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INFLAMMATORY BOWEL DISEASE

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Forty-Year Analysis of Colonoscopic Surveillance Program for Neoplasia in Ulcerative Colitis: An Updated Overview

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OBJECTIVES: This study provides an overview of the largest and longest-running colonoscopic surveillance program for colorectal cancer (CRC) in patients with long-standing ulcerative colitis (UC).

METHODS: Data were obtained from medical records, endoscopy, and histology reports. Primary end points were defined as death, colectomy, withdrawal from surveillance, or censor date (1 January 2013).

RESULTS: A total of 1,375 UC patients were followed up for 15,234 patient-years (median, 11 years per patient). CRC was detected in 72 patients (incidence rate (IR), 4.7 per 1,000 patient-years). Time-trend analysis revealed that although there was significant decrease in incidence of colectomy performed for dysplasia (linear regression, $R=-0.43$; $P=0.007$), IR of advanced CRC and interval CRC have steadily decreased over past four decades (Pearson's correlation, -0.99; $P=0.01$ for both trends). The IR of early CRC has increased 2.5-fold in the current decade compared with past decade (χ^2, $P=0.045$); however, its 10-year survival rate was high (79.6%). The IR of dysplasia has similarly increased (χ^2, $P=0.01$), potentially attributable to the recent use of chromoendoscopy that was twice more effective at detecting dysplasia compared with white-light endoscopy (χ^2, $P<0.001$). CRCs were frequently accompanied by synchronous CRC or spatially distinct dysplasia (37.5%). Finally, the risk of CRC was not significantly different between "indefinite" or low-grade dysplasia (log-rank, $P=0.78$).

CONCLUSIONS: Colonoscopic surveillance may have a significant role in reducing the risk of advanced and interval CRC while allowing more patients to retain their colon for longer. Given the ongoing risk of early CRC, patients with any grade of dysplasia who are managed endoscopically should be monitored closely with advanced techniques.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

INTRODUCTION

It has been more than 40 years since the colonoscopic surveillance program for colorectal cancer (CRC) in patients with long-standing ulcerative colitis (UC) was introduced (1). However, many uncertainties remain in managing this potentially challenging group of patients.

First, the true magnitude of CRC risk and how this has changed over time needs to be confirmed. In our earlier study, we have showed that the incidence of CRC had significantly decreased over time between 1971 and 2000 (1), and similar trends were observed in population-based studies from Denmark (2) and Sweden (3). However, it is unclear whether this trend has continued, as many aspects of surveillance programs have changed since our last study. For example, there has been an increase in use of advanced techniques, notably chromoendoscopy (4–6), and some dysplastic lesions are now increasingly being managed endoscopically instead of by colectomy (7–10).

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Second, there are limited data on the risk of CRC occurring between scheduled surveillance procedures (or interval CRC). It is important to quantify these risks and assess how this has changed over time, as it may allow us to evaluate the efficacy of the colonoscopic surveillance program.

Third, the prevalence of multifocal lesions occurring in UC patients is poorly understood. Previous studies reported the occurrence of synchronous cancers (11,12), but little attention has been given to solitary cancers that occur with distinct foci of dysplasia elsewhere in the colon. It is essential to distinguish between unifocal and multifocal neoplasia as it may indicate etiological differences in the underlying carcinogenic process, thus requiring different management approaches.

Finally, there are limited data on the natural history and risk of progression to CRC from each grade of premalignant change, namely sporadic adenoma, indefinite for dysplasia, low-grade dysplasia (LGD) and high-grade dysplasia (HGD). This may reflect the difficulties in histological grading of dysplasia (13,14), problems in distinguishing between a sporadic adenoma or UC-associated dysplasia (15), as well as challenges in the endoscopic detection of subtle dysplastic lesions (16).

In this study, we report data from the St Mark's Hospital UC surveillance program, one of the largest and longest-running programs in the world, with the aim of answering these important questions.

METHODS

Study population

St Mark's Hospital is a tertiary referral center based in the United Kingdom, and it started colonoscopic surveillance program in 1971. Patients with endoscopic and histological evidence of UC proximal to the splenic flexure were traditionally offered annual to biannual surveillance colonoscopies from 8 to 10 years after onset of UC symptoms.

Segmental random biopsies were taken throughout the colon, with multiple targeted biopsies from any suspicious area of mucosa at each surveillance colonoscopy. In more recent years (from 2003 onwards), chromoendoscopy has been gradually implemented where pancolonic dye spray was used to highlight abnormal mucosa for targeted biopsy.

Dysplasia management protocol

In our center, the management of a neoplastic lesion is based on its location within or outside of a diseased segment. Lesions arising proximal to the maximal extent of the colitis are considered sporadic and removed endoscopically. The management of lesions arising within the diseased segment has evolved over time.

Historically, colectomy was advised when the presence of dysplasia was confirmed and reviewed independently by two experienced pathologists. However, in our current policy, resectable dysplastic lesions are removed endoscopically and biopsies are taken from its surrounding mucosa with additional segmental biopsies taken from the colon. If the lesion is resected in full without evidence of further dysplasia elsewhere, the patient is usually advised to undergo close endoscopic surveillance, although the option of surgery is discussed. However, if complete resection cannot be achieved or if multifocal dysplasia is present, patients are advised to undergo colectomy.

Historically, lesion categorization into sporadic adenoma or UC-associated dysplasia was made on the basis of the endoscopic, histological, and immunohistochemical analysis. As there is no clearcut distinction between such lesions, the UC-associated dysplasia/adenoma categorization represented in this study reflects the *clinical* consensus made at the time of diagnosis.

Study protocol

Inclusion and exclusion criteria. All patients with a histological diagnosis of UC, with macroscopic and microscopic inflammation proximal to splenic flexure, were included. Index colonoscopy was defined as the first surveillance colonoscopy performed at our institution subsequent to the patient entering the surveillance program, occurring 8 to 10 years from onset of UC symptoms.

Patients were excluded from this study if they had the disease for <8 years, except for those considered to be at significant risk of CRC who began surveillance before 8 years from disease onset (e.g., patients with concomitant primary sclerosing cholangitis). Patients were excluded if they had a diagnosis of CRC before index colonoscopy or if they were referred from other centers with a diagnosis of dysplasia.

Data collection. This study was approved by the Brent Research Ethics Committee and R&D Department at North West London Hospitals NHS Trust (reference number: 09/H0717/4). Patient data were obtained from the prospective UC surveillance database, clinical notes, endoscopy and histology reports, as well as surgical records. If a patient had died, death certificate information was reviewed. Data on the date, grade, and site of all episodes of neoplasia (sporadic adenoma, UC-associated dysplasia, or CRC) were collected. Each dysplasia was graded according to the 1983 Inflammatory Bowel Disease Dysplasia Morphology Study Group Classification of Dysplasia (17). Episodes of dysplasia occurring before 1983 had been previously reclassified according to these standardized criteria (11). All data were collected into a custom Microsoft Access 2010 database (Microsoft, Redmond, WA).

End point categorization. Primary end points: the primary study end points were the earliest occurring of the following: (i) death, (ii) colectomy, (iii) withdrawal from the surveillance program, or (iv) censor date (1 January 2013).

Secondary end point (postsurveillance follow-up): to ensure identification of all cancer cases in patients who had left the surveillance program, data were obtained from the UK National Cancer Registry. Secondary end points were as follows: (i) CRC diagnosed since leaving surveillance and (ii) no documented diagnosis of CRC since leaving surveillance.

Categorization of CRC detection modalities. Each CRC case was categorized into two groups based on how the cancer diagnosis was made, defined as follows.

1. Per-Protocol Surveillance (PPS) CRC: cancer detected in patients who had good compliance to the surveillance program, where they had a regular surveillance with recommended interval. These are subdivided into two groups.

   1. Surveillance CRC: cancer detected in a planned surveillance procedure or colectomy performed for dysplasia, in otherwise asymptomatic patients.
   2. Interval CRC: cancer detected in symptom-driven investigations or surgery before the next scheduled surveillance procedure.

2. Non-Per-Protocol Surveillance (NPPS) CRC: cancer detected at least 6 months after the date of originally planned surveillance procedures. These are subdivided into two groups.

   1. Defaulted: cancer detected in poorly compliant patients who failed to attend scheduled surveillance before cancer diagnosis.
   2. Non-defaulted: cancer detected after the patients were transferred to another hospital for their care or whose surveillance was terminated because of their age or comorbidities.

Statistical analysis. The data analysis was performed using the SPSS statistical software (version 20, IBM, Armonk, NY). All continuous variables are reported as medians with interquartile range (IQR). Study end points were examined using time-to-event analysis using Kaplan–Meier and Cox proportional hazard methods. A linear regression model was developed to determine time trends in CRC incidence. A P value of <0.05 was considered statistically significant.

RESULTS
Study population
A total of 1,375 patients met the inclusion criteria (55.3% males, $n=760/1,375$). Of these patients, 57 had the concomitant history of primary sclerosing cholangitis (4.1% of study population). The median age of UC onset was 30 years (IQR, 22–40 years). The cumulative follow-up duration from the index colonoscopy to the primary end point was 15,234 patient-years (median, 11 years per patient; IQR, 7–17 years).

A total of 8,650 colonoscopies were performed during the study period (median, 5 per patient; IQR, 3–8), of which 1,098 were chromoendoscopy. Excluding 100 patients who underwent chromoendoscopy in 2002 as a part of the research protocol conducted in our center (6), there has been a significant increase in the proportion of chromoendoscopy (i.e., number of chromoendoscopy/total number of colonoscopy) performed per year over the past 10 years (linear regression, $R=0.98$, $P<0.001$; **Figure 1**). Overall, a total of 583 patients had at least one or more chromoendoscopy performed between 2003 and 2012 (54.5% of 1,070 patients who were under surveillance between 2003 and 2012).
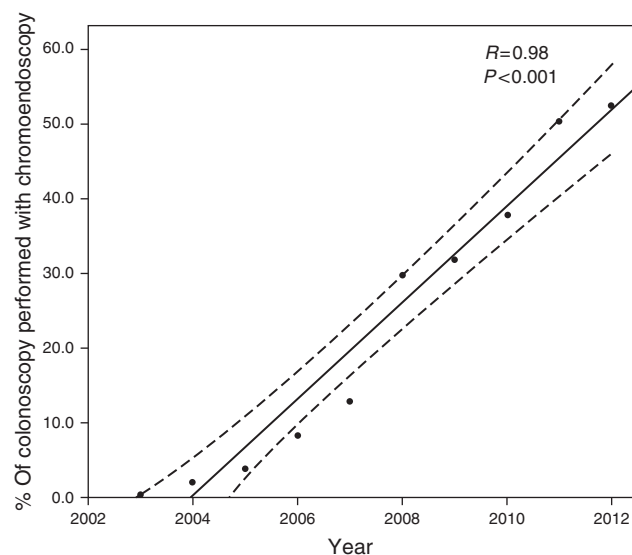

Figure 1. A linear regression plot showing the proportion of surveillance colonoscopies performed with chromoendoscopy (number of chromoendoscopy / total number of colonoscopy) from 2003 to 2012.

The mean colonoscopy interval in the first decade of surveillance (1973–1982) was 1.78 years and this remained unchanged for the second (1983–1992; 1.95 years), third (1993–2002; 1.89 years), and fourth (2003–2012; 1.77 years) decades. There were no documented perforations or deaths resulting from surveillance procedures.

Study outcome
The primary study outcome is shown in **Table 1**. As of 1 January 2013, 851 patients were undergoing active surveillance. Secondary follow-up (post-surveillance follow-up) data were obtained for 255 patients who had left the surveillance program for reasons other than colectomy or death, as shown in **Table 1**.

Colorectal cancer
Patient demographics. CRC was detected in 72 patients ($n=72/1,375$, 5.2% of study population) who were undergoing surveillance (incidence rate (IR), 4.7 per 1,000 patient-years).

Furthermore, an additional 16 patients ($n=16/1,375$, 1.2%) developed CRC in a median of 7.5 years (IQR, 5–11.3 years) after leaving surveillance (IR, 1.1 per 1,000 patient-years). Eight of these 16 patients who developed cancer after leaving the surveillance program had defaulted the recommended surveillance and were lost to follow-up until CRC diagnosis was made elsewhere. Another eight patients were transferred to another hospital, thereby terminating their surveillance at our institution.

Of the 88 patients who were diagnosed with CRC, 54 were male ($n=54/88$, 61.4%). The median duration of UC at the time of CRC diagnosis was 23.5 years (IQR, 16–30 years; **Figure 2a**). The median age at the time of CRC diagnosis was 55.5 years (IQR 44–63 years; **Figure 2b**).

Table 1. Primary end point categorization

Primary study outcome for 1,375 patients	Numbers (% of study population)
Patients on surveillance as of 1 January 2013 (n=851)	
No dysplasia	764 (55.6)
Dysplasia	87 (6.3)
• Indefinite dysplasia	11
• LGD	68
• HGD	7
CRC, awaiting surgery	1
Patients not on surveillance as of 1 January 2013 (n=524)	
Surgery	218 (15.9)
• For CRC: 22 had CRC in specimen	24
• For dysplasia: 31 had CRC in specimen	87
• For symptoms: 11 had CRC in specimen	103
Surgery elsewhere following CRC during surveillance	4
Died while under surveillance	51 (3.7)
• CRC without colectomy	3
• Unrelated	48
Other reason for leaving surveillance	255 (18.5)
• Age/comorbidities/defaulted/patient choice	150
• Transfer of care to another hospital	95
• Noncolorectal malignancy	10

CRC, colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Within surveillance, the cumulative incidence of CRC was 0.1% in the first decade since the UC symptom onset (**Figure 2a**), followed by 2.9%, 6.7%, and 10.0% by second, third, and fourth decade, respectively. After the first decade of the disease, there was no significant change in hazard rate of CRC with further increase in disease duration (χ^2; P=0.67), and remained relatively constant at ~0.37% per year.

Mode of CRC presentation and interval cancer. The mode of CRC detection is shown in **Table 2**. Cancer was detected in scheduled surveillance procedures in 48 asymptomatic patients (i.e., surveillance CRC; IR, 3.2 per 1,000 patient-years) or between surveillance interval in 15 patients (i.e., interval CRC; IR, 1.0 per 1,000 patient-years).

The proportion of Dukes' C or disseminated cancer was significantly lower in the surveillance-detected group (n=11/45, 24.4%) compared with interval CRC group (n=11/14, 78.6%; χ^2, P<0.001) or CRCs detected in patients who defaulted surveillance before the cancer diagnosis (n=7/13, 53.8%; P=0.04).

The proportion of Dukes' C or disseminated cancer was lower in the PPS group compared with the NPPS group, but this was not statistically significant (n=22/59, 37.3% vs. n=9/18, 50.0%; χ^2, P=0.34).

Change in CRC incidence over time. Linear regression showed a decreasing but nonsignificant change in the overall annual IR of CRC during the four decades of the surveillance program (R=−0.24; P=0.13). Similarly, there was no significant change in the incidence of the proximal (R=−0.25; P=0.11) or distal (R=0.03; P=0.83) cancer.

As the study performed in our center a decade ago showed a significant reduction in incidence of CRC over time (1), we performed an additional analysis to compare the per-decade CRC IR over the past 40 years—i.e., first (1973–1982; 790 patient-years), second (1983–1992; 2,251 patient-years), third (1993–2002; 4,602 patient-years) and fourth (2003–2012; 7,591 patient-years) decades. This revealed that although the overall CRC IR had decreased over the first three decades, there was a nonsignificant increase in CRC IR in the fourth decade (4.9 per 1,000 patient-years) compared with the third decade (3.7 per 1,000 patient-years; χ^2, P=0.30; **Figure 3a**).

The IR of Dukes' A or B had also decreased over the first three decades. However, this was followed by a significant increase in the fourth decade (3.2 per 1,000 patient-years) compared with the third decade (1.3 per 1,000 patient-years; χ^2, P=0.045). Contrastingly, the IR of Dukes' C or disseminated cancer had steadily decreased over the past four decades (Pearson's correlation, −0.99; P=0.01; **Figure 3b**).

There was a non-significant increase in the IR of Dukes' A or B in patients whose CRC was detected during surveillance colonoscopy or at the time of colectomy performed for dysplasia in the fourth decade compared with the third decade (3.0 vs. 1.3 per 1,000 patient-years; P=0.06). Contrastingly, the IR of Dukes' C or disseminated disease for this group of patients remained similar (1.1 vs. 1.1 per 1,000 patient-years; P=1.0).

The IR of interval cancer per decade had reduced significantly over the past four decades, from 2.5 per 1,000 patient years in the first decade to 0.4 per 1,000 patient-years in the fourth decade (**Figure 4a**; Pearson's correlation, −0.99; P=0.007). In the past three decades, at least one in three PPS cancers was interval cancer: 33.3% (n=2/6; 1973–1982), 50.0% (n=4/8; 1983–1992), and 37.5% (n=6/16; 1993–2002). However, this was reduced to 9.1% in the current decade (n=3/33; 2003–2012; Fisher's exact test between the past three decades vs. current decade, P=0.007; **Figure 4b**).

The IR of UC-associated dysplasia was significantly increased in the fourth decade compared with the third decade (17.7 vs. 11.7 per 1,000 patient-years; χ^2, P=0.01). The largest change was observed in IR of LGD (11.3 vs. 6.3 per 1,000 patient-years; χ^2, P=0.006) with smaller non-significant increase in IR of HGD (3.4 vs. 3.0 per 1,000 patient-years; P=0.72) and indefinite for dysplasia (2.9 vs. 2.4 per 1,000 patient-years; P=0.60). The IR of sporadic adenoma was similar between the two decades (5.3 vs. 6.9 per 1,000 patient-years; χ^2, P=0.24).

Tumor locations and multifocality. In relation to the splenic flexure, 41 CRCs were distal (n=41/72, 56.9% of all cancers excluding those detected in postsurveillance period) and 26 (n=26/72, 36.1%) were proximal. In three cases (n=3/72, 4.2%), synchronous tumors were found located in both segments. The primary site was not known for two patients (n=2/72, 2.8%) with disseminated disease. Colectomy specimens were available for analysis in 64 cases. Of these, 24 (n=24/64, 37.5%) revealed either multi-
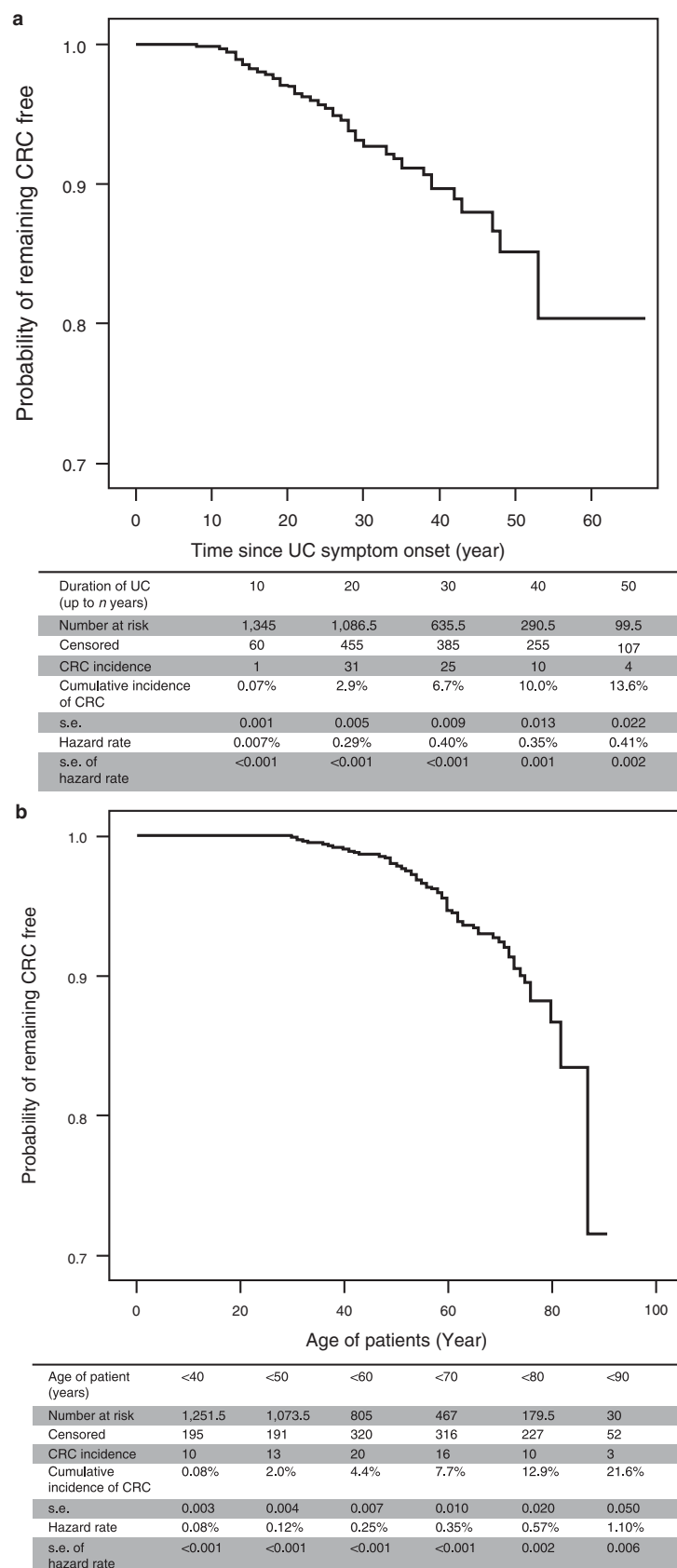
a

Duration of UC (up to *n* years)	10	20	30	40	50
Number at risk	1,345	1,086.5	635.5	290.5	99.5
Censored	60	455	385	255	107
CRC incidence	1	31	25	10	4
Cumulative incidence of CRC	0.07%	2.9%	6.7%	10.0%	13.6%
s.e.	0.001	0.005	0.009	0.013	0.022
Hazard rate	0.007%	0.29%	0.40%	0.35%	0.41%
s.e. of hazard rate	<0.001	<0.001	<0.001	0.001	0.002

b

Age of patient (years)	<40	<50	<60	<70	<80	<90
Number at risk	1,251.5	1,073.5	805	467	179.5	30
Censored	195	191	320	316	227	52
CRC incidence	10	13	20	16	10	3
Cumulative incidence of CRC	0.08%	2.0%	4.4%	7.7%	12.9%	21.6%
s.e.	0.003	0.004	0.007	0.010	0.020	0.050
Hazard rate	0.08%	0.12%	0.25%	0.35%	0.57%	1.10%
s.e. of hazard rate	<0.001	<0.001	<0.001	<0.001	0.002	0.006

Figure 2. Kaplan Meier plots and life tables showing cumulative risk of colorectal cancer (CRC) development. (**a**) Cumulative risk of CRC by duration of ulcerative colitis (UC). (**b**) Cumulative risk of CRC by age of patients.

Table 2. Mode of colorectal cancer (CRC) detection and Dukes' staging

Dukes' stage	Surveillance detected (per-protocol surveillance)	Interval (per-protocol surveillance)	Defaulted (non-per-protocol surveillance)	Nondefaulted (non-per-protocol surveillance)	Total (%)
A	24	1	3	0	28 (31.8)
B	10	2	3	3	18 (20.4)
C	11	7	5	1	24 (27.2)
D	—	4	2	1	7 (8.1)
Unknown	3	1	4	3	11 (12.5)
Total (%)	48 (54.5)	15 (17.1)	17 (19.3)	8 (9.1)	88 (100)
Incidence rate (per 1,000 patient-years)	3.2	1.0	1.1	0.5	5.8
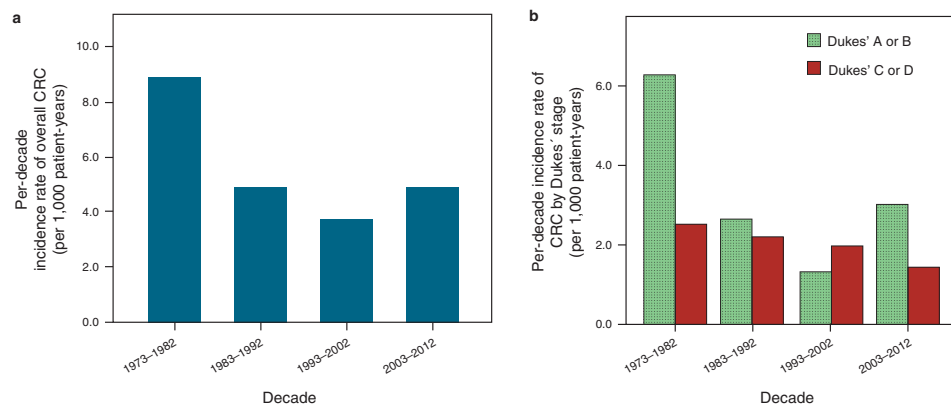
Figure 3. Histograms showing per-decade incidence rate of colorectal cancer (CRC) over past 40 years. (**a**) Incidence rate of all CRC combined. (**b**) Incidence rate of CRC by tumor stage: Early (Dukes' A or B; denoted in dotted green bars) and advanced CRC (Dukes' C or D; denoted in red plain bars).
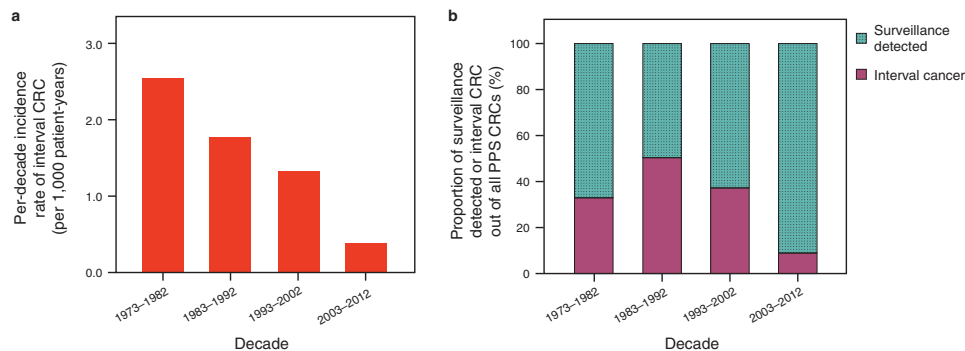
Figure 4. Histograms showing declining risk of interval colorectal cancer (CRC) over last 40 years. (**a**) Per-decade incidence rate of interval CRC. (**b**) Proportion of surveillance detected CRC (denoted by dotted green bars) or interval CRC (denoted by plain red bars) out of all per-protocol surveillance (PPS) CRCs.

synchronous CRC or solitary CRC with spatially distinct dysplastic lesion(s) elsewhere in the colon (**Table 3**).

Preceding dysplasia. In all, 44 patients (*n*=44/72, 61.1% of all cancers excluding those detected in post-surveillance) previously had neoplasia, of which 41 were UC-associated dysplasia and 3 were sporadic adenoma. The remaining 28 patients (*n*=28/72, 38.9%) had neither sporadic adenoma nor UC-associated dysplasia detected during surveillance.

Survival following CRC diagnosis. Ultimately, 37.5% of patients died from CRC (100% with disseminated disease, 47.8% with

Table 3. Dukes' staging and multifocality of colorectal cancer (CRC) cases (excluding CRC cases detected in postsurveillance period)

Dukes' stage	Solitary CRC	Solitary CRC with spatially distinct dysplasia(s)	Synchronous CRC	Unknown	Total (%)
A	16	7	4	—	27 (37.5)
B	7	5	1	—	13 (18.1)
C	16	2	4	—	22 (30.5)
D	—	—	—	4[a]	4 (5.6)
Unclassifiable	1[b]	—	—	1[c]	2 (2.8)
Operation elsewhere	—	—	1[d]	3	4 (5.6)
Total (%)	40 (55.6)	14 (19.4)	10 (13.9)	8 (11.1)	72 (100)

[a]Two patients did not have surgery and hence tumor locations were unknown. Full details on neoplasia locations were not available for the other two patients who had emergency operation elsewhere.
[b]Staging was not possible because of preoperative radiotherapy.
[c]Patient currently waiting for colectomy.
[d]Patient had multisynchronous CRCs in rectum, transverse colon, and hepatic flexure with widespread dysplasias detected during surveillance colonoscopy, and then had operation elsewhere.
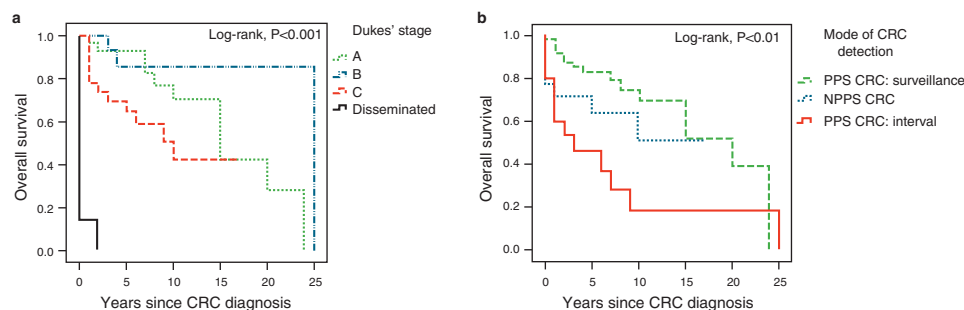
Figure 5. Kaplan-Meier plots showing overall survival rates following colorectal cancer (CRC) diagnosis. (**a**) Overall survival rates by Dukes' stage of tumor. (**b**) Overall survival rates by mode of CRC detection. PPS CRC: surveillance = cancers detected in scheduled surveillance procedure or colectomy performed for dysplasia, PPS CRC: interval = cancers detected in between scheduled surveillance procedures, NPPS CRC = cancers detected at least 6 months after the date of originally planned surveillance procedures.
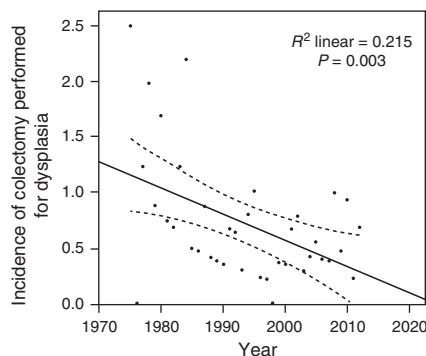

Figure 6. Linear regression plot showing a decrease in annual incidence of colectomy performed for dysplasia over past 40 years.

Dukes' C, 23.5% of Dukes' B, and 17.2% of Dukes' A cancer). The overall survival rate was significantly different depending on the Dukes' stage of the cancer (log-rank test, $P<0.001$). The 5-year survival rate was 92.3% for Dukes' A, 86.2% for Dukes' B, 68.9% for Dukes' C, and 100% for disseminated cancer (**Figure 5a**). The 10-year survival rate was 77.0% for Dukes' A, 86.2% for Dukes' B, and 51.7% for Dukes' C. The overall survival rate was 72.0% and 60.6% at 5 and 10 years, respectively.

The overall survival rate was significantly different depending on the mode of CRC detection (log-rank test, $P=0.01$; **Figure 5b**). The 5- and 10-year survival rate was 81.8% and 75.1% for PPS-Surveillance detected CRC, 68.8% and 59.6% for NPPS CRC, and 46.7% and 23.3% for PPS-Interval CRC, respectively.

Surgery

During their surveillance, 214 patients ($n=214/1,375$, 15.6% of the study population) underwent colonic surgery. The combined cumulative incidence of colonic surgery or cancer diagnosis by UC disease duration was 1.9% at 10 years, 10.8% at 20 years, 17.4% at 30 years, and 24.3% at 40 years. The combined cumulative incidence of colonic surgery or cancer diagnosis by patient age was 1.4% at 30 years, 4.2% at 40 years, 7.5% at 50 years, and 13.9% at 60 years.

Table 4. Indication for surgery and maximal neoplasia found in surgical specimen

Indication for surgery (no. of patients)	Findings in surgical specimen					
	No dysplasia	Adenoma only	Indefinite for dysplasia	LGD	HGD	CRC (%)
Symptoms (103)	81	4	0	6	1	11 (10.7)
Adenoma (1)	0	1	0	0	0	0 (0)
Indefinite for dysplasia (2)	1	0	0	0	0	1 (50.0)
LGD (47)	12	0	1	16	6	12 (25.5)
HGD (37)	0	0	2	5	12	18 (48.6)
CRC (24)	1	0	0	1	0	22 (91.7)
Total (214)	94	5	3	30	18	64 (100)

CRC, colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Linear regression revealed a significant decrease in the incidence of colectomy for any indication ($R=-0.37$; $P=0.02$). Particularly, the incidence of colectomy performed for dysplasia showed steeper decrease ($R^2=-0.22$; $P=0.003$) over time (**Figure 6**). Overall, when an indication for surgery was HGD, 48.6% ($n=18/37$) of the patients had CRC in surgical specimen (**Table 4**). For those who had colectomy for LGD, CRC was found in 25.5% ($n=12/47$) of cases. There was no time trend in proportion of CRC detected in colectomy specimen on performing colectomy for LGD (Pearson's correlation, -0.68; $P=0.32$) or HGD (Pearson's correlation, 0.42; $P=0.59$).

Neoplasia (sporadic adenoma, UC-associated dysplasia, or cancer)

Overall, 325 patients ($n=325/1,375$, 23.6% of study population) had a total of 635 episodes of neoplasia during the study period (IR, 41.7 per 1,000 patient-years). The median age of neoplasia diagnosis between 1993 and 2012 was 60 years (IQR, 49–68 years), and this was significantly older than in the previous two decades (1973–1992; 49 years; IQR, 38–57 years; Mann–Whitney U, $P<0.001$). There was no significant change in the median age of diagnosis between the recent two decades (i.e., 2003–2012 vs. 1993–2002; $P=0.7$).

The cumulative incidence of neoplasia by UC duration was 4.1% at 10 years, 14.1% at 20 years, 28% at 30 years, and 38.9% at 40 years (**Figure 7a**). The average hazard rate of developing neoplasia per year in the first 40 years of the UC was 1.0% (s.e., 0.056%).

Chromoendoscopy. We compared the lesion detection rate (defined as number of procedures in which one or more neoplasia was detected divided by total number of procedures) between the standard white-light colonoscopy and chromoendoscopy performed from 2002 to 2012 (**Table 5**). Overall, the neoplasia detection rate was twofold higher in the chromoendoscopy group ($n=92/1,098$, 8.4%) compared with the white-light colonoscopy group ($n=175/4,373$, 4.0%; χ^2, $P<0.001$).

Among the patients who were on surveillance between 2002 and 2012, the IR of CRC in patients who had at least one or more chromoendoscopies performed (median, 1 per patient; IQR, 1–2) was significantly lower (2.2 per 1,000 patient-years) than in those who had never had chromoendoscopy (4.6 per 1,000 patient-years; χ^2, $P=0.02$).
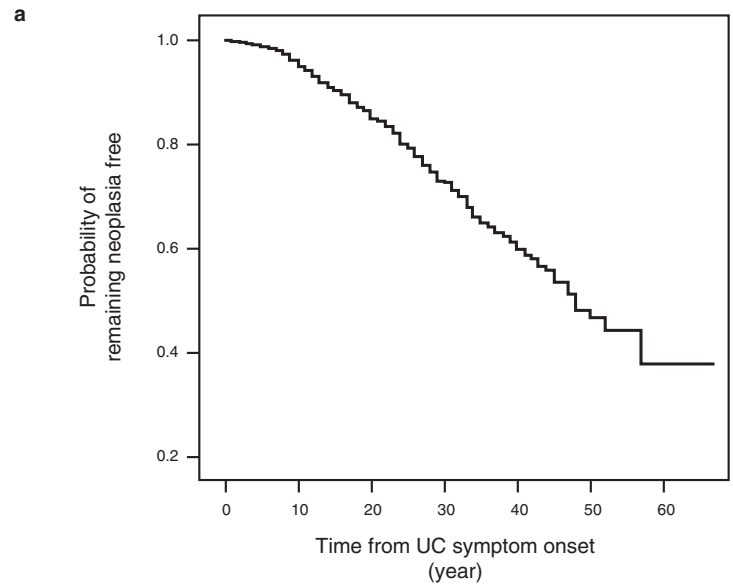
Since 2003, 13 cases of CRC were detected at colonoscopy following a "negative for dysplasia" colonoscopy performed a median of 23 months (IQR, 13–25 months) previously. Assuming that CRC was missed at the previous procedure, the postcolonoscopy colorectal cancer rate (i.e., PCCRC or miss rate) was 1.2 per 1,000 patient-years (2/1,726 patient-years) for chromoendoscopy and 1.8 per 1,000 patient-years (11/6,176 patient-years) for white-light endoscopy, although the difference was not statistically significant ($P=0.6$).

Sporadic adenoma. A total of 85 patients ($n=85/1,375$, 6.2% of the study population) had a total of 143 episodes of sporadic adenoma (IR, 9.4 per 1,000 patient-years). Neoplastic progression was studied in 76 patients excluding patients who have not had a follow-up colonoscopy ($n=9$).
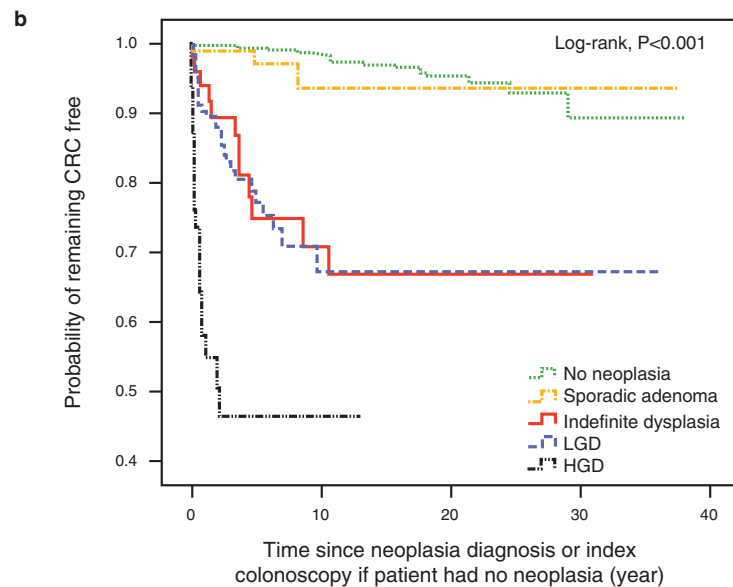
Thirty-seven patients ($n=37/76$, 48.7%) had adenoma detected outside the diseased segments. During 293 patient-years of follow-up (median, 7.5 years per patient; IQR, 4–11 years), 4 patients ($n=4/37$, 10.8%; IR, 13.7 per 1,000 patient-years) developed LGD and additional 2 patients had developed Dukes' A CRC ($n=2/37$, 5.4%; incidence rate, 6.8 per 1,000 patient-years): one within a severely dysplastic tubulovillous adenoma that was not endoscopically resectable, and the other at 2.5 years after having an adenoma resected from a different colonic segment.

The remaining 39 patients ($n=39/76$, 51.3%) had their adenoma detected within the diseased segment. During 369 patient-years of follow-up (median, 7 years per patient; IQR, 4–11 years), 5 had developed LGD ($n=5/39$, 12.8%; IR 13.6 per 1,000 patient-years) and 1 had progressed to Dukes' A CRC ($n=1/39$, 2.6%; IR, 2.7 per 1,000 patient-years) within an adenoma 5 years after having an adenoma resected from the same colonic segment.

There was no difference in CRC risk between adenoma detected within or outside the diseased segment of colon (χ^2, $P=0.44$).

Figure 7. Risk of developing neoplasia over time. (**a**) Kaplan–Meier plot and a life table showing the risk of developing any neoplasia (i.e. adenoma, dysplasia, or colorectal cancer (CRC)) by duration of UC. (**b**) Kaplan–Meier plot and a life table showing cumulative incidence of CRC for each type of neoplasia grade. HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Table 5. Comparison of the lesion detection rate between white-light endoscopy (WLE) and chromoendoscopy (CE) from 2002 to 2012

Type	Number detected in WLE: n=4,373 (detection rate %)	Number detected in CE: n=1,098 (detection rate %)	Superior technique	*P* value
Adenoma	28 (0.6)	16 (1.5)	CE	0.007
Indefinite for dysplasia	24 (0.6)	16 (1.5)	CE	0.002
LGD	99 (2.3)	48 (4.4)	CE	<0.001
HGD	24 (0.6)	12 (1.1)	CE	0.05
All neoplasias (excl. CRC)	175 (4.0)	92 (8.4)	CE	<0.001

CRC, colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Indefinite for dysplasia. Fifty-one patients (n=51/1,375, 3.7% of study population) had 64 episodes of indefinite for dysplasia (IR, 4.2 per 1,000 patient-years). Neoplastic progression was studied in 49 patients over 411 patient-years of follow-up (median, 4.6 years per patient; IQR, 2.7–13.1 years), excluding 2 patients who had no follow-up colonoscopy. Overall, 25 patients (n=25/49, 51.0%; IR, 60.8 per 1,000 patient-years) progressed to LGD, HGD, or CRC during the study period (**Supplementary Figure S1A** online). Furthermore, 12 of these patients (n=12/49, 24.5) had eventually progressed to CRC (IR, 29.2 per 1,000 patient-years). Six patients (n=6/49, 12%; IR, 14.6 per 1,000 patient-years) progressed to HGD (3 patients) or CRC (3 patients) without an episode of LGD in between.

Low-grade dysplasia. A total of 156 patients (n=156/1,375, 11.3% of study population) developed 280 episodes of LGD (IR of 18.4 per 1,000 patient-years). All patients were subsequently followed for 658 patient-years (**Supplementary Figure S1B**), except for 11 patients who did not have a follow-up colonoscopy (n=7) or their LGD was incidentally found in the surgical specimen after they had undergone colectomy for UC symptoms (n=4).

Thirty-two patients (n=32/145, 22.1%) with LGD underwent immediate colectomy, 9 of whom had CRC in the surgical specimen (n=9/32, 28.1% of those who underwent immediate colectomy). In 6 of these patients, cancer was found in the region where LGD was previously detected (n=6/9, 66.7%).

A total of 113 patients (n=113/145, 77.9% of patients with LGD) initially remained in the surveillance program. During the median follow-up of 4.2 years (IQR, 2.4–7.2 years), 18 developed CRC (n=18/113, 15.9% of LGD population who initially remained in surveillance). Overall, 47 out of 145 patients with LGD (32.4%) had progressed to more advanced neoplasia (IR, 71.4 per 1,000 patient-years); i.e., HGD (n=20/145, 13.8%; IR, 30.4 per 1,000 patient-years) or CRC (n=27/145, 18.6%; IR, 41.0 per 1,000 patient-years).

High-grade dysplasia. Forty-eight patients developed a total of 76 episodes of HGD (n=48/1,375, 3.5%; IR, 5.0 per 1,000 patient-years) and were subsequently followed for a cumulative total of 86.8 patient-years (**Supplementary Figure S1C**). Twenty-four patients with HGD (n=24/48, 50.0%) had previously had a diagnosis of LGD.

Twenty-nine patients with HGD underwent immediate colectomy, 16 of whom had CRC in surgical specimen (n=16/29, 55.2%). In nine of these patients, CRC was found in the region where HGD was previously detected (n=9/16, 56.3%).

Nineteen patients initially remained in the surveillance program. Over a median follow-up duration of 2.8 years (IQR, 1.6–6.0 years), recurrent dysplasia was detected in 16 patients, and 4 of these patients (n=4/19, 21.1% of those who initially remained in surveillance) had eventually progressed to CRC. Overall, 20 out of 48 HGD patients (41.7%) had progressed to CRC (IR, 230.4 per 1,000 patient-years).

Rate of progression to CRC by neoplastic grade (sporadic adenoma, indefinite for dysplasia, LGD, and HGD). The Kaplan–Meier plot and a table showing cumulative incidence of CRC for each type of neoplasia grade is shown in **Figure 5b**. There was no significant difference in the risk of CRC between indefinite and LGD group (log-rank test, *P*=0.79) or between sporadic adenoma and no dysplasia group (*P*=0.14).

The hazard ratio of developing CRC for each type of neoplasia compared with patients with no dysplasia was: sporadic adenoma, 0.50 (95% confidence interval, 0.2–1.6; *P*=0.3), indefinite for dysplasia, 6.1 (95% confidence interval, 1.7–21.5; *P*=0.005), LGD, 7.8 (95% confidence interval, 2.4–25.7; *P*<0.001), and HGD, 33.1 (95% confidence interval, 9.7–112.9; *P*<0.001).

The annual hazard rate for developing CRC in the first 5 years from the time of initial neoplasia diagnosis was as follows: sporadic adenoma (0.64%; s.e., 0.005), indefinite for dysplasia (5.5%; s.e., 0.017), LGD (4.8%; s.e., 0.010), and HGD (14.8%; s.e., 0.031).

DISCUSSION

This study provides an overview of the largest and longest-running UC surveillance program in the world over its 42-year history, revealing an important recent trend in CRC risk, tumor characteristics, and progression of dysplasia.

Reduction in risks of advanced cancer and interval cancer

Our data show that the advanced cancer IR has decreased consistently over the past four decades, potentially indicating that the efficacy of colonoscopic surveillance in early detection of CRC

may have improved over time. A reasonably good prognosis of early CRC compared with the advanced CRC shown in our study highlights the importance of early detection of CRC in reducing the cancer mortality.

The risk of interval cancer, although once common, is rapidly decreasing. This is a particularly reassuring finding as interval cancers tended to be advanced and hence associated with poor prognosis (78.6% of interval cancers were Dukes' C or disseminated disease), and consequently the reduction in advanced cancer risk is likely to have resulted from the decreasing IR of interval cancers. The steepest decrease in its risk was seen in the current decade, suggesting that the use of chromoendoscopy, which was more effective in lesion detection, may have been a significant contributory factor in minimizing the risk of missing prior dysplastic lesions at colonoscopy. Indeed, the IR of HGD or CRC detected in patients with no previous indefinite for dysplasia or LGD was significantly reduced in the current decade (2.1 per 1,000 patient-years) compared with the past decade (4.6 per 1,000 patient-years; χ^2, *P*=0.02), indicating that the negative predictive value of the surveillance colonoscopy may have improved significantly.

Interestingly, patients who had chromoendoscopy had a lower risk of developing CRC compared with those who never had the procedure. Moreover, the postcolonoscopy colorectal cancer rate was lower following chromoendoscopy compared with white-light endoscopy, although this was not statistically significant. Although these initial data support the use of chromoendoscopy, it should be emphasized that the prospective multicenter trials over long period of follow-up is required to accurately assess the efficacy of chromoendoscopy as it is equally possible that other external factors, such as better medical treatments, may have also had a significant role in reduction of these risks.

Decreasing colectomy for dysplasia and increase in early cancer incidence

Despite falling IR of advanced cancer, an increase in the IR of early cancers (Dukes' A and B) meant that there was no significant difference in the *overall* IR CRC in the current decade compared with the past decade. Furthermore, there was no significant change in the proportion of CRCs detected at colectomy for dysplasia over time.

A likely explanation for this trend is the recent significant tendency to manage dysplasia endoscopically instead of by colectomy: indeed, the colectomy rate has fallen despite a rise in the incidence of dysplasia. Thus, it is possible that some of these patients who were managed endoscopically have subsequently progressed to CRC. As increasing number of patients are retaining their colon for longer, one can argue that this may be an acceptable outcome as it may indicate that patients are being offered delayed but timely colectomy (e.g., before progressing to advanced CRC). Furthermore, we observed an increase in patient age at dysplasia diagnosis that is perhaps the result of reduction in the risk of competing interests in recent years (such as heart disease), and coupled with the relatively good prognosis associated with early CRC, these data suggest that prophylactic colectomy is a less favored and acceptable option for dysplasia management.

Increasing IR of dysplasia: overdiagnosis?

The fact that no reduction in CRC risk was seen despite the introduction of advanced endoscopy and the concomitant increase in the neoplasia detection rate in recent years raises the possibility of *overdiagnosis*: that advanced endoscopy leads to the detection of proportionally more indolent lesions. If this were true, one would expect that the rate of progression from dysplasia to CRC would be lower in the chromoendoscopy era as many of the "extra" lesions detected will not progress to CRC.

We tested for this possibility using the cohort of patients who were diagnosed with LGD in the current decade (90 patients followed up for 264 patient-years) and the past decade (29 patients followed up for 153 patient-years), as the increase in IR of UC-associated dysplasia had mainly resulted from the LGD group. This revealed that the rate of progression from LGD to CRC was in fact similar (45.5 vs. 52.3 per 1,000 patient-years in the current and past decades; *P*=0.96), making overdiagnosis an unlikely possibility. In other words, these "extra" dysplastic lesions that are detected in the current decade are likely to have equivalent risk of progression of CRC compared with those detected in the previous decade.

Overall cancer risk by disease duration remains low

Consistent with our previous study (1), the overall risk of CRC by disease duration remained low (only 10.0% of patients developed cancer at 40 years of disease duration). The CRC risk also remained relatively constant after 10 years of the disease, and this is in agreement with the recent Danish nationwide cohort study (2), suggesting that intensifying the surveillance interval with increasing duration of the UC is not necessary.

Frequent synchronous lesions

The frequency of synchronous CRC was high (15.6%), comparable to previous reports (18,19). However, none of these studies reported multifocal dysplasia occurring with unifocal cancers: our data indicate that a significant proportion of patients with CRC also have synchronous dysplasia elsewhere in the colon (37.5%). Evidence suggests that inflammatory bowel disease-associated cancers arise from a larger field of colorectal mucosa that is "preconditioned" with a mutational burden that confers an increased propensity for further neoplastic progression, a phenomenon known as "field cancerization" (20–22). The high frequency of multifocal cancer/dysplasia reported in our cohort likely reflects that field cancerization is a common phenomenon in patients with UC.

Neoplastic progression of sporadic adenoma and dysplasia

In accordance with other previous studies (23,24), the rate of CRC in patients undergoing immediate colectomy for HGD was high (50%). Furthermore, 84% of those who remained in surveillance had a recurrence of HGD or progression to CRC after a median of 1.13 years (IQR, 1–1.5 years). In this context, given the high risk of recurrence of HGD and progression to cancer, patients with HGD would likely benefit from an early colectomy.

Both indefinite for dysplasia and LGD had a moderate risk of progression to CRC and the risks were similar to each other. It

is well documented that grading of dysplasia is difficult, and the inter-observer agreement in grading dysplasia among pathologists is poor, particularly for the indefinite and LGD categories (13,14). Our data demonstrate that a diagnosis of LGD vs. indefinite for dysplasia does not predict etiological differences in disease progression as suggested by other studies (25–27). These findings suggest that differential patient management decisions should not be made solely on the basis of an indefinite for dysplasia vs. LGD diagnosis. Sporadic adenomas did not confer an additional CRC risk, and their risk was no different to those without any neoplasia. This indicates that these lesions can be appropriately managed endoscopically without colectomy.

Study limitations

Our study has several limitations. First, this study was conducted on a population at the tertiary referral center with higher proportion of patients with more severe or complex disease. This has a potential impact on generalizability of our results. For example, although our findings reflect CRC risk in extensive UC patients, a significant proportion of patients will have left-sided disease or proctitis only in general populations that may decrease the estimate of overall CRC risk. Second, the number of CRC cases was relatively small in our study, particularly for the time-trend analysis. Hence, it is possible that some observations were over- or underinterpreted because of relatively small number of cancer cases. Our findings thus should be confirmed in a population-based study before further conclusion can be made.

Conclusions

In conclusion, our data provide an overview of dysplasia/CRC surveillance in UC over its 40-year history. The advent of chromoendoscopy in recent years has increased the rate of dysplasia detection. This has not led to the reduction in overall CRC risk, but has allowed the early identification of high-risk patients and played an important role in reducing the risk of advanced and interval cancer. The colectomy rate for dysplasia has significantly reduced over the past four decades with continued reduction in advanced cancer risk, but perhaps at the cost of a rise in early cancer incidence. However, given the good postsurgical outcome of early cancers, patients may be able to retain their colon despite a dysplasia diagnosis, although they should be fully informed of the risks and benefits associated with undergoing endoscopic or surgical management of dysplasia. Finally, patients with *any* grade of dysplasia should be regarded as a significant risk, and given the frequency of multifocal neoplasia, these patients require careful inspection of the entire colon with advanced techniques to ensure lesions are not missed.

CONFLICT OF INTEREST

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✔ Patients with long-standing ulcerative colitis (UC) have an increased risk of developing colorectal cancer (CRC), although the recent literature suggests that this risk might be decreasing.

✔ However, it is unknown how emergence of new endoscopic techniques such as chromoendoscopy in recent years may have affected the incidence rates of CRC and dysplasia.

✔ Furthermore, the risk of interval cancer and prevalence of multifocal neoplasia occurring in these patients are unknown.

✔ The risk of CRC associated with each grade of dysplasia, especially "indefinite for dysplasia" remains unclear.

WHAT IS NEW HERE

✔ The incidence rate of UC-associated dysplasia has increased by 1.5-fold in the current decade (2003–2012) compared with the past decade (1993–2002), attributable to increased use of chromoendoscopy that was twofold more effective in detecting adenoma or dysplasia compared with white-light endoscopy.

✔ Despite a significant decrease in incidence of colectomy performed for dysplasia over time, the incidence rate of Dukes' C or disseminated cancer and interval cancer has decreased. However, there was a 2.5-fold increase in the incidence rate of Dukes' A or B cancer in the recent decade compared with the past decade. Reassuringly, the 10-year postsurgical survival rate was high for Dukes' A or B cancers (79.6%).

✔ Multifocal neoplasia is a common phenomenon, with approximately one in three CRCs (37.5%) having either a spatially distinct cancer or dysplasia in the colectomy specimen.

✔ The risk of CRC associated with "indefinite for dysplasia" or low-grade dysplasia was similar, with the cumulative incidence of CRC exceeding 20% within 5 years since the initial dysplasia diagnosis.

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