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Characteristics of Missed or Interval Colorectal Cancer and Patient Survival: A Population-Based Study

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BACKGROUND & AIMS: Colorectal cancers (CRCs) diagnosed within a few years after an index colonoscopy can arise from missed lesions or the development of a new tumor. We investigated the proportion, characteristics, and factors that predict interval CRCs that develop within 6–60 months of colonoscopy. **METHODS:** We performed a population-based cohort study of Utah residents who underwent colonoscopy examinations from 1995 through 2009 at Intermountain Healthcare or the University of Utah Health System, which provide care to more than 85% of state residents. Colonoscopy results were linked with cancer histories from the Utah Population Database to identify patients who underwent colonoscopy 6–60 months before a diagnosis of CRC (interval cancer). Logistic regression was performed to identify risk factors associated with interval cancers. **RESULTS:** Of 126,851 patients who underwent colonoscopies, 2659 were diagnosed with CRC; 6% of these CRCs (159 of 2659) developed within 6 to 60 months of a colonoscopy. Sex and age were not associated with interval CRCs. A higher percentage of patients with interval CRC were found to have adenomas at their index colonoscopy (57.2%), compared with patients found to have CRC detected at colonoscopy (36%) or patients who did not develop cancer (26%) ($P < .001$). Interval CRCs tended to be earlier-stage tumors than those detected at index colonoscopy, and to be proximally located (odds ratio, 2.24; $P < .001$). Patients with interval CRC were more likely to have a family history of CRC (odds ratio, 2.27; $P = .008$) and had a lower risk of death than patients found to have CRC at their index colonoscopy (hazard ratio, 0.63; $P < .001$). **CONCLUSIONS:** In a population-based study in Utah, 6% of all patients with CRC had interval cancers (cancer that developed within 6 to 60 months of a colonoscopy). Interval CRCs were associated with the proximal colon, earlier-stage cancer, lower risk of death, higher rate of adenoma, and family history of CRC. These findings indicate that interval colorectal tumors may arise as the result of distinct biologic features and/or suboptimal management of polyps at colonoscopy.

Keywords: Colon Cancer; Detection; Screening; Missed or Interval Cancer.

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Colorectal cancer (CRC) is the third most common cancer in the United States and the second leading cause of cancer-related mortality in men and women.[1] Adenomatous polyps are accepted as the precursor lesion for most colorectal cancer. Colonoscopy can detect and remove precursor lesions and diagnose patients at an earlier stage of cancer. Colonoscopy is the preferred option for CRC screening in the United States.[2] It is hypothesized that most CRCs diagnosed within a few years (3–5 y) after an index colonoscopy are owing to missed lesions or new interval cancer development. In the literature, these tumors variously have been referred to as missed, interval, or postcolonoscopy CRC. Controversy exists around the effectiveness of colonoscopy for preventing CRC and the risk of interval cancers after screening colonoscopy.

The few large population-based studies that have evaluated the risk and predictors of interval CRCs at colonoscopy have reported rates as high as 14%.[3] Six population-based studies, 2 from Canada,[4,5] 1 from Germany,[6] 1 from The Netherlands,[7] a US study limited to the Medicare population,[8] and an analysis of 3 chemoprevention polyp trials,[9] have

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; EMR, electronic medical record; FAP, familial adenomatous polyposis; HR, hazard ratio; IHC, Intermountain Healthcare; OR, odds ratio; UPDB, Utah Population Database; UUHSC, University of Utah Health Sciences.**

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described the development of colorectal cancer after colonoscopy with rates ranging between 2.9% and 7.9%. An additional study limited to a single Veterans Affairs medical center also reported an interval CRC rate of 5.1%.[10]

Most of these previous reports came from countries with health care systems that differ from those of the United States Studies completed solely in Veterans[11] or Medicare[8] populations also may not be generalizable to the US population and routine clinical practice.

In this study we assessed the proportion, characteristics, and predictors of interval CRCs occurring within 5 years of colonoscopy in a large population-based study from Utah, reflecting usual clinical care in the United States.

Materials and Methods

Design

This study was approved by the Institutional Review Boards of the University of Utah and Intermountain Healthcare (IHC), and by the Resource for Genetic and Epidemiologic Research (http://www.research.utah.edu/rge/), an administrative oversight board created to govern access to the Utah Population Database (UPDB).

We performed a population-based retrospective cohort study of residents in the state of Utah, between 50 and 80 years of age, who underwent colonoscopy between February 15, 1995, and January 31, 2009, at IHC and/or the University of Utah Health Sciences (UUHSC) clinical facilities. By using the UPDB, de-identified medical information on these patients was merged with cancer histories from the Utah Cancer Registry.

Description of Databases

This investigation took advantage of unique Utah databases. The study required patient-level data integration between IHC, the UUHSC, and the UPDB. The UPDB combines genealogies with data from statewide resources, including the Utah Cancer Registry, statewide inpatient discharge and ambulatory surgery records, driver's license data, as well as birth and death certificates. This resource also has been linked to the demographic records from the UUHSC[12] and IHC.[13] In combination, the UUHSC and IHC together provide care to more than 85% of the Utah population. Previous demographic and genetic analyses have shown that the population recorded in the Utah Population Database is genetically representative of US white and northern European populations with a low level of inbreeding.[14] Of particular interest for this study was the inclusion of the Utah Cancer Registry records as part of the UPDB. The Utah Cancer Registry is a statewide cancer registry established in 1966, and since 1973 it has been part of the Surveillance, Epidemiology, and End Results network of the National Cancer Institute registries. State law requires that all cancer diagnosis be notified to the Utah Cancer Registry.

Linkage of Electronic Medical Record Data to the UPDB

These linked resources have been used to assess colonoscopy screening rates in high-risk individuals[15] as well as recent studies on preeclampsia,[16] spontaneous preterm delivery,[17] cancer in twins,[18] heritability of inflammatory bowel disease,[19] and effects of family conditions on later-life mortality.[20]

Study Definition

Colonoscopy procedure information was extracted from the Intermountain Healthcare and University of Utah Health Sciences electronic medical records (EMRs) using Current Procedural Teminology codes 45378, 45379, 45380, 45383, 45384, or 45385. A diagnosis of colorectal cancer in patients undergoing colonoscopy was identified through the Utah Cancer Registry. We defined interval CRCs as cases in which a colonoscopy was performed between 6 and 60 months (primary definition) or 6 and 36 months (secondary definition) before CRC diagnosis and detected CRCs as those diagnosed within 6 months of a colonoscopy as outlined in Figure 1. Both of these definitions have been used in multiple prior studies to determine the CRC miss rate at the index procedures.[3,5,6,8,10] This is based on the assumption that CRCs suspected/detected on a colonoscopy would be diagnosed within 6 months of the index procedure. A period of 36–60 months was used in this analysis to define interval cancers because this window is the estimated mean sojourn time (the duration of the preclinical screen-detectable period) for CRC. Polypectomy and resultant adenomas and villous adenomas (defined as those

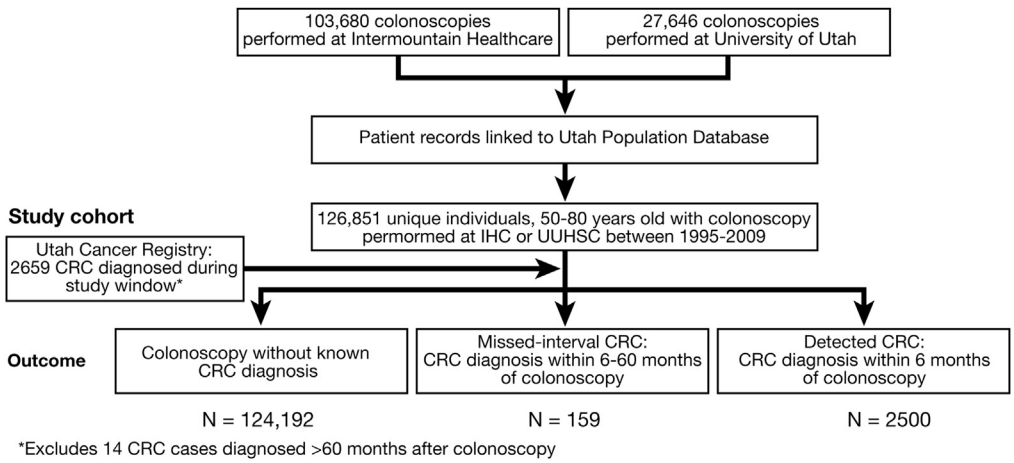

Figure 1. Study flow diagram.

that had ≥25% villous histology) were identified through pathology reports from their index colonoscopy. We could not identify the other criteria associated with a definition of an advanced adenoma (≥10 mm or high-grade dysplasia) through a search of the EMR. Therapeutic colonoscopy was defined as a procedure in which a polyp was removed or a biopsy sample was taken vs a diagnostic (nontherapeutic) colonoscopy in which no polyp tissue was sampled. Diagnostic (nontherapeutic) colonoscopy also included screening examinations. This was determined by the presence of pathology results in the database in association with the procedure. Family history of CRC in a first-degree relative was determined from the Utah Population Database, which has genealogic records linked to the state cancer registry.

Chart Review

To review our diagnostic algorithm for identifying interval CRCs we selected all available charts of patients diagnosed with an interval CRC at one of the two health centers between 2002 and 2009 and manually reviewed endoscopy reports, physician notes, genetic test results, and histologic and radiologic information. Chart extractions were conducted by the principal investigator (N.J.S.). Additional variables not available from the enterprise data warehouse also were extracted for these charts, including confirmation of cecal intubation, adequacy of bowel preparation, diverticulosis, polyp size 10 mm or larger, type of polypectomy (biopsy forceps, cold snare, or hot snare), incomplete polypectomy, location of polypectomy, or evidence of familial cancer syndrome such as Lynch syndrome or familial adenomatous polyposis. The presence of an inherited cancer predisposition syndrome was determined from a review of endoscopy reports, pathology results for immunohistochemistry/microsatellite instability, and medical and genetic consultation notes in the electronic medical record. Incomplete polypectomy was defined as a notation in the endoscopy report stating "incomplete polypectomy," "incomplete polyp removal," "piecemeal resection," or "polyp tissue remains intact at end of procedure."

Statistical Analysis

The primary analysis focused on factors associated with the presence of interval CRCs. We explored differences between patients diagnosed with an interval CRC and those in the reference groups: detected cancers (patients who had a colonoscopy within 6 months of diagnosis) or those colonoscopy patients with no known CRC diagnosis. We evaluated patient characteristics (age at index colonoscopy, sex, family history of CRC), tumor characteristics (cancer stage and location in colon), and procedure characteristics (diagnostic colonoscopy or colonoscopy with polypectomy). Location was classified as the proximal colon (cecum, ascending colon, hepatic flexure, transverse colon), distal colon (splenic flexure, descending colon, sigmoid colon), and rectum (rectosigmoid junction and rectum).

SAS version 9.1 (SAS Institute, Cary, NC) was used for data management and analysis. Standard descriptive statistics were used, along with chi-square tests to compare proportions between the groups. Logistic regression analyses were performed with interval vs detected CRCs or no known CRC diagnosis as the outcome variable. Age and sex were included in all models.

Overall survival after CRC diagnosis of the patients with interval CRC was compared, stratified by diagnosis stage, with those with detected CRC by Kaplan–Meier estimation, log-rank tests, and Cox proportional hazard ratios. The survival time was measured from the date of CRC diagnosis to date of death or censoring resulting from emigration outside of Utah or the end of the study period (January 31, 2009). Chi-square tests were used to compare proportions, and all probability values were 2-sided.

Results

Proportion of Interval Cancers

When combined and accounting for patients who had procedures performed in both hospital systems there were 127,205 individuals who received a colonoscopy during our study timeframe. A total of 340 patients with a history of CRC before 1995 (beginning of study window) and 14 individuals with a diagnosis of CRC more than 60 months after colonoscopy were excluded, leaving 126,851 unique individuals. There were 2659 patients who had a diagnosis of CRC at or within 60 months of their index colonoscopy. Of these 2659 CRC cases, 2500 patients had a colonoscopy within 6 months of diagnosis and were classified as detected cancers. A total of 159 individuals had a colonoscopy 6–60 months before the CRC diagnosis and are referred to as *interval cancers*; of these, 91 had a colonoscopy within 6–36 months before the CRC diagnosis. The proportion of cancers that developed within a short interval of colonoscopy were as follows: 6% for a window of 6–60 months (primary definition of interval CRC in this study) and 3.5% for a window of 6–36 months. A total of 124,192 remaining patients in the colonoscopy cohort had no known diagnosis of CRC before or during the study window.

Patient Demographics

The demographic characteristics of patients in the cohort with no known CRC diagnosis, those with detected CRC, and those with interval CRC occurring in 2 different windows of time (6–36 mo and 6–60 mo) are listed in Table 1. For the discussion hereafter, *interval CRCs* refers to CRCs occurring within the 6- to 60-month period. The mean age (at index colonoscopy) of those with interval cancer was 67, with a range of 34–92 years old. A total of 59% of patients with interval CRCs were older than 65 years compared with 56% of those with detected cancers. There was a nearly equitable distribution of interval and detected cancers between both males and females. By comparison, the cohort of patients undergoing colonoscopy who never had a CRC diagnosis were younger, with a mean age of 56.7 years, and also had a nearly equitable gender distribution. Most patients (42%–64%) had more than 60 months of follow-up evaluation in their respective health systems (Table 1).

Patient and Colonoscopy Characteristics Associated With Interval CRC

There were significant differences in the location of the tumor in the detected and interval cancer groups, with

Table 1. Characteristics Comparing Patients With Interval Cancers (Colonoscopy From 6–60 Months) Versus Patients With Detected Cancers (Colonoscopy Within 6 Months) and Patients Without Colorectal Cancer

Characteristic	Characteristics of cancers at diagnosis					
	Interval cancer		Detected cancers,		Colonoscopy without CRC diagnosis	
Colonoscopy window	6–36 mo, N (%)	6–60 mo, N (%)	<6 mo, N (%)	*P* value[b]		*P* value[a]
Total, N (%)	91 (3.5)	159 (6.0)	2500 (94.0)	—	124,192	
Patient characteristics						
Sex						
Men	55 (39.6)	86 (54.1)	1291 (51.6)	$\chi^2 = 0.36$	60,853 (49.0)	$\chi^2 = 1.65$
Women	36 (60.4)	73 (45.9)	1209 (48.4)	$P = .5492$	63,339 (51.0)	$P = .1996$
Age at index colonoscopy						
Mean (SD)	66 (14)	67 (13)	66 (14)		56.7 (12.7)	
Range	29–89 y	34–92 y	18–98 y		22–100 y	
<65 y	41 (45.0)	65 (40.9)	1093 (43.7)	$\chi^2 = 0.49$	88,602 (75.0)	$\chi^2 = 98.5$
≥65 y	50 (55.0)	94 (59.1)	1407 (56.3)	$P = .4903$	29,523 (25.0)	**$P < .001$**
Cancer characteristics						
Cancer stage					N/A	
Carcinoma in situ	1 (1.1)	1 (0.6)	1 (0.0)	$\chi^2 = 15.24$		
Localized	54 (59.3)	88 (55.4)	1135 (45.4)	**$P = .009$**		
Regional, direct extension	4 (4.4)	10 (6.3)	235 (9.4)			
Regional with lymph nodes	19 (20.9)	38 (23.9)	621 (24.8)			
Distant metastasis	11 (12.1)	18 (11.3)	382 (15.3)			
Unknown stage	2 (2.2)	4 (2.5)	126 (5.0)			
Cancer location					N/A	
Proximal colon	45 (49.5)	88 (55.4)	975 (39.0)	$\chi^2 = 57.09$		
Cecum	18 (19.8)	31 (19.5)	419 (16.8)	**$P < .001$**		
Ascending colon	13 (14.3)	26 (16.4)	315 (12.6)			
Hepatic flexure	2 (2.2)	9 (5.7)	82 (3.3)			
Transverse colon	12 (13.2)	22 (13.8)	159 (6.4)			
Distal colon	24 (26.4)	31 (19.5)	764 (30.6)			
Splenic flexure	4 (4.4)	5 (3.1)	57 (2.3)			
Descending colon	3 (3.3)	7 (4.4)	112 (4.5)			
Sigmoid colon	17 (18.7)	19 (12.0)	595 (23.8)			
Rectum/rectosigmoid	18 (19.8)	32 (20.1)	747 (39.9)			
Unspecified	4 (4.4)	8 (5.0)	14 (0.6)			
Characteristics and findings from index colonoscopy						
Colonoscopy type						
Diagnostic (nontherapeutic)	13 (14.3)	25 (15.7)	0 (0)	$\chi^2 = 396.8$	59,867 (48.2)	$\chi^2 = 67.07$
Therapeutic procedure	78 (85.7)	134 (84.3)	2500 (100)	**$P < .001$**	64,348 (51.8)	$P < .0001$
Adenoma rate						
Overall	53 (58.2)	91 (57.2)	900 (36.0)	$\chi^2 = 28.8$	34,167 (27.5)	$\chi^2 = 70.31$
Male	32 (58.2)	50 (58.1)	498 (38.6)	**$P < .001$**	19,874 (32.7)	**$P < .001$**
Female	21 (58.3)	41 (56.2)	402 (33.3)		14,287 (22.6)	
Villous adenoma						
Overall	26 (30.6)	40 (26.3)	473 (19.2)	$\chi^2 = 4.64$	4796 (3.9)	$\chi^2 = 204.28$
Male	18 (34.0)	25 (30.1)	239 (18.8)	**$P = .031$**	2737 (4.5)	**$P < .001$**
Female	8 (25.0)	15 (21.7)	234 (19.6)		2056 (3.3)	
Family history of CRC (FDR)				$\chi^2 = 0.72$		$\chi^2 = 16.5$
No	86 (94.5)	146 (91.8)	2406 (96.2)	$P = .3965$	120,703 (97.2)	**$P < .001$**
Yes	5 (5.5)	13 (8.2)	94 (3.8)		3512 (2.8)	
Length of follow-up period, mo						
From last colonoscopy						
<6 mo	0 (0)	0 (0)	292 (11.68)	$\chi^2 = 41.5$	3916 (3.2)	$\chi^2 = 23.9$
6–36 mo	24 (26.4)	24 (15.1)	599 (24.0)	**$P < .001$**	11,772 (9.5)	**$P < .001$**
36–60 mo	20 (22.0)	31 (19.5)	543 (21.7)		32,299 (26.0)	
>60 mo	47 (51.7)	104 (65.4)	1066 (42.6)		69,552 (56.0)	
Valid dates not available	0 (0)	0 (0)	0 (0)		6676 (5.4)	

NOTE. Bolded *P* values represent statistical significance with $P < .05$.
FDR, first-degree relative.
[a]For difference between cases with interval cancer (window of 6–60 mo) and colonoscopy cases without CRC.
[b]For differences between cases with interval cancer (window of 6–60 mo) and cases detected by screening.

proximal colon tumors much more common in the interval cancer group. The proportion of interval cancers was 55% in the proximal colon, 19.5% in the distal colon, and 20% in the recto-rectosigmoid junction (Table 1). Compared with the detected group, patients with interval cancers were more likely to have earlier stage tumors.

As compared with colonoscopy patients without a CRC diagnosis, interval cancers were more likely to be associated with a procedure in which a polypectomy or a biopsy was performed. Eighty-four percent of the patients with interval cancers had a therapeutic procedure with a biopsy or polypectomy vs only 52% of patients without CRC (Table 1). Patients with interval cancers also were more likely to have adenomas (57.2%) or villous adenomas (26.3%) found at their index colonoscopy compared with the detected cancer patients or those colonoscopy patients without CRC (Table 1).

Medical Chart Review

Our chart review of 37 patients confirmed 36 had an interval CRC. One patient did not have an electronic endoscopy report available for review. The electronic medical record began linking endoscopy reports between 2002 and 2003. This one patient's colonoscopy reports were in that time frame and thus may not have been linked to our EMR system.

From this chart review of 37 patients we were able to examine additional variables from the colonoscopy report (Table 2). More than 30% had a report of incomplete polypectomy (including piecemeal resection in 4 patients). Fifty-seven percent of patients had a polyp removed in the same segment of the colon in which their interval cancer was located 3–5 years later. When this definition was extended to include the same or adjacent colon sites this increased to 85.5%. Only 1 patient with an interval CRC had a known diagnosis of an inherited cancer predisposition syndrome (Lynch syndrome). Diverticulosis was reported in approximately a third of the colonoscopies. Cecal intubation was confirmed and bowel preparation was marked as adequate in 92% of patients.

Comparison of Patients With Interval CRC Versus Detected CRC

We determined demographic, tumor, and procedure-related factors associated with interval cancers compared with detected cancer in logistic regression models (Table 3). Sex and age group at colonoscopy were not associated significantly with interval CRC. Interval cancers were more often early stage tumors at diagnosis. In models that accounted for stage and demographics, interval cancers showed a strong association with the proximal cancer site for intervals of both 6–36 months (odds ratio [OR], 2.18; 95% confidence interval [CI], 1.24–3.83) and 6–60 months (OR, 2.24; 95% CI, 1.46–3.42). Interval cancers also were more common in patients who had an adenoma (OR, 2.96; 95% CI, 2.0–4.38) or villous adenoma (OR, 2.04; 95% CI, 1.34–3.11) at their index colonoscopy. A family history of CRC in a first-degree relative was also more common in patients with an interval cancer compared with those with detected cancer (OR, 2.27; 95% CI, 1.24–4.16).

Table 2. Endoscopic Characteristics of Medical Chart Review Cohort

Characteristic	Frequency, N (%) (total N = 36)
Interval CRC tumor site	
Proximal	23 (63.9)
Cecum	7 (19.44)
Ascending	9 (25)
Hepatic flexure	2 (5.6)
Transverse	5 (13.9)
Distal	5 (13.9)
Splenic flexure	2 (5.5)
Descending	1 (2.8)
Sigmoid	2 (5.6)
Rectum	7 (19.4)
Colon (not otherwise specified)	1 (2.8)
Polyp found	
No (0 polyps)	4 (11.1)
Yes	32 (88.9)
Polyp frequency (n = 36)	
Mean (range)	2 (0–9)
Polypectomy at same site as CRC	
No	15
Yes	17 (53.1)
Polypectomy at same or adjacent site as CRC	
No	4
Yes	28 (87.5)
Report of incomplete polypectomy	
No	20 (62.5)
Yes	12 (37.5)
Not applicable (no polyp found)	4
Polyp ≥10 mm	
No	20 (62.5)
Yes	12 (37.5)
Not applicable (no polyp found)	4
Polyp histology (n = 25)	
Hyperplastic polyp	8 (32)
Tubular adenoma	14 (56)
Tubulovillous adenoma	8 (32)
Adenoma with high-grade dysplasia	4 (16)
Type of polypectomy	
Not applicable (no polyp found)	4
Polyp not removed	2
Cold snare	3 (8.33)
Hot snare	13 (36.11)
Forceps	14 (38.9)
Cecal intubation	
Yes	33 (91.7)
Bowel preparation	
Inadequate	2 (5.6)
Adequate (fair, good, excellent, or adequate)	33 (91.6)
Missing	1 (2.8)
Diverticulosis	
No	22
Yes	14
Hereditary cancer syndrome	
Lynch syndrome	1 (2.8)

Table 3. Multivariable ORs and 95% CIs of Patients, Procedures, and Tumor Predictors of Interval Cancers Compared With Patients With Detected CRC

Characteristic	Odds of interval cancer diagnosis, 6–36 mo		Odds of interval cancer diagnosis, 6–60 mo	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age (in yearly increments)	1.00 (0.99–1.02)	.959	1.00 (0.99–1.01)	.725
Age group, y[a]				
<65	1.0 (ref)		1.0 (ref)	
≥65	0.97 (0.63–1.47)	.871	1.14 (0.82–1.59)	.423
Sex[b]				
Women	1.0 (ref)		1.0 (ref)	
Men	1.43 (0.93–2.19)	.103	1.10 (0.80–1.52)	.567
Cancer stage[c]				
CIS or localized (stage 1)	1.0 (ref)		1.0 (ref)	
Regional (stage 2)	**0.36 (0.13–1.00)**	**.051**	0.54 (0.28–1.06)	.073
Regional lymph nodes (stage 3)	0.64 (0.38–1.08)	.097	0.79 (0.53–1.16)	.230
Distant metastasis (stage 4)	0.59 (0.31–1.15)	.121	**0.60 (0.36–1.02)**	**.058**
Unknown stage	0.33 (0.08–1.37)	.126	0.40 (0.15–1.11)	.079
Dichotomize stage				
Early stage (stage 1)	1.0 (ref)		1.0 (ref)	
Advanced stage (2–4)	**0.58 (0.38–0.89)**	**.013**	**0.70 (0.50–0.96)**	**.03**
Cancer location[d]				
Rectum/rectosigmoid junction	1.0 (ref)		1.0 (ref)	
Distal colon	1.41 (0.76–2.63)	.277	0.99 (0.60–1.64)	.969
Proximal colon	**2.18 (1.24–3.83)**	**.007**	**2.24 (1.46–3.42)**	**<.001**
Unspecified	**17.52 (4.83–63.49)**	**<.001**	**21.74 (7.83–60.32)**	**<.001**
Adenoma polypectomy[d]				
No adenoma	1.0 (ref)		1.0 (ref)	
Adenoma	**2.90 (1.70–4.92)**	**<.001**	**2.96 (2.00–4.38)**	**<.001**
Villous adenoma	**2.47 (1.44–4.24)**	**.001**	**2.04 (1.34–3.11)**	**<.001**
Family history[d]				
No	1.0 (ref)	.387	1.0 (ref)	**.008**
Yes	1.51 (0.60–3.80)		**2.27 (1.24–4.16)**	

NOTE. Bolded entries refer to those that are statistically significant with $P < .05$.
CIS, carcinoma in situ.
[a]Adjusted for sex.
[b]Adjusted for age group.
[c]Adjusted for age group and sex.
[d]Adjusted for age group, sex, and stage.

Comparison of Patients With Interval CRC Versus Patients Without CRC

We were able to examine associations between demographic and procedure-related factors between patients who developed interval CRC and those with no known CRC diagnosis before or during the study timeline. Compared with those without CRC, interval cancers occurred in older patients; age older than 65 was associated with a greater than 4-fold risk for an interval cancer (OR, 4.33; 95% CI, 3.12–5.94). Interval cancers also were more likely to occur in patients with an adenoma (OR, 1.89; 95% CI, 1.29–2.77) or villous adenoma (OR, 8.40; 95% CI, 5.57–12.66) found at their index colonoscopy. A family history of CRC also was more common among patients with interval CRC compared with patients without CRC (OR, 3.00; 95% CI, 1.70–5.30) (Table 4).

Survival Analysis

Kaplan–Meier survival curves and hazard ratios are shown in Figure 2 and Table 5. Cox proportional hazards models were used to investigate differences in survival between interval and detected CRC groups, adjusting for sex and age group. Kaplan–Meier analysis showed a distinct survival advantage (lower risk of death) for interval CRC compared with detected CRCs across all cancer stages (hazard ratio [HR], 0.63; 95% CI, 0.49–0.81) (Figure 2*A*, Table 5). Subgroup analysis by stage showed a trend toward better survival for early stage cancers (stage 1: HR, 0.77; 95% CI, 0.52–1.15; and stage 2: HR, 0.54; 95% CI, 0.17–1.72) (Figure 2*B* and *C*, Table 5). Later-stage cancers showed a statistically significant survival advantage for interval CRC compared with detected cancers (stage 3: HR, 0.50; 95% CI, 0.29–0.88; and stage 4: HR, 0.48; 95% CI, 0.29–0.80) (Figure 2*D* and *E*, Table 5).

Discussion

This study was a US population-based study to reflect usual clinical care colonoscopy and comprises colonoscopy data from a large academic medical center and managed care organization, that together provide care to more than 85% of the state population. We found that 3.5%–6% of colorectal

Table 4. Multivariable ORs and 95% CIs of Patients, Procedures, and Tumor Predictors of Interval Cancers Compared With Colonoscopy Patients Without CRC Diagnosis

	Odds of interval cancer diagnosis, 6–36 mo		Odds of interval cancer diagnosis, 6–60 mo	
Characteristic	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age group, y[a]				
<65	1.0 (ref)	**<.001**	1.0 (ref)	**<.001**
≥65	**3.86 (3.56-4.18)**		**4.33 (3.12–5.94)**	
Sex[b]				
Women	1.0 (ref)	.062	1.0 (ref)	.284
Men	1.08 (0.99–1.17)		1.19 (0.87–1.62)	
Adenoma polypectomy[c]				
No adenoma	1.0 (ref)		1.0 (ref)	
Adenoma	**0.60 (0.54–0.67)**	**<.001**	**1.89 (1.29–2.77)**	**.001**
Villous adenoma	**3.82 (3.42–4.27)**	**<.001**	**8.40 (5.57–12.66)**	**<.001**
Family history[c]				
No	1.0 (ref)	**.011**	1.0 (ref)	**<.001**
Yes	**1.31 (1.06–1.62)**		**3.0 (1.70–5.30)**	

NOTE. Bolded entries refer to those that are statistically significant with $P < .05$.
[a]Adjusted for sex.
[b]Adjusted for age group.
[c]Adjusted for age group and sex.

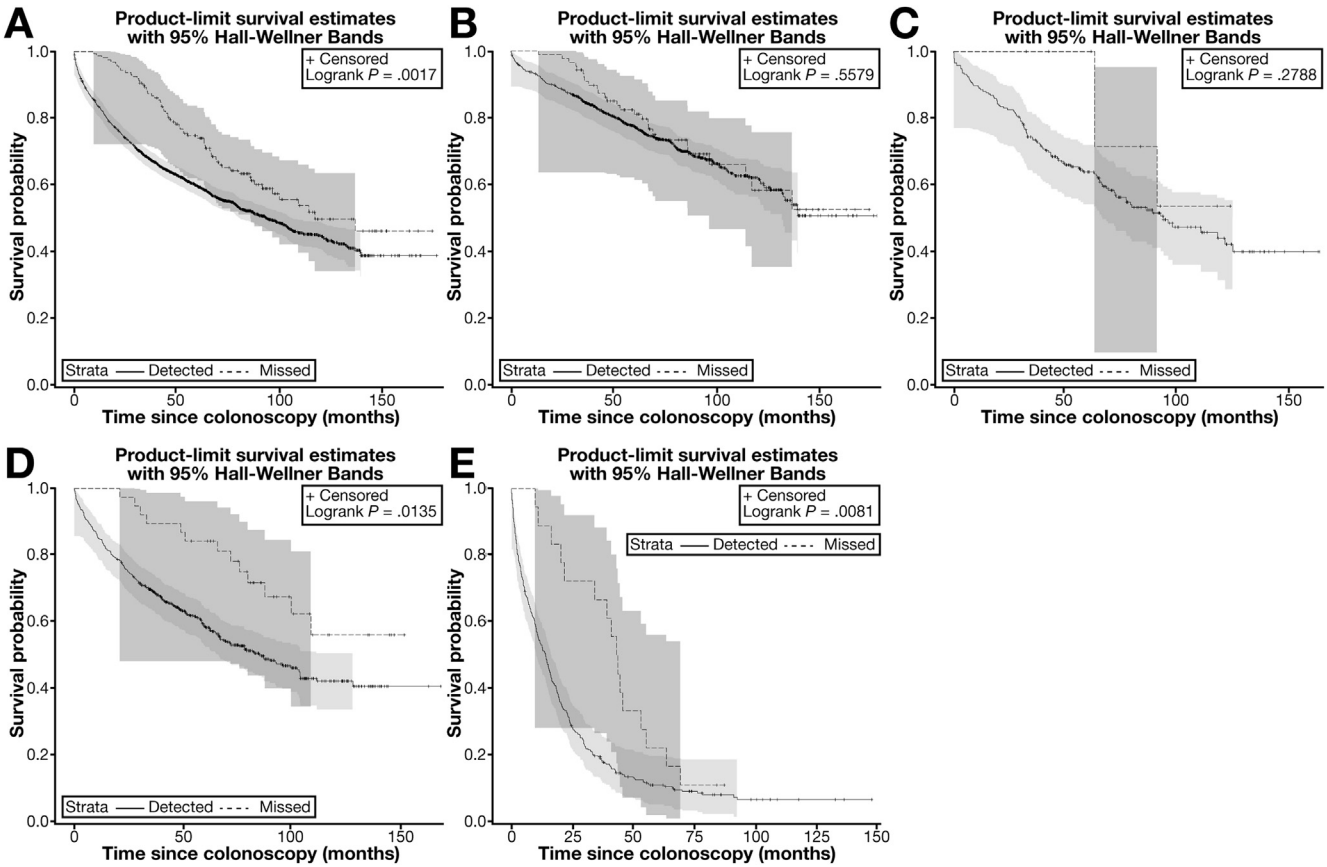

Figure 2. Kaplan–Meier survival curves by cancer stage. (*A*) Kaplan–Meier survival curves across all cancer stages. (*B*) Kaplan–Meier survival curves for carcinoma in situ and localized stage 1 cancers. (*C*) Kaplan–Meier survival curves for regional stage 2 cancers. (*D*) Kaplan–Meier survival curves for regional stage 3 cancers with lymph node involvement. (*E*) Kaplan–Meier survival curves for distant metastasis stage 4 cancers.

Table 5. Hazard Ratios and 95% Confidence Intervals for Interval Versus Detected Cancers by Stage Adjusted for Age Group and Sex

	Hazard ratio	95% CI	*P* value
Interval cancers vs detected cancers across all cancer stages (1–4)	**0.63**	**0.49–0.81**	**<.001**
Detected cancers (reference for all categories)	1 (Ref)		
CIS and localized (stage 1)	0.77	0.52–1.15	.20
Regional (stage 2)	0.54	0.17–1.72	.30
Regional with lymph nodes (stage 3)	**0.50**	**0.29–0.88**	**.02**
Distant metastasis (stage 4)	**0.48**	**0.29–0.80**	**.005**

NOTE. Bolded entries refer to those that are statistically significant with $P < .05$.
CIS, carcinoma in situ.

cancers may be "missed" at colonoscopy in usual clinical practice in Utah. The proportion of interval CRCs found in this study was nearly identical to that reported from a population-based study from Ontario,[5] which reported an overall rate of 3.4%, but was less than half that reported in a similar study from another province in Canada.[3] The higher proportion of interval cancers in Canada may be partly owing to the large number of colonoscopies performed by nongastroenterologists (83% of colonoscopies in Manitoba were performed by nongastroenterologists) or the high rate of incomplete colonoscopies that do not visualize the right colon (>15% in Ontario were incomplete).[3,5,21] A recent study limited to Medicare recipients reported an interval cancer rate of 7.2%.[8] This may reflect a higher risk of interval cancers in patients older than age 65.

In our study, the proportion of interval CRC was similar between both sexes, but was more frequent in older patients (age, >65) when compared with those without a CRC diagnosis. Similar to prior studies we found proximal tumor location to be a strong risk factor for interval cancers compared with those cancers detected at colonoscopy. Proximal location has been associated with a more than 2-fold increased risk for interval cancers in other studies.[3,5,6] Interval cancers were more likely to occur in patients who underwent polypectomy at the time of their colonoscopy vs a diagnostic (nontherapeutic) procedure without any polyp removal attempted. Assessment of our chart review cohort for additional findings in the colonoscopy report showed that a large proportion of interval cancer cases had evidence of a large polyp (≥10 mm) removed at the index colonoscopy, use of hot snare polypectomy, and report of possible incomplete polypectomy with tissue remaining at the end of the procedure. We show that patients with interval CRC had a much higher adenoma and villous adenoma rate than those with detected cancers or colonoscopy patients without a known CRC diagnosis. Those with interval cancers may represent a segment of the population that are polyp formers, consistent with the very high rate of adenomas and villous adenomas seen in our study. From our chart review, 57% of patients had a polyp removed in the same segment of the colon in which their interval cancer was located 5 years later, raising the issue of incomplete polypectomy. A prospective study by Pohl et al[22] found that 10% of polyps at colonoscopy were resected incompletely, with residual neoplastic tissue found at the postpolypectomy margins and this was more common for sessile serrated lesions compared with traditional pedunculated adenomas. Similarly, a population-based study from The Netherlands found that incomplete resection was the probable etiology for 9% of interval (postcolonoscopy) colorectal cancers.[7] Several studies from both the United States[23] and Europe[24] have found that polyps with advanced neoplasia in the right colon are more likely to be smaller and nonpolypoid (sessile) compared with left-sided polyps. Both of these features (small size and sessile form) may be associated with incomplete polypectomy.[22] These reports, along with our findings, may support that an accelerated polyp formation rate or an incompletely removed polyp that may have progressed to cancer or a field effect in that segment of the colon serves as a risk factor for subsequent cancer development.

Unlike studies from Canada that have reported high rates of incomplete colonoscopy,[5,21] in our chart review cohort 92% of endoscopists reported cecal intubation with visualization of endoscopic landmarks. Inadequate bowel preparation also has been hypothesized to be a risk factor for missed-interval cancers and explain the right-sided predominance. Although we only have data from a subset of all the interval cancers in our study, 33 of 36 patients (92%) in our chart review cohort had an adequate bowel preparation. Cancer predisposition syndromes do not seem to be an explanation for the majority of interval cancers because only 1 patient of 36 in our chart review cohort had a known diagnosis of Lynch syndrome and no patients had clinical or endoscopic features concerning for familial adenomatous polyposis (FAP) based on review of endoscopy reports or the medical chart. Interval CRCs tended to be of earlier stage than detected cancer. This is similar to data from Medicare beneficiaries in whom interval tumors were more often stage 1 cancer.[8] We also found a distinct and statistically significant survival advantage for interval cancers compared with detected CRCs overall and for advanced stages (stages 3–4). The underlying reason for the consistent findings of a higher frequency of interval cancers in the right colon and our data showing a survival advantage is unclear and likely multifactorial. However, the association of proximal tumor location, earlier stage at diagnosis, and survival advantage compared with detected CRCs suggest that tumor biology may play an important role in the pathogenesis of these lesions. There are at least 3 predominant pathways for sporadic CRC development: the chromosomal instability pathway, the mismatch repair pathway, and the serrated pathway.[25] These pathways have been associated with different clinicopathologic associations and prognostic potential.[26] Microsatellite instability even in patients without Lynch syndrome is associated with proximal tumor location and improved survival compared with microsatellite-stable cancers and more rapid lesion growth.[27,28] Tumors that arise from precursor sessile

serrated lesions also may contribute to these interval cancers because of their proximal colon predominance and difficulty in being able to detect them at colonoscopy.[11] Proximally located serrated adenocarcinoma also was shown to be associated with improved survival in one study.[29] In a large prospective cohort study of health professionals, interval cancers more likely were found to be characterized by methylation abnormalities (CpG island methylator phenotype and LINE-1) and microsatellite instability.[30] One possible unifying theory for interval cancers that would combine issues related to quality of endoscopic examination and biological differences in tumor biology relate to the serrated pathway of tumorigenesis. These sessile serrated lesions develop from a pathway characterized by defects in methylation (CpG island methylator phenotype high) and phenotypically occur in the right colon and are sessile (nonpolypoid) in appearance, making their detection and removal more difficult.[23,24] Our results would be consistent with interval cancers showing features compatible with mismatch repair or serrated pathways of tumorigenesis. Further research is needed to clarify the role of these different CRC pathways in the etiology of interval cancers.

We found that a family history of colorectal cancer is more common among patients with an interval CRC compared with those with detected cancer or no known diagnosis of CRC. This is consistent with findings from a large Dutch study in which a family history of CRC was more common in those with interval cancer than those with prevalent CRC (5.4% vs 1.6%).[7] By using statewide cancer records linked to validated Utah genealogy records, our study was able to avoid recall bias in assessing familial relationships and familial cancer risk. These results further support the notion that some fraction of interval cancers may have a biological basis (genetic or epigenetic) that further increases risk of CRC in their relatives. It also emphasizes the importance of taking a thorough family history and strict adherence to surveillance guidelines in high-risk groups.

This study had many strengths. The present study used the unique resources of the Utah Population Database to confirm a cancer diagnosis from the Utah Cancer Registry, and medical records from the University of Utah Health Sciences and Intermountain Healthcare to ascertain the date of colonoscopy. This was a large population-based study, reflecting standard-of-care clinical practice in both a large academic medical center and a managed care organization, which together provide care to a large portion of the state's population. Health care systems outside the United States have several important differences that may impact the generalizability of their findings to US practice. Studies from Canada have reported high rates of incomplete colonoscopy (failure to reach the cecum in >15%), and a majority of the procedures were performed by nongastroenterologists (>50%).[3,5,21] The findings from our chart review are more consistent with US practices, in which cecal intubation is performed in more than 90% of procedures and gastroenterologists perform the vast majority of colonoscopies. Hence, our results are more likely to be generally applicable than those from academic centers with a referral center bias, health care systems outside the United States, or restricted populations such as Medicare beneficiaries or Veterans.

The present study also had limitations. The 2 health systems used for this study account for more than 85% of all patient care in the state. This may lead to some cancers misclassified as "detected" when in reality they had a colonoscopy completed 6–60 months before diagnosis at a non-University of Utah/Intermountain Healthcare facility. Our estimate is conservative; the interval CRC number can only be higher if this misclassification occurs. This misclassification will only represent a small number of cases for the following reasons: (1) more than 85% of patients in the state receive care at one of these two centers; (2) the University of Utah represents indigent care in the state and thus would be the primary source for patients who are uninsured, underinsured, or lose insurance during the study window; and (3) the vast majority of patients in this study had follow-up evaluation within the respective health systems for more than 60 months (42%–65%). Even with the lengthy follow-up time (>80% of patients had at least 36 months of follow-up postcolonoscopy) for each of the patient groups (interval CRC, detected CRC, colonoscopy without CRC), there is the possibility of differential exposure to subsequent colonoscopy examinations that could lead to under-ascertainment of interval cancer. We were unable to specifically exclude patients with inflammatory bowel disease or a known hereditary cancer syndromes (FAP or Lynch syndrome), although only 1 patient had such a diagnosis (Lynch syndrome) in our chart review cohort. Both Lynch and FAP are very rare and account for less than approximately 3% of all colon cancers, and therefore are unlikely to modify the strong statistical associations found in this study if they could be identified and excluded. Extraction of data from electronic medical records has limitations in the information that can be gathered. The indication for colonoscopy was not ascertained specifically and also may introduce bias. Many screening procedures also are coded for a diagnosis found at colonoscopy or other unrelated symptoms and thus it would be nearly impossible to establish a study population of only screening colonoscopies. This reflects gastroenterologists' usual clinical practice of colonoscopy, with patients referred for screening as well as other indications. We did not have information on the documented completeness of the colonoscopic examination, quality of the bowel preparation, or specialty of the physician performing the examination outside of our limited chart review cohort. Our limited chart review only explored the causes of interval cancer at a single institution. Finally, our study design was slightly different from that used in prior reports of interval cancer, which started with a cohort of CRC patients instead of a cohort of patients undergoing colonoscopy. This may limit the direct comparison of results between studies.

In conclusion, this population-based study from Utah showed that up to 6% of colorectal cancers may be missed on the index colonoscopy or develop in the interval between colonoscopies in usual clinical practice. Findings of proximal tumor location, increased adenoma and villous adenoma rates, a higher rate of family history of CRC, earlier stage at diagnosis, and improved survival compared with detected

tumors may reflect differences in the biology of interval vs detected cancers. Suboptimal management of precancerous lesions (such as incomplete polypectomy) likely also plays a role. Our study also identified several factors comparing patients with interval cancers with those without colorectal cancer, including older age, presence of adenoma/villous adenomas at index colonoscopy, and a family history of CRC that can be used by physicians to stratify their population at risk for an interval cancer. Our study further highlights the limitations of colonoscopy as practiced in the United States and the similarities with findings from other health systems. Additional studies are needed to determine if interval cancers are different biologically from those detected at colonoscopy or simply are overlooked or incompletely removed during the index procedure as a result of endoscopist, patient, or procedural factors. If colonoscopy is to reduce the burden of colorectal cancer to its maximum extent then further research is needed to reduce cancers missed at colonoscopy, improve polyp detection and complete removal, and identify patients at increased biologic risk for rapidly growing cancers.

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Conflicts of interest
These authors disclose the following: Randall Burt has been a consultant for Myriad Genetics, and N. Jewel Samadder has been a consultant for Cook Medical and Covidien, Inc. The remaining authors disclose no conflicts.

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