the ADR of practitioners, is crucial to the reduction of the rate of interval cancers.

Keywords Interval cancer · Post-colonoscopy cancer · Colorectal cancer · Screening

✉ Deirdre M. Nally
deirdrenally@rcsi.com

Athena Wright Ballester
athenawballester@rcsi.com

Gintare Valentelyte
gintarevalentelyte@rcsi.com

Dara O. Kavanagh
darakavanagh@rcsi.com

1 Department of Surgical Affairs, 2nd Floor, Royal College of Surgeons of Ireland, 121 St. Stephen's Green, Dublin 2, Ireland

2 Department of Health Outcomes Research, Royal College of Surgeons, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland

Introduction

Colon cancer is an important cause of mortality and morbidity with a lifetime risk in the UK of 1 in 14 for men and 1 in 19 for women [1]. The accepted natural history of carcinogenesis in this condition, via the adenoma-carcinoma sequence in colonic polyps, provides a rationale for the provision of a screening programme. Screening focuses upon early detection of a disease process where intervention can have a lasting, curative effect. Screening for colorectal cancer improves mortality [2] through the early identification, and hence treatment, of established disease, and also reduces the incidence of colorectal cancer by facilitating the removal of precancerous lesions [3]. A Cochrane Review of screening for colorectal cancer found that screening reduces the relative risk of mortality by up to 16% [4].

One significant limitation of screening is the development of an interval (IC) or post-colonoscopy colorectal cancer (PCCRC). The Expert Working Group on Interval Cancers of the Colorectal Cancer Screening Committee, World Endoscopy Organisation, defines an interval colorectal cancer as one 'diagnosed after a colorectal screening examination or test in which no cancer is detected, and before the date of the next recommended exam' [5]. A variety of time points are used as a cut off in the literature when defining ICs with previous papers using 3 years, 5 years, recommended screening intervals and 10 years. The prevalence of ICs ranges from 1.8 to 9.0% [5]. Patients with interval cancers are older than those with primary screen-detected cancers and have more comorbidities [6].

Interval cancers arise due to a number of factors, either in isolation or in combination. They may be related to a failure in endoscopy (missed or incompletely excised established or precursor lesions) or rapid polyp progression due to aggressive tumour biology. Adler et al. attributes 50–60% of IC to missed lesions, 20% to incomplete resection and 25% to new lesions [7]. The frequency with which lesions are missed is demonstrated in tandem colonoscopy studies: A systematic review of such studies demonstrated a missed rate of polyps of any size of 22% [8]. Rex showed that 6% of adenomas > 1 cm were missed [9]. The CARE study, which quantified the rate of incomplete polyp resection by-taking biopsies from the bases of macroscopically excised polyps, showed that 10.1% (95% confidence interval (CI) 6.9–13.3%) were incompletely excised. This increased with the size of the polyp and varied between endoscopists [10].

Population-based studies have demonstrated a higher likelihood of stage IV disease and higher risk of emergency presentation with IC, resulting in lower resectability rates and poorer oncological outcomes when compared to primary detected cancers [11]. Thus, a high IC rate has significant implications for efficacy of organised screening programmes in reducing colorectal cancer mortality. Both the British Society of Gastroenterology [12] and the U.S. Multi-Society Task Force on Colorectal Cancer [13] have issued guidelines and quality assurance standards to improve the quality of colonoscopy delivery and hence to reduce IC. Examining the exact relationship between these key performance indicators and IC can inform specific quality improvement projects to address any deficiencies and ensure optimum detection rates for the patient.

PICO

- Population: Patients diagnosed with an interval cancer within 3 or 5 years of a negative colonoscopy
- Intervention: The endoscopy process (specific endoscopy quality measures defined below).
- Comparison: Patients who had cancer diagnosed on index colonoscopy either as reported with each paper or with norms established in the literature.
- Outcome: The primary outcome is to quantify the rate of interval cancer. The secondary outcome is to synthesise the characteristics of the endoscopy process associated with interval cancers.

Methods

A systematic review of the literature was performed in accordance with the PRISMA principles [14].

Inclusion Primary studies, both prospective and retrospective (population-based/multicentre/cohort or case-control studies), reporting the rate of interval cancers were considered for inclusion. For the purposes of this study, two definitions of interval cancers were applied (from 6 to 36 months or 6 to 60 months following a negative colonoscopy). Both definitions are employed in the literature and were considered in this review in order to maximise the insights gained into endoscopy processes associated with IC. Cancers diagnosed less than 6 months after colonoscopy were included as detected cancers. The rate of interval cancer was expressed as a percentage of the total number of cancers diagnosed for that specific period. Papers which contained the necessary data to calculate the IC in this way were also considered for inclusion. Only studies reporting at least (≥) one of the following characteristics of the endoscopy process were included for analysis.

- The adenoma detection rate (ADR), defined as the proportion of colonoscopies that detect ≥ 1 histologically confirmed adenoma
- The polypectomy rate of the endoscopist as a proxy measure for ADR
- Procedure volume as quantified in the primary study
- Speciality of the endoscopist: gastroenterology, surgery, other; including trainee status
- Type of endoscopy centre: examples include hospital (academic or community), out-patient and ambulatory centre
- Withdrawal times as recorded in the primary studies
- Quality of preparation using scoring systems adopted by the primary studies
- Caecal intubation rates documented in the primary studies

Patients were included irrespective of age or indication for colonoscopy (diagnostic, screening or surveillance).

Exclusion Papers that did not report the rate of interval cancers (or did not include the data required to calculate as outlined above) or did not report at least one of the endoscopy processes specified above were excluded. Further exclusion criteria included an entirely selected patient population (e.g. inflammatory bowel disease, Lynch syndrome), or initial colonic assessment via a combination of colonoscopy/sigmoidoscopy and radiology (e.g. barium study or computerised tomography colonography).

Information sources and search strategies

In collaboration with an expert librarian, a considered search strategy using a combination of MESH terms and keywords was developed, trialled and refined. A full search strategy is included as Appendix Table 5 of this manuscript. Three electronic databases (Ovid MEDLINE, Ovid EMBASE, *Cochrane*) were interrogated according to this strategy on August 11, 2017. Automated searches were augmented by manual review of the reference lists of included articles to search for additional studies. Retrieved studies were imported and merged in an Endnote library (Endnote X7.7.1, Thomson Reuters Scientific LLC). Duplicate references were discarded.

Study selection

Two reviewers (D.N., A.WB.) screened the titles of retrieved articles. The abstracts and full texts of potentially relevant articles were reviewed independently to determine eligibility for inclusion based on the predefined conditions outlined above. All ambiguities were discussed and decided by agreement.

Data extraction processes and data items

A data collection spreadsheet was devised in Microsoft Excel (Version 14, Microsoft Office Professional Plus 2010) to capture the variables of interest. This was piloted on two studies and modified as required. The studies used to pilot the data collection tool were included in the final analysis. Data points from supplementary appendices to individual papers were included. Studies that included IC diagnosed within 3 or 5 years of the index colonoscopy were extracted for analysis. A list of the variables retrieved from each study is provided as Appendix Table 6. Data extraction was performed independently by two investigators. Any discrepancies were resolved by consensus or by adjudication by the senior author.

Quality assessment

A quality appraisal of included studies was performed using the Nottingham Ottawa Scale (NOS) for assessing the quality of nonrandomised studies [15]. This previously validated tool consists of eight items, addressing selection, comparability and, for cohort studies, ascertainment of outcome. Each study is awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for comparability giving a maximum of nine stars.

Summary measures and synthesis of results

- Primary outcome: To determine the overall rate, the three-year and five-year rates of interval cancer and describe the clinical features of these cancers.
- Secondary outcome: To appraise and evaluate how the endoscopy quality measures, specified above, contribute to the development of interval cancer.

Statistical analysis

The rate of interval cancer was expressed as a percentage of the total number of cancers. The proportion of patients with interval cancer in all studies was combined and the pooled prevalence of interval CRCs was estimated for all studies, along with the standard deviation (SD) and a 95% confidence interval (CI). We also calculated separately the pooled prevalence of interval cancers at 3 and 5 years, along with SD and 95% CI. The pooled prevalence was reported both in terms of the number of patients and the rate of interval cancer. We compared this with the pooled prevalence of detected cancer—both the rates and the number of patients, calculated separately at 3 and 5 years, as well as the overall variance, and the SD and 95% CI reported. A probability level of < 0.05 was considered as statistically significant. All statistical calculations were performed using Excel (Version 14, Microsoft Office Professional Plus 2010).

Results

Search results and quality assessment

A PRISMA flowchart demonstrating the search and study selection process is provided in Fig. 1.

A quality assessment for included studies is tabulated according to the NOS in Appendix Table 7.

Characteristics of included studies

Fifteen studies met the criteria for inclusion in this review. The characteristics and patient cohorts of these studies are outlined in Table 1. Nine papers originated from the USA [17, 18, 21, 23–27, 30], 3 were Canadian [19, 20, 22] and there was one each from Taiwan [16], the Netherlands [28] and Poland [29]. The studies included in this review spanned the period from 1988 to 2014.

The demographic and clinical features of interval and detected cancers are compared in Table 2.

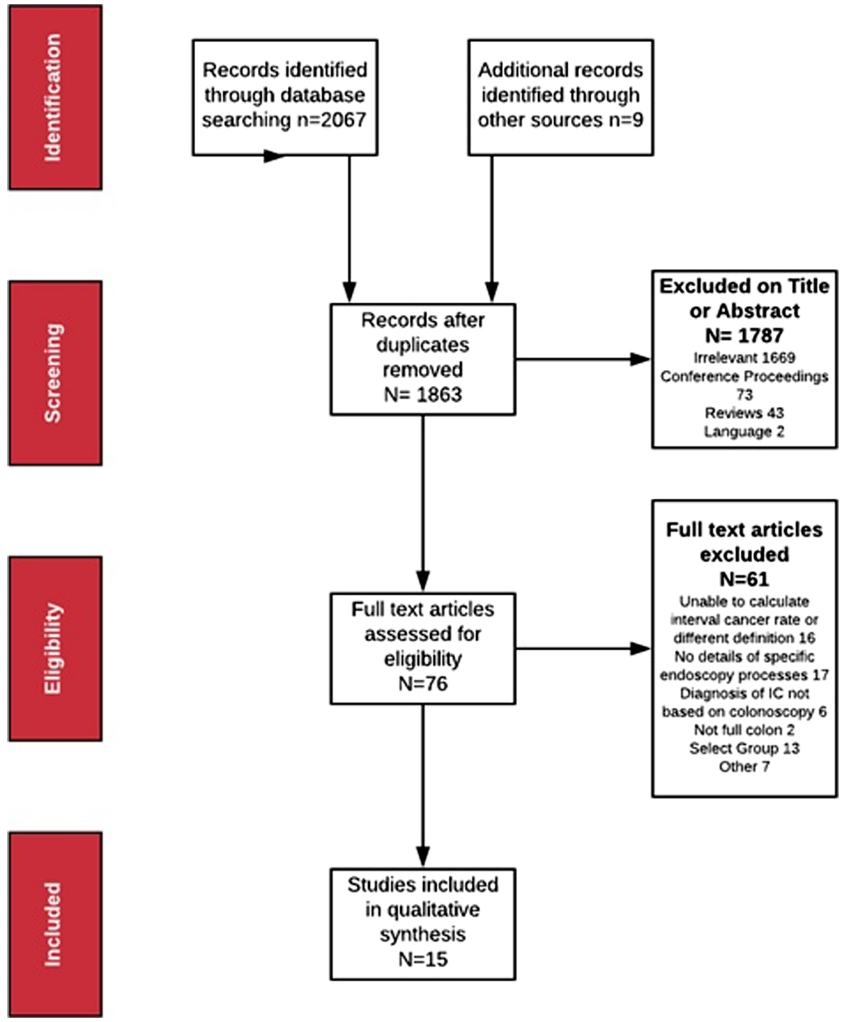

Fig. 1 PRISMA flowchart of the search and study selection process

Primary outcome: rate of interval cancer

The number of patients included in each study, the definition of interval cancer used and the rate of interval cancer reported in each study are given in Table 3 and illustrated in Fig. 2. The 15 studies included a total of 117,793 patients with 110,512 detected cancers and 7281 interval cancers which give an overall rate of 6.2% of total cancers detected (median (%): 4.6; interquartile range (IQR) 3.1–7.9%).

Eight papers [16–23] adopted a 6–36-month definition for interval cancers. These papers included 100,761 cancers, of which 6553 were interval cancers which gives a 3-year interval cancer rate of 6.5%. Seven papers [24–30] employed a 6–60-month definition for interval cancer. These studies reported 17,032 cancers of which 728 were interval cancers—an interval cancer rate of 4.3% (median percentage 5.4%; IQR 3.1–9.2%).

The pooled variance of the 3-year interval cancer rate was 6.3%, with a SD of 2.5% (95% CI = 2.9–7.1%). The 5-year pooled variance rate was 7.3%, with a SD of 2.7% (95% CI = 3.5–9.4%). The overall pooled variance for interval cancer rate across all studies (3 and 5 years combined) was 6.8% with a SD of 2.6% (95% CI = 3.9–6.9%).

Where reported, the mean age of patients with interval cancer was 69.4 years (Of note, one paper provided the median age of all patients, not specifically those with IC [20]); two papers reported the median age of IC patients, not appropriate to include in our mean calculation [18, 30]. The overall mean age of patients with detected cancer calculated among the studies that reported the mean age (8 studies) was 68.8. Among IC cancer patients, the mean prevalence (reported by 13 of the 15 studies) among male patients was 56.4% relative to a mean prevalence of 47.2% among females, suggesting an overall higher IC prevalence among male patients. The detected cancer rate (only reported by 10 studies), with the mean prevalence among male patients, was 61.7% and 38.3% for females.

Nine studies reported the stage of IC at diagnosis. Overall, 61% of IC patients had early (stages I and II) disease; 38.9% had late disease (stage III or stage IV). Seven studies reported the stage of detected cancers: 56.1% of patients had early and 43.9% of patients had

Table 1 Characteristics of Included studies SFVAMC = San Francisco Veterans Administration Medical Centre; KP = Kaiser Permanente; CRC = colorectal cancer; IBD = inflammatory bowel disease; NS = not stated; SEER = surveillance, epidemiology, and end results

Paper	Year	Location	Study design	Associated database	Time period	Number of sites	Study cohort
Tsai [16]	2017	Taiwan	Retrospective Cohort	Institutional Pathology Database	Jan 05–Nov 14	1	> 18 diagnosed with CRC. IBD, previous CRC or polyposis or failed colonoscopy excluded
Gotfried [17]	2015	Pennsylvania, USA	Retrospective Cohort	Pennsylvania Cancer Registry (PCR)	1993–2011	1	Colonoscopies (diagnostic and therapeutic) performed in a single institution. IBD, Previous CRC or resection excluded
Baxter [22]	2011	Ontario, Canada	Retrospective Population-based Study	Ontario Cancer Registry	2000–2005	NS	Patients > 20 years, diagnosed with CRC 6 months after complete colonoscopy. Previous cancer, IBD or outside region excluded
Samadder [24]	2014	Utah, USA	Retrospective Population-based Study	Utah Cancer Registry	Feb 95–Jan 09	NS	Utah residents 50–80 years diagnosed with CRC on colonoscopy
Farrar [25]	2006	Minneapolis, USA	Retrospective Case Controlled study	Institutional Cancer Registry	Jan 91–Aug 04	1	Veterans diagnosed with CRC after complete colonoscopy. Familial syndromes/IBD excluded
Haseman [23]	1997	Indiana, USA	Retrospective Cohort	None stated	1988–1993	20	Patients diagnosed with IC after primary colonoscopy with adequate preparation.
Nayor [26]	2017	Boston, USA	Retrospective Cohort	Institutional Research Patient Data Repository	Jan 07–Dec 14	3	Patients diagnosed with CRC. Patients at increased risk not excluded
Richter [27]	2015	Massachusetts, USA	Retrospective Cohort	None stated	1998–2006	1	Patients who had a colonoscopy, deemed 'neoplasia free.' IBD excluded. Genetic predispositions included
le Clercq [28]	2014	South-Limburg, Netherlands	Population-based	Netherlands Cancer Registry	2001–2010	5	Patients diagnosed with CRC in the region. Previous/familial cancer, IBD, external referrals excluded
Cooper [21]	2012	Nationwide, USA	Population-based	SEER	1994–2005	NS	Patients > 69 with new diagnosis of cancer after complete colonoscopy. Previous cancer / other insurance excluded
Kaminiski [29]	2010	Poland	Population-based	National Colorectal Cancer Screening Program Poland	Oct 00–Dec 04	NS	Patients 40–66 undergoing screening colonoscopy with adequate preparation
Singh [20]	2010	Manitoba, Canada	Population-based	Manitoba Cancer Registry	Apr 92–Mar 08	NS	Patients 50–80 with first diagnosis of CRC registered for 5 years. IBD or resection excluded
Bressler [19]	2007	Ontario, Canada	Population-based	Ontario Cancer Registry	Apr 97–Mar 02	NS	Patients > 20, new diagnosis of CRC, colonoscopy inserted to site of CRC within 36 months of diagnosis. IBD Excluded
Shergill [30]	2015	San Francisco, USA	Nested case-control study	SFVAMC cancer registry	1998–2011	1	> 50 with CRC diagnosed by pathology who had seen primary care provider at least 6 months before diagnosis. Previous/familial cancer, previous cancer or polyps, IBD, excluded
Corley [18]	2014	Northern California, USA	Population-based	KP Northern California & California cancer registries	Jan 1998–Dec 2010	17	Patients > 50, undergoing a screening, surveillance or diagnostic scope in KP facility where endoscopist performed > 300

Table 2 Demographic and clinical features of interval and detected cancers. M = male; Mod = Moderate; Prox = Proximal; Undif = undifferentiated. Early = stage I&II; Late = stage III&IV; Proximal = caecum to transverse colon; Distal = splenic flexure to rectum

Paper	Gender		Age (years)		Stage		Grade of differentiation		Location	
	Interval	Detected	Interval	Detected	Interval	Detected	Interval	Detected	Interval	Detected
Tsai [16]	M: 40.9%	M: 59%	65.7	65.5	Early: 86.4% Late: 13.6%	Early 49.9% Late 50.1%	Well: 9.1% Mod: 90.9% Poor: 0%	Well: 4.6% Mod: 89.3% Poor: 5.9%	Prox: 31.8% Distal: 68.2%	Prox: 41.6% Distal: 58.4
Gotfried [17]	M: 44%	NR	69.3	NR	Early: 69% Late: 31%	NR	NR	NR	Prox: 47% Distal: 53%	NR
Baxter [22]	M: 52.7%	M: 56.6%	71	68	NR	NR	NR	NR	Prox: 53.7% Distal:46.3%	Prox: 37.5% Distal: 62.5%
Samadder [24]	M: 54.1%	M: 51.6%	67	66	Early: 64% Late: 36%	Early: 58% Late: 42%	NR	NR	Prox: 62% Distal: 38%	Prox: 42% Distal: 58%
Farrar [25]	M: 99% (veterans)	M: 98% (veterans)	71.5	70	Early: 68.5% Late: 31.5%	Early: 59% Late: 41%	Well: 3% Mod: 77% Poor: 20%	Well: 1% Mod: 84% Poor: 15%	Prox:66% Distal: 34%	Prox: 52% Distal: 48%
Haseman [23]	NR	NR	72	69.8	Early: 48% Late: 52%	Early: 63% Late: 37%	NR	NR	Prox: 63% Distal: 37%	Prox: 45% Distal: 55%
Nayor [26]	M: 56.3%	NR	69.4	NR	NR	NR	NR	NR	Prox: 55.9% Distal:44.1%	NR
Richter [27]	M: 54.5%	NR	68.4	NR	NR	NR	NR	NR	Prox: 62.4% Distal:37.6%	Prox: 67% Distal: 33%
le Clercq [28]	M: 55.1%	M: 53.8%	72.8	69.9	Early:55.6% Late: 44.4%	Early:49.7% Late: 50.3%	Well/ Mod: 69% Poor/ Undif: 31%	Well/Mod: 75.6% Poor/ Undif:24.4%	Prox: 60% Distal: 40%	Prox: 31.9% Distal: 68.1%
Cooper [21]	M: 43.4%	M: 44%	74% > 74	71.2% > 74	Early: 65% Late: 35%	Early: 61% Late: 39%	Well/ Mod: 71.3% Poor/ Undif:28.7%	Well/Mod: 72.7% Poor/ Undif:27.3%	Prox: 77.1% Distal: 28.3%	Prox: 51.8% Distal: 48.2%
Kaminiski [29]	M: 35.7%	M: 40.5%	58	NR	NR	NR	NR	NR	Prox: 29.7% Distal:70.2%	NR
Singh [20]	M: 51%	M: 57%	NR	NR	Early: 51% Late: 49%	Early:52% Late: 48%	Well/ Mod: 83% Poor/ Undif:17%	Well/Mod: 86% Poor/ Undif:14%	Prox: 60.5% Distal:39.5%	Prox: 41.6% Distal: 58.4%
Bressler [19]	M: 47.1%	M: 56.1%	73.3	67.5	NR	NR	NR	NR	Prox: 55.3% Distal:44.7%	Prox: 31.7% Distal: 68.3%
Shergill [30]	M: 100% (veterans)	M: 100% (veterans)	72.5	69.5	Early: 41.7% Late: 58.3%	NR	NR	NR	Prox:61.5% Distal:38.5%	Prox: 36.4% Distal: 63.6%
Corley [18]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 3 Primary outcome-definitions and rates of interval cancer

Paper	Definition	Total number of CRC	Number of detected	Number of interval cancers	Rate of interval cancer
Tsai [16]	3 years	670	648	22	3.3
Gotfried [17]	3 years	1147	1102	45	3.9
Corley [18]	3 years	8730	8541	189	2.2
Bressler [19]	3 years	12,487	12,057	430	3.4
Singh [20]	3 years	4883	4495	388	7.9
Cooper [21]	3 years	57,839	53,647	4192	7.2
Baxter [22]	3 years	14,064	12,804	1260	9
Haseman [23]	3 years	941	914	27	2.9
Samadder [24]	5 years	2659	2500	159	6
Farrar [25]	5 years	830	785	45	5.4
Nayor [26]	5 years	5345	5100	245	4.6
Richter [27]	5 years	2509	2432	77	3.1
le Clercq [28]	5 years	5107	4960	147	2.9
Kaminiski [29]	5 years	458	416	42	9.2
Shergill [30]	5 years	124	111	13	10.5
TOTALS		117,793	110,512	7281	6.2

late stage disease. Grade of differentiation was reported by 5 studies. Overall, 80.7% of interval cancers were well or moderately differentiated and 19.3% were poor or undifferentiated. In the detected cancers group, 82.6% were well or moderately differentiated and 17.3% were poor or undifferentiated. The mean rates of proximal (caecum to transverse colon) and distal (splenic flexure to rectum) IC cancer, where reported, were 56.1% and 44.2% respectively. The mean rates of proximal and distal detected cancers were 43.5% and 56.5%.

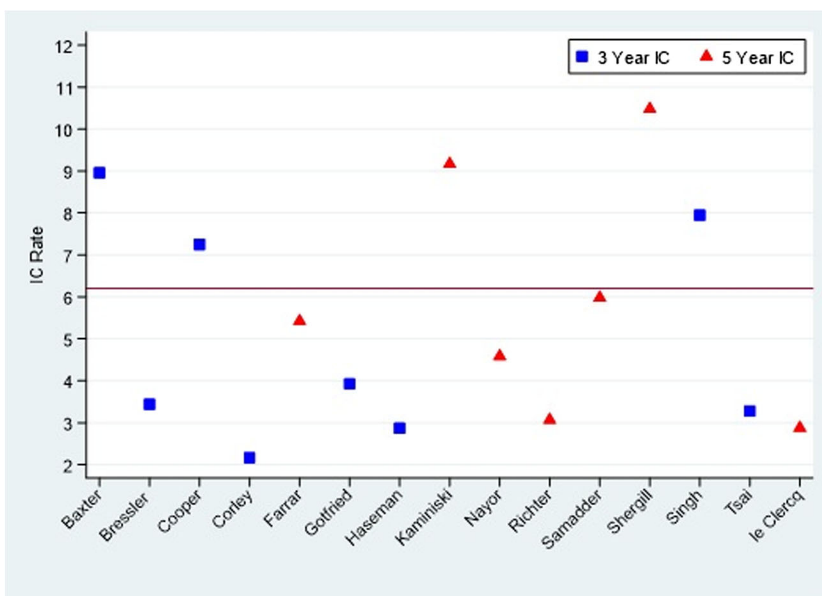

Fig. 2 Interval cancer rate per study referenced to the overall interval cancer rate. The overall rate across all studies (6.2%) is represented by the red line. IC = interval cancer

Secondary outcome: endoscopy quality measures

The endoscopy quality measures examined by each paper and their findings are presented in Table 4.

Adenoma detection rate (ADR)

Two studies, Kaminski [29] and Corley [18], examined the association between ADR and interval cancers. The crude ADR of each endoscopist in both programmes was determined. Kaminski used predefined cut-offs to delineate ADR categories (<11.0%, 11.0 to 14.9%, 15.0 to 19.9%, or ≥20.0%). Corley considered ADR both as a continuous variable and categorised into quintiles (7.35–19.05%, 19.06–23.85%, 23.86–28.40%, 28.41–33.50%, 33.51–52.51%). Both studies demonstrated an inverse relationship between ADR and the incidence of IC which is illustrated in Fig. 3: Kaminski showed that, compared to a reference ADR > 20%, an ADR < 11% led to a cumulative hazard ratio (HR) of IC of 12.5 (95% confidence interval (CI) 1.51–103.43; $p = 0.008$) when adjusted for age. Corley found that for patients undergoing colonoscopy by physicians with ADR in the highest quintile (33.5–52.5%), as compared to physicians with ADR in the lowest quintile (ADR 7.35–19.05%), the hazard ratio for receiving a diagnosis of an interval cancer was 0.4 (95% CI 0.23–0.68). This hazard ratio is adjusted for age, Charlson comorbidity score, sex and indication for colonoscopy.

Polypectomy rate

Baxter defined the polyp detection rate as the proportion of colonoscopies (irrespective of completion) associated with a code indicating removal of a polyp > 3 mm over a 2-year period [22]. Proximal cancers were located between the caecum and the transverse colon; distal cancers were located between the splenic flexure and the rectum based on ICD 9 codes. She found a correlation between the polypectomy rate and proximal IC only: patients undergoing colonoscopy performed by an endoscopist with a polypectomy rate > 30% were less likely to develop an IC compared to those undergoing colonoscopy performed by an endoscopist with a < 10% polypectomy rate (odds ratio (OR) 0.61; 95% CI 0.42–0.89 $p = 0.001$). The OR for polypectomy rates and distal IC were not statistically significant ($p = 0.39$) [22].

Cooper obtained the polypectomy rate from the ratio of colonoscopy with polypectomy divided by the total number of colonoscopies by that provider in the SEER database. The adjusted OR for IC, where the endoscopist was in the highest quartile (> 43%) polypectomy rate compared to the lowest quartile (<24%), was 0.7 (95% CI 0.63–0.78; $p < 0.001$).

Speciality/trainee

The association between endoscopists' speciality and IC was inconsistent between the studies reporting this outcome: Three studies [26, 28, 29] found that the speciality of the endoscopist did not influence the rate of interval cancers. However, Baxter found that non-gastroenterologists/non-surgeons had higher OR of IC: OR 1.87 (95% CI 1.34–2.60 $p = 0.006$) for proximal IC; 1.67 (95% CI 1.13–2.46 $p = 0.001$) for distal IC [22]. In Cooper's study, the OR for IC between gastroenterologists and colorectal surgeons was not statistically significant but, relative to gastroenterologists, general surgeons, family practitioners and internists, were at greater risk of IC: general surgery OR 1.38 (95% CI 1.17–1.63); family practice OR 4.15 (95% CI 1.16–1.83) and internal medicine OR 1.42 (95% CI 1.24–1.62) [21]. In Singh's multivariate logistic regression analysis, full colonoscopy by family practitioners was associated with IC: OR 1.59 (95% CI 1.01–2.47) [20]. Bressler found that procedures performed by family practice and internal medicine doctors were associated with IC in uni- and multivariate analysis ((crude OR 1.71 (95% CI 1.13–2.63) adjusted OR 1.77 (95% CI 1.14–2.74)) in male patients (similar figures for female patients) [19]. Haseman found a higher risk of 'failed detection' in scopes performed by non-gastroenterologists (OR 5.36 95% CI 2.94–9.77) [23].

In Tsai's study, the level of experience of the endoscopist (fellow/attending) was not significantly different between interval and detected cancer groups; HR 1.05 (95% CI 0.44–2.4 $p = 0.921$) [16]. Similarly, In the Farrar paper, there was no association between interval cancers and trainee participation ($p = 0.06$) [25].

Type of centre

The relative importance of the type of endoscopy centre was inconsistent: Baxter found that colonoscopy in a non-hospital setting was associated with proximal and distal IC (proximal IC OR 1.88 95% CI 1.2–2.92; distal IC OR 1.67(95% CI 1.13–2.46) [22]. Bressler also found an increased risk of IC in a non-hospital setting OR 2.32 (95% CI 1.57–3.44 $p < 0.01$) [19]. Cooper found that the risk of IC in outpatient, ambulatory surgical centre or other facilities was higher than in the inpatient setting: OR 1.43 (95% CI 1.32–1.56); OR 1.58 (1.34–1.86) and OR 1.64 (1.33–2.01) respectively [21]. Conversely, Le Clercq found no difference between university and non-university hospitals ($p = 0.67$) [28] and Singh found the site of index colonoscopy (rural/ambulatory/hospital) to be non-significant ($p = 0.59$) [20].

Endoscopy volume

Three studies examined the relationship between procedure volume and IC. Baxter calculated procedure volume for each endoscopist from billing data from the 2 years before each

Table 4 Contribution of endoscopy quality measures to the development of interval cancers: HR = hazard ratio; CI = confidence interval; IC = interval cancer; DC = detected cancer; OR = odds ratio

Paper	Adenoma detection rate (ADR)	Polyp detection rate	Speciality/trainee	Type of centre	Volume	Withdrawal times	Bowel preparation	Caecal intubation rate
Tsai [16]			No difference in the proportion of colonoscopies performed by fellow univariate analysis Fellow to endoscopist HR 1.045 (95% CI 0.440–2.479) p 0.921			No difference in total withdrawal time; Sorter withdrawal time in ascending colon Univariate Analysis HR: 0.561 (95% CI 0.345–0.9-13)	No difference in preparation between IC and detected groups ($p = 0.829$)	
Gotfried [17]							43% of IC had an incomplete colonoscopy due to poor prep; of which 33% failed to attend scheduled follow up	
Baxter [22]		Polypectomy rate associated with proximal IC (not distal). Polypectomy rate > 30% compared to polypectomy rate < 10%: OR 0.61 (95% CI 0.42–0.89; $p < .0001$)	Scope performed by non-gastroenterologist, non-surgeon) associated with IC Proximal IC OR 1.87 (95% CI 1.34–2.60) $p = 0.006$ Distal IC OR 1.67 (95% CI 1.13–2.46) $p = 0.001$	Colonoscopy in non-hospital setting associated with IC Proximal IC OR 1.88 (95% CI 1.2–2.92) Distal IC OR 1.67 (95% CI 1.13–2.46)	Procedure volume not significant Volume as log: Proximal IC OR 1.00 (95% CI 0.89–1.13) $p = 1$ Distal IC OR 0.94 (95% CI 0.84–1.05) $p = 0.28$			Risk of IC lower if colonoscopy performed by endoscopist with a high completion rate Completion rate of > 95% compared to completion rate < 80% for proximal (OR 0.72; 95% CI, 0.53–0.97 $p = 0.002$) and distal (OR 0.73; 95% CI, 0.54–0.97 $p = 0.03$) cancers
Samadder [24]							Inadequate preparation in 5.7% of IC cases	Caecal intubation rate 91.7% for IC cases
Farrar [25]			No difference in the proportion of scopes performed by trainee between IC and DC groups				Not associated with increased risk of IC	

Table 4 (continued)

Paper	Adenoma detection rate (ADR)	Polyp detection rate	Speciality/trainee	Type of centre	Volume	Withdrawal times	Bowel preparation	Caecal intubation rate
							$p = 0.3$	
Haseman [23]			Non-gastroenterology scope associated with increased risk of IC OR for failed detection compared to a gastroenterologist was 5.36 (95% CI 2.94–9.77).					
Nayor [26]			Not significant predictor of IC ($p = 0.34$)				25% of IC had fair/poor/-inadequate preparation	7% of IC had an incomplete exam
Richter [27]							No difference in the quality of preparation between IC and reference groups ($p = 0.799$)	Lower caecal intubation rates in IC groups ($p = 0.016$)
le Clercq [28]			No association between speciality and IC Gastroenterologist to non-gastroenterologist OR 1.33, 95% CI 0.81 to 2.19 $p = 0.27$	No difference between university and non-university hospitals OR 1.22 (95% CI 0.82–1.83) $p = 0.67$			5% of IC ascribed to poor preparation	9.5% of IC ascribed to incomplete examination
Cooper [21]		Polypectomy rate associated with IC polypectomy rate highest (> 43%) to lowest quartile (< 24%) OR 0.70 (95% CI, 0.63–0.78; $p < 0.001$)	Non-gastroenterology specialty associated with increased risk of IC general surgery OR 1.38 (95% CI 1.17–1.63); Family Practice OR 4.15 (95% CI 1.16–1.83) and internal medicine OR 1.42 (95% CI 1.24–1.62).	Type of facility associated with IC outpatient OR 1.43 (95% CI 1.32–1.56); Ambulatory OR 1.58 (1.34–1.86) Other facility OR 1.64 (1.33–2.01)	Colonoscopy volume by physician associated with IC OR 1.27 (95% CI 1.13–1.43) $p < .001$			
Kaminiski [29]	ADR significantly associated with risk of IC ADR < 11% compared to ref. ADR > 20% Cumulative HR 12.5 (95%		Specialisation of endoscopist was not significant ($p = 0.72$)					Rate of caecal intubation not significantly associated with risk of IC ($p = 0.50$)

Table 4 (continued)

Paper	Adenoma detection rate (ADR)	Polyp detection rate	Speciality/trainee	Type of centre	Volume	Withdrawal times	Bowel preparation	Caecal intubation rate
	CI 1.51–103.43) ($p = 0.008$)							
Singh [20]			Speciality of endoscopist associated with increased risk when compared to gastroenterology Family practitioner OR 1.59 (95% CI 1.01–2.47).	Site of index colonoscopy (rural/ambulatory/-hospital) Not significant $p = 0.59$	Volume of colonoscopies performed 6 months prior to the index colonoscopy. Not significant $p = 0.43$			
Bressler [19]			Increased risk of IC where scope performed by an internist crude OR 1.71 (95% CI 1.13–2.63) adjusted OR 1.77 (95% CI 1.14–2.74 in male patients	Increased risk of IC in a non-hospital setting OR 2.32 (95% CI 1.57–3.44) $p < 0.01$				
Shergill [30]			92% performed by gastroenterology 8% by other				57% had excellent/good prep 29% fair 14% failed due to poor prep	
Corley [18]	Inverse association between ADR and risk of IC Highest ADR quintile compared to lowest quintile ADR Adjusted HR 0.52 (95% CI 0.39–0.69)							

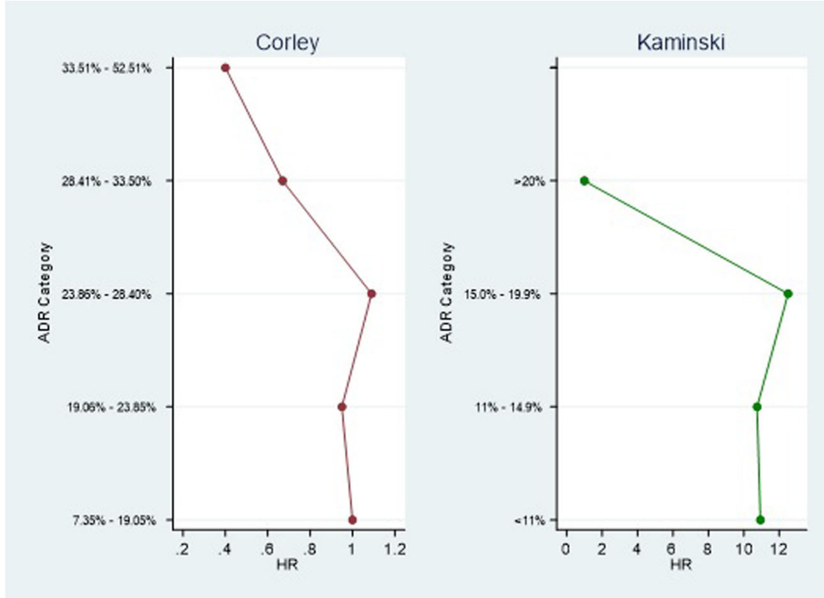

Fig. 3 Relationship between ADR and IC. The reference ADR category for Corley is 7.35–19.05% with HR 1. The reference ADR category for Kaminski is > 20% with HR 1. HR = hazard ratio

colonoscopy associated with a cancer diagnosis. Procedure volume was non-significant in continuous, log transformed and categorical statistical models (p value not reported) [22]. Singh categorised the volume of colonoscopies performed by the endoscopist in the 6 months prior to the index colonoscopy into quartiles. This variable was not significantly different in the IC group ($p = 0.43$) [20].

Cooper showed a higher risk of IC with increasing volume: The colonoscopy volume per physician from a non-cancer control group was extracted from the SEER database and divided into quartiles. Compared to the lowest quartile of procedure volume (1–48 scopes), the highest quartile (> 141 scopes) was associated with a higher risk of IC (OR 1.27; 95% CI, 1.13–1.43; $p < 0.001$) [21].

Of note, some studies stipulated a minimum number of examinations to be performed by each endoscopist in order to be included. For example, in the Corley study, endoscopists were required to complete 300 or more total colonoscopies and 75 or more screening examinations during the study period [18]; a minimum of 30 screening exams was required per endoscopist to be included into the data analysis by Kaminski [29].

Withdrawal times

Tsai determined withdrawal time based on timed photographs at the caecum, hepatic flexure, splenic flexure, sigmoid-descending junction, recto-sigmoid junction and anus. There was no statistically significant difference in total withdrawal time (univariate hazard ratio (HR) 0.992 (95% CI 0.935–1.052 0.789)) but uni- and multivariate analysis found that a shorter ascending colon withdrawal time (defined as time from caecum to hepatic flexure) increased the risk of IC (HR 0.556 (95 CI 0.356–0.870) $p = 0.02$) [16].

Bowel preparation

The selection criteria of the primary studies vary with respect to quality of preparation required for inclusion. In the study by Kaminski et al., only subjects with adequate preparation were included [29].

Three studies found that the quality of bowel preparation was not significantly associated with an increased risk of IC [16, 25, 27]. Le Clerq determined the aetiology of the interval cancers diagnosed during the study period and ascribed 5% to poor preparation [28]. Samadder performed a manual chart review of interval cancers identified and found that preparation was inadequate in 5.4% of cases [24] In Shergill's study, 14% failed due to poor bowel preparation. Gotfried divided IC into 'true IC' and 'administrative failure IC' groups and found that 43% of those with poor or inadequate preparation failed to attend for a follow-up colonoscopy or barium study [17]. In contrast, Nayor found that 25% of those diagnosed with IC had inadequate bowel preparation but that this was an independent, protective factor against the development of IC before the next scheduled examination as per guidelines. The explanation offered was that this group of patients was offered expedited appointments and more frequent examinations [26].

Caecal intubation rate

Baxter found that patients undergoing colonoscopy performed by an endoscopist with a completion rate of > 95% were almost a third less likely to develop IC compared to patients who received a colonoscopy from a practitioner with a < 80% completion rate (OR for proximal cancers 0.72; 95% CI 0.53–0.97; OR for distal cancers 0.73; 95% CI 0.54–0.97) [22]. Richter found significantly lower caecal intubation rates in IC groups ($p = 0.016$) [27] and Le Clercq attributed 9.5% of IC to incomplete examination. Kaminski, however, found that the rate of caecal intubation was not significantly associated with risk of IC ($p = 0.50$) although this rate was adjusted for incomplete examinations owing to poor bowel preparation or a stricture caused by a tumour impeding the passage of the endoscope. Samadder and Nayor provide descriptive statistics only for this variable and did not attempt to correlate with ICs: The caecal intubation rate was 91.7% in IC cases in the former study and 93% in the latter.

Discussion

Effective screening for colorectal cancer depends on the identification of early and precursor lesions. Colonoscopy remains the gold standard investigation [31]. However, this systematic review demonstrates that, even with colonoscopy, there is an overall interval cancer rate of 6.2%.

Garborg considers the IC rate the ultimate measure of colonoscopy quality and thus a priority quality assurance metric. Monitoring the IC rate is challenging due to the relative rarity of an IC event, the inherent time delay involved and the need for national registries to ensure accurate data capture [32]. The 'UK Key Performance Indicators & Quality Assurance Standards for Colonoscopy' guidelines, issued by the British Society of Gastroenterology (BSG), include IC as a quality indicator and recommends that all units have a policy for capturing IC data. An IC diagnosed within 3 years of a colonoscopy is considered an adverse outcome. Previous papers have used 3 years, 5 years, recommended screening intervals and 10 years as cut-offs. The Expert Working Group on interval cancers asserts that inconsistent definitions hamper comparisons between results and yet they, themselves, fail to prescribe a specific cut-off or time interval [5].

The heterogeneity in IC definition is compounded by variation in calculations used to determine the IR rate: Morris applied four different formulae to a single dataset (National Cancer Data Repository (NCDR) 2001–2010) and found that the IC rate ranged from 2.5 to 7.8% depending on the formula used [33]. For meaningful comparisons, a standardised approach is required or adjustments/exclusions applied and detailed clearly. Morris argues in favour of citing the IC as a ratio of the number of colonoscopies performed, not the number of cancers diagnosed. Adler estimates this risk as one case per 1000 average risk patients undergoing a screening colonoscopy [7].

Adenoma detection rate, polyp detection rates and sessile serrated adenoma (SSA) detection are markers of the neoplasia yield of a colonoscopy. This review demonstrates an association between ADR and polyp detection rates and IC. There was a consistent inverse relationship between adenoma detection rate (ADR) or polypectomy rate and IC rates. The ADR is a key quality indicator recognised by professional organisations including the US Multi-Society Task Force on Colorectal Cancer [13], who describe it as 'the most important and highly variable measure of the quality of mucosal inspection during colonoscopy.' ADR varies by age, gender, geographical location, indication for diagnostic colonoscopy and criteria for index screening colonoscopy. However, based on 10,034 examinations performed by experienced gastroenterologists in a single-centre study, Chen demonstrated that the endoscopist is the most important predictor of adenoma detection at colonoscopy [34]. This operator dependence of colonoscopy examination has implications for screening since it contributes to interval cancers. A prospective study by Kaminski within the Polish Colon Cancer Screening Programme demonstrated the association between the ADR and the incidence and mortality of interval cancers. Furthermore, this group showed that the ADR can be improved with annual feedback and quality benchmark indicators: 74.5% of endoscopists improved their baseline ADR quintile category (or maintained the highest category). This improvement was associated with a significantly reduced risk of interval colorectal cancer (adjusted hazard ratio 0.63; 95% CI 0.45–0.88; $p < 0.006$) and colorectal cancer death (adjusted hazard ratio 0.50; 95% CI, 0.27–0.95; $p < 0.035$) [35].

There are some limitations to ADR as a quality indicator. Wieszczy suggests that the optimal ADR and upper cut-off limit are unclear and that the association between ADR and ideal surveillance intervals is not determined [36]. A singular focus on the ADR can be misleading and give an incomplete indication of quality: The ADR equates identification of a single adenoma per scope with the detection and removal of multiple adenomas if present. This can foster 'a one and done' attitude to cynically maintain a satisfactory ADR rate. An alternative, more discriminating measurement, the mean number of adenomas per colonoscopy (MNA), has been proposed [37]. The variation between practitioners in the number of adenomas per colonoscopy is greater than ADR variation.

Calculating the ADR is laborious as it requires histology results and, hence, a delayed compilation of communicating databases [38]. The polyp detection/ polypectomy rate may be more feasible and practicable and has been shown to correlate with ADR [38]. In this review, studies by Baxter [22] and Cooper [21] demonstrated reduced rates of IC as the polypectomy rate increased. This is consistent with a study by Fedewa based on 2735 Medicare patients: The risk of interval cancer was highest in patients who received their test by an endoscopist in the lowest polypectomy quartile when compared to those who underwent a colonoscopy by an endoscopist in the highest quartile (HR 1.95 (95% CI 1.74–2.20)) [39].

This review suggests that the rate of IC is lowest when colonoscopy is performed by gastroenterologists and colorectal surgeons. Interval cancers have previously been shown to be 2.4 times more prevalent in the proximal colon [6]. There is an increasing appreciation of the alternative serrated adenoma-neoplasia pathway to carcinogenesis, particularly in right-sided colon cancers [40]. Given this increased frequency of both SSA and IC on the right side of the colon, it is noted that gastroenterologists had higher detection rates of proximal sessile serrated adenomas (PSSA) when compared to non-gastroenterologists ($p = 0.001$, based on 4151 screening colonoscopies in which 140 PSSA were detected) [41]. Given the operator dependence demonstrated in ADR and polyp detection rates (including SSA), education and training is required to improve performance, reduce variability between endoscopists and hence minimise interval cancers.

Other key performance indicators including withdrawal time, bowel preparation and caecal intubation are process measures. It is likely that they contribute to IC if they influence adequate inspection of the mucosa and hence the adenoma detection rate. In this review, only Tsai examined the relationship between withdrawal times and IC and found no difference in the total withdrawal time between interval and detected cancer groups [16]. This finding conflicts with a study by Shaukat et al. (excluded from this review, due to alternative definitions used) [42], who found that physicians' mean annual withdrawal times were inversely associated with IC: when compared to a withdrawal time ≥ 6 min, colonoscopies with withdrawal times < 6 min had an incident rate ratio of interval cancer of 2.3 (95% CI 1.5–3.4; $p < 0.0001$). Longer mean withdrawal times were associated with higher ADR (3.6% per minute; 95% CI 2.4–4.8%, $p < 0.0001$). The authors advocate for focused interventions to increase withdrawal times. However, Rex argues that quality improvement changes focused on time alone are insufficient and misplaced and argues that emphasis on lesion recognition and withdrawal technique will naturally extend average withdrawal times in a more efficacious way [43]. In a separate study, he demonstrated that technique is associated with adenoma detection rates: Four experts scored endoscopy videos on four criteria (examining the proximal sides of flexures, folds and valves, cleaning and suctioning, adequacy of distention, and adequacy of time spent). The endoscopist with the previously established highest adenoma detection rate scored highest on each of the four criteria ($p < 0.001$ for each measure) [44].

The higher rate of IC in the proximal colon reinforces the importance of high caecal intubation rates, adequate preparation to examine the proximal colon and appropriate follow-up in cases of incomplete colonoscopy. The BSG guidelines recommend a minimum unadjusted caecal intubation rate of 90% and an aspirational level of 95%. Bowel preparation should be of a sufficient standard not to warrant a repeat or alternative test for at least 90% of patients. Of note, however, assessment of bowel preparation is a subjective variable which limits its use as a quality measure.

Not all IC are due to technical factors. Despite high-quality colonoscopy which meets recommended standards, some patients still develop IC: Gotfried asserts that 53% of the IC diagnosed were due to administrative errors [17], which must be addressed at the organisational level. Furthermore, unfavourable biology, with abnormalities in underlying molecular pathways, can contribute to the rapid progression of a new polyp into invasive cancer between screening intervals. Interval cancers demonstrate greater microsatellite instability [40], CIMP (CpG island methylator phenotype) [45] and KRAS mutation [46] than sporadic cancers.

There are numerous limitations to the current study. The quality of all systematic reviews is contingent on that of the primary research available for inclusion. The studies included in this review are heterogeneous with respect to study design, definitions of IC adopted, patient cohorts (including age and indication for colonoscopy) and statistical analysis performed. This limits comparisons and precludes full meta-analysis. Further research, with standardised methods and definitions, is required to gain reliable data and hence fully examine and quantify the important relationships between endoscopy quality and IC. However, assimilating studies addressing screening, surveillance and diagnostic endoscopy gives pragmatic insights into common processes which may contribute to IC and increases the generalisability of results.

Conclusion

This review provides convincing evidence that lesion (adenoma/ polyp) detection and removal reduce the rate of IC. Adherence to professional guidelines and quality improvement projects which promote and facilitate meticulous attention to mucosal inspection will increase the rates of adenoma removal and hence enhance the efficacy of colonoscopy and reduce interval cancers. This in turn will maximise the benefits of colorectal cancer screening thereby optimising patient outcomes.

Acknowledgements Paul J Murphy, Information Specialist, RCSI Library.

Funding statement This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

Table 5 Search strategy

OVID MEDLINE 11 August 1108		
1.	exp Colorectal Neoplasms/	
2.	(colorectal adj (cancer* or neoplasm* or tumor* or tumour* or carcinoma*)).mp.	
3.	1 or 2	
4.	colonoscop*.mp. or exp Colonoscopy/ or polypectomy.mp.	
5.	exp Endoscopy, Gastrointestinal/ or exp Endoscopy, Digestive System/	
6.	4 or 5	
7.	((early or missed or interval or postcolonoscop*) adj2 (cancer* or neoplasm* or tumor* or tumour* or carcinoma*)).mp.	
8.	3 and 6 and 7	
EMBASE 11 August 1421		
#4 AND #8 AND #9		1421
#9	((early OR missed OR interval OR postcolonoscop*) NEAR/2 (cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma*)):ti,ab	50,428
#8 #5 OR #6 OR #7		182,983
#7	‘digestive tract endoscopy’/exp	175,934
#6	‘gastrointestinal endoscopy’/exp	122,890
#5	‘colonoscopy’/exp. OR colonoscopy:ti,ab,de OR polypectomy:ti,ab	70,080
#4 #2 OR #3		178,648
#3	colorectal NEAR/1 (cancer* OR neoplasm* OR tumor* OR tumour*)	178,648
#2	‘colorectal carcinoma’/exp OR ‘colorectal carcinoma’	28,507
#1	‘colorectal cancer’/de	111,650
COCHRANE 11 August 122		
#1	colorectal near/1 (cancer* or neoplasm* or tumor* or tumour* or carcinoma*)	9604
#2	MeSH descriptor: [Colorectal Neoplasms] explode all trees	6428
#3	#1 or #2	1144
#4	MeSH descriptor: [Colonoscopy] explode all trees	1961
#5	MeSH descriptor: [Endoscopy, Digestive System] explode all trees	5524
#6	MeSH descriptor: [Endoscopy, Gastrointestinal] explode all trees	4604
#7	colonoscopy:ti,ab	2845
#8	#4 or #5 or #6 or #7	7011
#9	(early or missed or interval or postcolonoscop*) near/2 (cancer* or neoplasm* or tumor* or tumour* or carcinoma*)	4011
#10	#3 and #8 and #9	122

Table 6 Variables retrieved from each study

Study details	Author
	Year
	Title
	Location
	Number of sites
	Time period
	Study design
Interval cancer definition and rate	Definition of interval cancer
	Total number of patients
	Number of patients
	Rate of interval cancer
Patient demographics	Age
	% Male
	Body mass index (BMI)
	Comorbidities
	Indication for colonoscopy (screening/surveillance/symptomatic)
	% of patients with family history
	Previous polypectomy
Endoscopy processes	Setting (academic/community/other)
	Adenoma detection rate
	Polypectomy rate
	Withdrawal time
	Prep (excellent or good/fair/poor/failed due to poor prep/not recorded)
	Caecal intubation rates
	Procedure volume
	Endoscopy specialty and experience (gastroenterology/surgery/other/trainee
Oncological features of cancers	Stage
	Pathology grade
	Location of cancers (individual segments and proximal/distal)

Table 7 Assessment of quality of included studies using the Nottingham-Ottawa Scale

Paper	Selection (max 4*)	Comparability (max 2*)	Outcome (max 3*)	Total
Tsai [16]	****		**	6*
Gotfried [17]	****		**	6*
Corley [18]	****	**	***	9*
Bressler [19]	****		***	7*
Singh [20]	****	*	***	8*
Cooper [21]	****	*	***	8*
Baxter [22]	****	*	***	8*
Haseman [23]	***		**	5*
Samadder [24]	****	*	***	8*
Farrar [25]	***	*	***	7*
Nayor [26]	****	*	***	8*
Richter [27]	****		***	7*
le Clercq [28]	****	*	***	8*
Kaminiski [29]	****	**	***	9*
Shergill [30]	***	*	***	7*

References

1. Ito E, Yoshida M, Suzuki N, Imakita T, Tsutsui N, Ohdaira H, Kitajima M, Suzuki Y (2018) Prophylactic retention suture for surgical site infection: a retrospective cohort study. J Surg Res 221:58–63
2. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E (2007) Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev (1):Cd001216
3. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Waye JD (2012) Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 366(8):687–696
4. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L (2008) Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol 103(6):1541–1549
5. Sanduleanu S, le Clercq CM, Dekker E, Meijer GA, Rabeneck L, Rutter MD et al (2015) Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. Gut 64(8):1257–1267
6. Singh S, Singh PP, Murad MH, Singh H, Samadder NJ (2014) Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. Am J Gastroenterol 109(9):1375–1389
7. Adler J, Robertson DJ (2015) Interval colorectal Cancer after colonoscopy: exploring explanations and solutions. Am J Gastroenterol 110(12):1657–1664 **quiz 65**
8. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E (2006) Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 101(2):343–350
9. Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG (1997) Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 112(1):24–28
10. Pohl H, Srivastava A, Bensen SP, Anderson P, Rothstein RI, Gordon SR et al (2013) Incomplete Polyp Resection During Colonoscopy—Results of the Complete Adenoma Resection (CARE) Study. Gastroenterology 144(1):74–80.e1
11. Govindarajan A, Rabeneck L, Yun L, Tinmouth J, Paszat LF, Baxter NN (2016) Population-based assessment of the outcomes in patients with postcolonoscopy colorectal cancers. Gut 65(6):971–976
12. Rees CJ, Thomas Gibson S, Rutter MD, Baragwanath P, Pullan R, Feeney M, Haslam N (2016) UK key performance indicators and quality assurance standards for colonoscopy. Gut 65(12):1923–1929
13. Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Levin TR, Lieberman D, Robertson DJ (2017) Colorectal Cancer screening: recommendations for physicians and patients from the U.S. multi-society task force on colorectal Cancer. Gastroenterology 153(1):307–323
14. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097
15. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605
16. Tsai CE, Wu KL, Chiu YC, Chuah SK, Tai WC, Hu ML, et al. (2018) The incidence and clinical associated factors of interval colorectal cancers in Southern Taiwan. J Formos Med Assoc 117(3): 185–90
17. Gotfried J, Bernstein M, Ehrlich AC, Friedenberg FK (2015) Administrative database research overestimates the rate of interval Colon Cancer. J Clin Gastroenterol 49(6):483–490
18. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP (2014) Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 370(14): 1298–1306
19. Bressler B, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L (2007) Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology 132(1):96–102
20. Singh H, Nugent Z, Demers AA, Bernstein CN (2010) Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. Am J Gastroenterol 105(12): 2588–2596
21. Cooper GS, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM (2012) Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. Cancer 118(12):3044–3052
22. Baxter NN, Sutradhar R, Forbes SS, Paszat LF, Saskin R, Rabeneck L (2011) Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. Gastroenterology 140(1):65–72
23. Haseman JH, Lemmel GT, Rahmani EY, Rex DK (1997) Failure of colonoscopy to detect colorectal cancer: evaluation of 47 cases in 20 hospitals. Gastrointest Endosc 45(6):451–455
24. Samadder NJ, Curtin K, Tuohy TM, Pappas L, Boucher K, Provenzale D et al (2014) Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. Gastroenterology 146(4):950–960
25. Farrar WD, Sawhney MS, Nelson DB, Lederle FA, Bond JH (2006) Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 4(10):1259–1264
26. Nayor J, Saltzman JR, Campbell EJ, Perencevich ML, Jajoo K, Richter JM (2017) Impact of physician compliance with colonoscopy surveillance guidelines on interval colorectal cancer. Gastrointest Endosc 85(6):1263–1270
27. Richter JM, Campbell EJ, Chung DC (2015) Interval colorectal cancer after colonoscopy. Clin Colorectal Cancer 14(1):46–51
28. le Clercq CM, Bouwens MW, Rondagh EJ, Bakker CM, Keulen ET, de Ridder RJ et al (2014) Postcolonoscopy colorectal cancers are preventable: a population-based study. Gut 63(6):957–963
29. Kaminski MF, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, Zwierko M, Rupinski M, Nowacki MP, Butruk E (2010) Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 362(19):1795–1803
30. Shergill AK, Conners EE, McQuaid KR, Epstein S, Ryan JC, Shah JN et al (2015) Protective association of colonoscopy against proximal and distal colon cancer and patterns in interval cancer. Gastrointest Endosc 82(3):529–37.e1
31. Duarte RB, Bernardo WM, Sakai CM, Silva GL, Guedes HG, Kuga R et al (2018) Computed tomography colonography versus colonoscopy for the diagnosis of colorectal cancer: a systematic review and meta-analysis. Ther Clin Risk Manag 14:349–360
32. Garborg K, de Lange T, Bretthauer M (2017) Quality indicators in colonoscopy. Curr Treat Options Gastroenterol 15(3):416–428
33. Morris EJA, Rutter MD, Finan PJ, Thomas JD, Valori R (2015) Post-colonoscopy colorectal cancer (PCCRC) rates vary considerably depending on the method used to calculate them: a retrospective observational population-based study of PCCRC in the English National Health Service. Gut 64(8):1248–1256
34. Chen SC, Rex DK (2007) Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. Am J Gastroenterol 102(4):856–861
35. Kaminski MF, Wieszczy P, Rupinski M, Wojciechowska U, Didkowska J, Kraszewska E, Kobiela J, Franczyk R, Rupinska M, Kocot B, Chaber-Ciopinska A, Pachlewski J, Polkowski M, Regula J (2017) Increased rate of adenoma detection associates

with reduced risk of colorectal Cancer and death. Gastroenterology 153(1):98–105

36. Wieszczy P, Regula J, Kaminski MF (2017) Adenoma detection rate and risk of colorectal cancer. Best Pract Res Clin Gastroenterol 31(4):441–446
37. Denis B, Sauleau EA, Gendre I, Exbrayat C, Piette C, Dancourt V, Foll Y, Hadad HA, Bailly L, Perrin P (2014) The mean number of adenomas per procedure should become the gold standard to measure the neoplasia yield of colonoscopy: a population-based cohort study. Dig Liver Dis 46(2):176–181
38. Williams JE, Holub JL, Faigel DO (2012) Polypectomy rate is a valid quality measure for colonoscopy: results from a national endoscopy database. Gastrointest Endosc 75(3):576–582
39. Fedewa SA, Flanders WD, Ward KC, Lin CC, Jemal A, Goding Sauer A, Doubeni CA, Goodman M (2017) Racial and ethnic disparities in interval colorectal Cancer incidence: a population-based cohort study. Ann Intern Med 166(12):857–866
40. Sawhney MS, Farrar WD, Gudiseva S, Nelson DB, Lederle FA, Rector TS, Bond JH (2006) Microsatellite instability in interval Colon cancers. Gastroenterology 131(6):1700–1705
41. Parikh MP, Muthukuru S, Jobanputra Y, Naha K, Gupta NM, Wadhwa V et al (2017) Proximal sessile serrated adenomas are more prevalent in Caucasians, and gastroenterologists are better than nongastroenterologists at their detection. Gastroenterol Res Pract 2017:6710931
42. Shaukat A, Rector TS, Church TR, Lederle FA, Kim AS, Rank JM, Allen JI (2015) Longer withdrawal time is associated with a reduced incidence of interval Cancer after screening colonoscopy. Gastroenterology 149(4):952–957
43. Rex DK (2017) Polyp detection at colonoscopy: Endoscopist and technical factors. Best Pract Res Clin Gastroenterol 31(4):425–433
44. Rex DK (2000) Colonoscopic withdrawal technique is associated with adenoma miss rates. Gastrointest Endosc 51(1):33–36
45. Arain MA, Sawhney M, Sheikh S, Anway R, Thyagarajan B, Bond JH, Shaukat A (2010) CIMP status of interval colon cancers: another piece to the puzzle. Am J Gastroenterol 105(5):1189–1195
46. Shaukat A, Arain M, Anway R, Manaktala S, Pohlman L, Thyagarajan B (2012) Is KRAS mutation associated with interval colorectal cancers? Dig Dis Sci 57(4):913–917