EPIDEMIOLOGY, CHARACTERISTICS AND SURVIVAL OF POST-COLONOSCOPY COLORECTAL CANCER IN ASIA: A POPULATION-BASED STUDY

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Abbreviations

aOR	Adjusted odds ratio
aHR	Adjusted hazard raito
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
CDARS	Clinical Data Analysis and Reporting System
ICD-9	International Classification of Diseases, Ninth Revision
IQR	Interquartile range
PCCRC	Post-colonoscopy colorectal cancer

ABSTRACT

Background and Aims: Population-based studies on post-colonoscopy colorectal cancer (CRC) from Asia are sparse. We aimed to determine the characteristics and predictive factors and survival of post-colonoscopy CRC in Hong Kong.

Methods: This is a territory-wide retrospective cohort study. Patients aged ≥40 years with colonoscopies performed between 2005 and 2013 without history of CRCs, inflammatory bowel disease and prior colectomy were included. Post-colonoscopy colorectal cancer for an interval of 3 years (PCCRC-3y) was defined as CRC diagnosed between 6 and 36 months after index colonoscopy, whereas CRC diagnosed within 6 months of index colonoscopy was regarded as "detected CRC". We used multivariable logistic regression to derive adjusted odds ratio (aOR) of PCCRC-3y, and Cox model for adjusted hazard ratio (aHR) of cancer-specific mortality after CRC diagnosis.

Results: Of the 197,902 eligible patients, 10,005 (92.1%) were detected CRC and 854 (7.9%) PCCRC-3y. The median age at PCCRC-3y diagnosis was 75.9 years (IQR: 65.5-83.8) – a delay of 1.2 years (IQR:0.8-1.9) from index colonoscopy, and 60.1% were male. Predictive factors for PCCRC-3y included older age (aOR:1.07), male sex (aOR:1.45), history of colonic polyps (aOR:1.31), polypectomy/biopsy at index colonoscopy (aOR:3.97), surgical endoscopists (aOR:1.53) and a higher center annual endoscopy volume. Independent predictive factors for cancer-specific mortality after CRC diagnosis included PCCRC-3y (aHR:1.32), proximal cancer location (aHR:1.80) and certain patient factors.

Conclusion: The PCCRC-3y rate was 7.9% in Hong Kong, with a high proportion (>80%) of distal cancers and a higher cancer-specific mortality compared to detected CRC.

INTRODUCTION

Colorectal cancer (CRC) is the third commonest cancer in males and the second commonest in females worldwide, accounting for 1.65 million new cases and 835,000 deaths in 2015.[1] Overwhelming evidences have shown that screening colonoscopy is effective in reducing both the incidence[2-4] and mortality of CRC.[4-6] However, it is increasingly recognized that CRCs can still occur before the expected surveillance interval after colonoscopy, known as post-colonoscopy CRC (PCCRC), which could account for up to 9% of all CRCs.[7] A meta-analysis showed that 1 in 27 CRCs were PCCRC and were 2.4 times more likely to arise in the proximal colon (1 in 15 in the proximal and 1 in 34 in the distal colon).[8] Missed lesions due to suboptimal quality of the index colonoscopy may account for 50% of PCCRC.[7] Other contributing factors to the development of PCCRC may include residual lesions after polypectomy, sessile serrated polyps which are more likely to evade detection by colonoscopy, and rapidly progressive cancer arising from alternative carcinogenesis pathway.[9-11]

Recently, the PCCRC rate has been proposed to be the principal performance measure to monitor quality of a colonoscopy service to detect and prevent CRC.[12] However, population-based studies from Asia are sparse. In Hong Kong, the overall incident CRC cases were 4,605 per year between 2007 and 2016, corresponding to a crude incidence rate of 64.7 cases per 100,000 person-years. In the recently launched pilot CRC screening program in Hong Kong, around 6.6% of persons aged between 61 and 75 with positive fecal immunochemical tests (FITs) were diagnosed with CRC during screening colonoscopy. In this territory-wide study based on Hong Kong population, we aimed to determine the epidemiology, characteristics, risk factors and mortality of PCCRC as compared to detected CRC.

METHODS

Data source

Data were retrieved from the Clinical Data Analysis and Reporting System (CDARS), an electronic database system managed by the Hong Kong Hospital Authority for both audit and research purposes. The Hong Kong Hospital Authority is the only public healthcare provider serving a local population of 7.3 million and covers 90% of all primary, secondary and tertiary care.[13] Essential clinical information including patient's demographics, death, hospitalization, outpatient visits, diagnoses, investigations, drug prescription and dispensing history are all recorded in CDARS. A large number of high-quality, population-based studies had been reported by retrieving data from CDARS.[14-19] The International Classification of Diseases, Ninth Revision (ICD-9) was used for disease coding, with a high degree of coding accuracy (90 – 100 %) as reported in previous studies.[14, 15, 20, 21] Patient's confidentiality was protected by anonymization of individuals by a unique reference key in the CDARS. The study protocol was approved by the Institutional Review Board of the University of Hong Kong and the West Cluster of the Hong Kong Hospital Authority (reference no: UW 18-253).

Outcome definition and study subjects

Although the term "interval CRC" was loosely adopted by previous studies, majority of these studies failed to meet the definition as proposed: "CRC diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of next recommended exam".[7] In particular, "interval cancer" applies to screening and surveillance programs only and hence is not optimal for routine colonoscopy quality assurance purposes.[12] In this study, we followed the recent World Endoscopy Organization (WEO) consensus on advocating the PCCRC rate for an interval of 3 years (PCCRC-3y) for benchmarking purposes. PCCRC-3y was defined as CRC cases with prior colonoscopy performed between 6 and 36 months in

which no CRC was diagnosed. This definition was commonly adopted by previous studies to define interval CRC, as it is the estimated mean sojourn time of preclinical cancer progressing to detected cancer.[22-26] PCCRC-3y cases were further subdivided into PCCRC 6-12m (i.e. CRC developed within 6-12 months after index colonoscopy) and PCCRC 1-3y (i.e. CRC developed within 1-3 years after index colonoscopy) for subgroup analysis. Detected CRC was defined as CRC diagnosed within 6 months of the index colonoscopy, assuming that CRC suspected at index procedure would be confirmed within this time period.[22]

We identified all patients, aged 40 years or above, who had undergone colonoscopy between 2005 and 2013. Data on CRC were traced from 2005 to 2016. Exclusion criteria included history of CRC (dated back to year 1993 when CDARS was first established), inflammatory bowel disease and prior colectomy. **Figure 1** shows the patient selection process. Sites of CRC were categorized into distal and proximal colon. Proximal cancer referred to cancer from cecum to transverse colon (ICD-9 codes 153.4, 153.6, 153.0, 153.1), while distal cancer referred to cancer from splenic flexure to rectum (ICD-9 codes 153.2, 153.3, 153.7, 154.0, 154.1).

Study variables

Potential factors associated with PCCRC development included patient factors and endoscopy centers' performance were considered.[22, 24, 25, 27] Patient factors included age at index colonoscopy, sex, history of colonic polyps, biopsy/polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (obesity, diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism). These comorbidities were

included because they are risk factors for inadequate bowel preparation, which in turn increase PCCRC risk.[25, 28]

The details of ICD-9 codes were listed in **Supplementary Table 1**. Smoking was identified by ICD-9 code of V15.82 and chronic obstructive pulmonary disease (COPD) as a proxy of heavy smoking. Alcohol consumption was identified by presence of alcohol-related diseases, including hepatic, gastrointestinal, neurological and psychiatric diseases.

Altogether, there are 18 public hospitals that provide colonoscopy services in Hong Kong. Only medical gastroenterologist and surgical specialties are qualified to perform colonoscopy. Endoscopy centers' characteristics including annual colonoscopy volume (divided in 4 quartiles: <2033, 2033-2923, 2924-3363, >3363) and annual polypectomy rate (divided in 4 quartiles: <21.3%, 21.3-24.0%, 24.1-27.7%, >27.7%) were also included into analysis.

Statistical analyses

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing) statistical software. Continuous variables were expressed as median and interquartile range (IQR). Mann-Whitney U test was used to compare continuous variables of two groups. Chi-square test or Fisher's exact test was applied for categorical variables. The PCCRC-3y rate was calculated as per WEO consensus: False negatives / (True positives + False negatives), where false negatives refer to colonoscopy with CRC subsequently diagnosed between 6 and 36 months after the procedure and true positives refer to colonoscopy with CRC diagnosed at or within 6 months of the procedure.[12] Count data and temporal trends were assessed by Poisson regression model.

We identified (1) differences in the characteristics between PCCRC-3y and detected CRC and (2) predictive factors for PCCRC-3y with adjusted odds ratio (aOR) being calculated from multivariable logistic regression. For survival analysis, patients were observed from CRC diagnosis date until death or end of study (31 December 2017). Multivariable Cox proportional hazards model was used to calculate the adjusted hazards ratio (aHR) of predictive factors for cancer-specific mortality after CRC diagnosis. The Kaplan-Meier method was used to analyze cancer-specific mortality, and statistical significance was determined by log-rank test. All statistical tests were two-sided, and a p-value of <0.05 was used to define statistical significance.

RESULTS

Epidemiology of PCCRC-3y in Hong Kong

A total of 234,827 patients underwent colonoscopies during the 9-year period and 197,902 patients were included in the final analysis (**Figure 1**). Among them, 10,005 (5.1%) patients were diagnosed to have detected CRC and 854 (0.4%) with PCCRC-3y (PCCRC 6-12m: 338 and PCCRC 1-3y: 516). Of the 854 cases of PCCRC-3y, 707 (82.8%) were in the distal colon and 147 (17.2%) in the proximal colon. **Figure 2** shows the numbers of detected CRC and PCCRC-3y between 2005 and 2013. The overall PCCRC-3y rate during this period was 7.9%. There was a significant increase in the PCCRC-3y rate from 4.1% to 9.7% (Poisson p<0.001) between 2005 and 2009, but a significant decrease in the PCCRC-3y rate from 9.7% to 7.7% (Poisson p=0.046) between 2009 and 2013.

PCCRC-3y vs Detected Cancer

Table 1 shows the demographics of patients with PCCRC-3y and detected cancer. Patients with PCCRC-3y were older at index colonoscopy (74.6 vs 71.9 years, p<0.001) and at CRC diagnosis (75.9 vs 72.0 years, p<0.001), when compared to patients with detected CRC. The

median time from index colonoscopy to PCCRC diagnosis was 1.2 years (IQR:0.8–1.9 years).

Proximal cancer was more common among PCCRC-3y than detected cancer (17.2% vs 9.8%, p<0.001). A higher proportion of PCCRC-3y patients had history of colonic polyps (35.8% vs 25.4%, p<0.001). They also had more comorbidities including atrial fibrillation and congestive heart failure.

When comparing the PCCRC 6-12m and PCCRC 1-3y groups, there was no statistically significant difference in most of the variables, except for a higher proportion of hypertension (25.4% vs 18.8%, p=0.021) and congestive heart failure (10.4% vs 5.0%, p=0.003) in PCCRC 6-12m group (**supplementary Table 2**).

Predictive factors for PCCRC-3y

Table 2 shows the predictive factors for PCCRC-3y. On multivariate analysis, older age (aOR:1.07;95% CI:1.06-1.08), male sex (aOR:1.45;95% CI:1.26-1.67), history of colonic polyps (aOR:1.31;95% CI:1.13-1.51), polypectomy/biopsy at index colonoscopy (aOR:3.97;95% CI:3.46-4.56), index colonoscopy by surgical specialty (aOR:1.53;95% CI:1.31-1.78) and a higher annual colonoscopy volume of the center (compared with quartile 1, aORs were 1.09 [95% CI:0.89-1.35] for quartile 2; 1.50 [95% CI:1.22-1.85] for quartile 3 and 1.83 [95% CI:1.50-2.24] for quartile 4) were all associated with development of PCCRC-3y.

Survival analysis

The follow-up of this study cohort was up to 13 years and 6,011 (55.4%) of all CRC patients died, with 3,413 (31.4%) being cancer-related. The 1-year, 3-year, 5-year and 10-year cancer-specific survival probability for the whole cohort was 83.2% (81.5-82.9%), 70.6% (69.8-71.6%), 66.1% (65.1-67.1%) and 63.4% (62.4-64.4%), respectively.

PCCRC-3y vs Detected CRC

Figure 3 shows PCCRC-3y had a worse cancer-specific survival than detected CRC (log-rank p <0.001). The 1-year, 3-year, 5-year and 10-year cancer-specific survival probability for PCCRC-3y was 74.3% (95% CI:71.2-77.4%), 60.8% (95% CI:57.3-64.5%), 57.7% (95% CI:54.1-61.5%) and 55.3% (95% CI: 51.3-59.7%), respectively. The corresponding 1-year, 3-year, 5-year and 10-year cancer-specific survival probability for detected CRC was 84.0% (95% CI: 83.2-84.7%), 71.4% (95% CI:70.5-72.4%), 66.8% (95% CI:65.8-67.8%) and 64.0% (95% CI: 63.0-65.1%).

Table 3 shows the predictive factors for cancer-specific mortality in all CRC patients. On multivariable analysis, PCCRC-3y was a significant predictive factor compared with detected CRC (aHR:1.32;95% CI:1.18-1.49). Proximal cancer was also a significant predictive factor for cancer-specific mortality as compared with distal cancer (aHR:1.80;95% CI:1.63-1.98). Patient's factors included older age at CRC diagnosis (aHR:1.013;95% CI:1.009-1.016), alcohol use (aHR:1.80;95% CI:1.23-2.66) and history of stroke (aHR:1.20;95% CI:1.04-1.38).

PCCRC 6-12m vs PCCRC 1-3y

There was no significant difference in the cancer-specific survival probability between PCCRC 6-12m and PCCR 1-3y groups (log-rank p=0.165) (**Supplementary Figure 1**). On Cox model, PCCRC 1-3y was also not a predictive factor for cancer-specific mortality as compared with PCCRC 6-12m (HR:0.85, 95% CI:0.68-1.07; p=0.163).

DISCUSSION

While population-based studies on PCCRC from Asia are sparse, our current study described the epidemiology, predictive factors and survival of PCCRC in Hong Kong based on the territory-wide electronic health database. We found that the PCCRC-3y rate was 7.9%, which was consistent with the data in the West that ranged from 0.8% of all colonoscopies to 9% of all diagnosed CRCs.[7] Intriguingly, the PCCRC-3y increased between 2005 and 2009, but decreased between 2009 and 2013 in our locality. The reasons for this decline remain unknown but could be related to the increasing awareness of interval cancers, the use of high-definition endoscope[29] and the recognition of the importance of adenoma detection rate.[30] Recently, PCCRC rate has been proposed by the WEO as a more important performance measure of colonoscopy quality than other parameters such as cecal intubation rate, adenoma detection rate and withdrawal time which are only surrogates of the outcome.[12] The PCCRC rate allows direct determination of a center or locality's efficacy in detecting and preventing CRC, which in turn could drive performance improvement within the service by providing a benchmark. It also helps to identify interventions for system-wide quality improvement. Hence, this kind of territory-wide epidemiological data from real world practices would be important as a reference for the quality of colonoscopy performed in daily clinical practices in Asia.

In this study, we identified certain characteristics of our patients with PCCRC-3y including older age at cancer diagnosis (75.9 vs 72.0 years), a higher frequency of involvement of the proximal colon (17.2 vs 9.8%) and history of colonic polyps (35.8 vs 25.4%). History of colonic polyps and polypectomy at index colonoscopy were found to confer a 1.31-fold and 3.97-fold increase in risk of PCCRC-3y after index colonoscopy showing no cancer, respectively. In fact, incomplete polypectomy has been proposed to be one of the mechanisms for the development of PCCRC. A prospective study revealed that 10% of polyps were incompletely resected during colonoscopy with residual neoplastic tissue detected at the polypectomy margins, particularly sessile serrated lesions which tends to be of flat and proximal in location.[31]

Although our study also shows that proximal colon involvement was more common in PCCRC-3y compared with detected CRC, distal cancers were the predominant tumor locations of PCCRC-3y in our population. This is in contrast to previous studies which reported proximal colon to be more frequently involved in interval CRC (ranging from 50% to 68%).[22-24] While incomplete colonoscopy was reported in some studies on interval CRC to be >15%, [5, 25, 26] the cecal intubation rate or complete colonoscopy rate of our center was more than 95% according to our latest colonoscopy registry (unpublished data). It is also important to know that distal cancer is still more prevalent than proximal cancer in Chinese patients (56.5% vs 43.5%) that may account for the higher proportion of distal PCCRC-3yr as well.[32] As for our center, distal CRC constituted 68.6% of all CRC cases in 2017 (unpublished data).

We also characterized the association of endoscopy center metrics with risk of PCCRC-3y. Because our aim was to explore benchmark measures to provide system-wide quality

improvement interventions, we determined the impact of colonoscopy volume and polypectomy rate at the endoscopy center instead of individual endoscopist. We found that a higher annual colonoscopy volume was associated with a higher risk of PCCRC-3y (aOR of 1.56 for quartile 4 compared with quartile 1). Since the duration for individual colonoscopy procedure was not available in the electronic database, one may speculate that a higher center endoscopy volume may infer a shorter procedure time with ensuing increased risk of missed lesions. Although there are conflicting data on the interval cancer risk with individual endoscopist's procedure volume,[24,33] data on correlation with the center's volume are lacking.

In our study, patients with PCCRC-3y had a poorer survival than those with detected CRC (aHR:1.32). This is in contrary to what was reported by a study from Utah, in which patients with PCCRC had a survival advantage (HR: 0.63;95% CI:0.49-0.81).[22] Previous studies postulated that the better survival for interval CRC may be related to the fact that they are usually of earlier stage than detected CRC.[22, 23] Also, the higher frequency of proximal colon involvement in interval CRC,[22] which are more commonly associated with aberrant methylation and microsatellite instability, may implicate different tumor biology that renders a better survival compared with microsatellite-stable CRC.[34, 35] As yet, recent studies from Norway and Korea found no difference in cancer mortality between interval and detected CRC.[36, 37] It remains to be determined in other populations whether interval or PCCRC have different survival rates. In addition, as screening colonoscopy for average risk subjects was generally not an approved indication of colonoscopy in public hospitals in Hong Kong during the study period, patients included in this study were more likely made up of predominantly symptomatic patients. Hence, the characteristics may not be directly comparable to patients who were diagnosed with interval cancers after negative screening colonoscopy.

The strength of this study is the population-based design which includes all public endoscopy centers in Hong Kong, hence minimizing selection bias stemming from data of specialized centers only. Second, the use of electronic healthcare database allows us to capture other important variables that may modulate cancer risk. Third, the long duration of follow-up from CRC diagnosis allows for meaningful comparison of the survival between patients with PCCRC and detected CRC.

Several limitations of the current study should be acknowledged, which are largely related to the use of administrative database. First, procedure-related quality measures such as the cecal intubation rate, experience of endoscopists, withdrawal time and quality of bowel preparation which may affect adenoma detection rates were not available in the database. Second, indications of index colonoscopy were not available from the CDARS, precluding stratified analysis of PCCRC-3y rate and its associated risk factors according to symptomatic and screening populations. Third, adenoma detection rate of individual endoscopist or center could not be derived as calculation should be based on screening colonoscopy in asymptomatic patients ≥50 years who are at average risk for colon polyps and cancer.[38] However, center polypectomy rate was used instead as polypectomy rate has been shown to have a good correlation with ADR (r=0.80)[39]. Fourth, polyp histology, number and location of the polyps could not be ascertained, precluding the study of mechanisms for PCCRC development. Data on polyp removal technique and completeness of polyp removal was also lacking. Fifth, certain risk factors for CRC including family history, presence of Lynch syndrome and lifestyle factors could not be captured. The use of surrogate markers of smoking and alcohol use (COPD and alcohol-related diseases) may also underestimate their true prevalence. Lastly, data on CRC staging, treatment received (surgery, chemotherapy,

radiation and palliative care) and presence of microsatellite instability were not available, which were important prognostic factors of CRC.

CONCLUSION

In conclusion, this territory-wide study showed that the PCCRC-3y rate was 7.9% in Hong Kong. The characteristics of PCCRC in our population differ from those reported in the West, with a predominance of distal colon involvement and lower cancer-specific survival. We also identified certain patient's and endoscopy center's factors that may be potential targets for interventions to reduce PCCRC risk in Asia.

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Table 1. Characteristics of PCCRC-3y and detected CRC

	PCCRC-3y (n=854)	Detected CRC (n=10,005)	p-value
Patient's characteristics			
Age at index colonoscopy	74.6 (63.8 – 82.4)	71.9 (61.8 – 79.4)	**<0.001**
Age at CRC diagnosis	75.9 (65.5 – 83.8)	72.0 (61.9 – 79.5)	**<0.001**
Male sex	513 (60.1%)	6247 (62.4%)	0.171
Proximal cancer*	147 (17.2%)	982 (9.8%)	**<0.001**
History of colon polyps	306 (35.8%)	2546 (25.4%)	**<0.001**
Smoking	44 (5.2%)	393 (3.9%)	0.081
Alcoholism	2 (0.2%)	59 (0.6%)	0.182
Diabetes mellitus	89 (10.4%)	1244 (12.4%)	0.085
Hypertension	183 (21.4%)	1945 (19.4%)	0.160
Dyslipidemia	34 (4.0%)	491 (4.9%)	0.226
Atrial fibrillation	55 (6.4%)	404 (4.0%)	**<0.001**
Ischemic heart disease	73 (8.5%)	694 (6.9%)	0.078
Congestive heart failure	61 (7.5%)	485 (4.8%)	**0.003**
Stroke	58 (6.8%)	604 (6.0%)	0.376
Chronic renal failure	20 (2.3%)	199 (2.0%)	0.481
Cirrhosis	2 (0.2%)	58 (0.6%)	0.329
Dementia	17 (2.0%)	145 (1.4%)	0.210
Parkinsonism	7 (0.8%)	63 (0.6%)	0.506
Center performance			
Specialty (surgical)#	622 (72.8%)	7698 (76.9%)	**0.006**
Annual center colonoscopy volume (continuous variable)	3069 (2131 – 3419)	2892 (2031 – 3363)	**<0.001**
Annual center colonoscopy volume per year (categorical variable)			
Quartile 1(< 2033)	161 (18.9%)	2536 (25.3%)	**<0.001**
Quartile 2 (2033 – 2923)	201 (23.5%)	2522 (25.2%)	
Quartile 3 (2924 – 3363)	227 (26.6%)	2387 (23.8%)	
Quartile 4 (> 3363)	265 (31.0%)	2560 (25.6%)	

Annual center polypectomy rate (continuous variable)	24.0% (21.2% - 27.9%)	24.1% (21.3% - 27.8%)	0.807
Annual center polypectomy rate (categorical variable)			
Quartile 1 (< 21.3%)	214 (25.1%)	2464 (24.6%)	0.072
Quartile 2 (21.3% - 24.0%)	220 (25.8%)	2344 (23.4%)	
Quartile 3 (24.1% – 27.7%)	192 (22.5%)	2644 (26.4%)	
Quartile 4 (> 27.8%)	228 (26.7%)	2553 (25.5%)	

Significant p-values were bolded

* Distal colon included splenic flexure, descending colon, rectosigmoid junction and rectum. Proximal colon included cecum, ascending colon, hepatic flexure and transverse colon

Compared with medical specialty

Abbreviations: PCCRC-3y, post-colonoscopy colorectal cancer at for an interval of 3 years; CRC, colorectal cancer; DM, diabetes mellitus; HT, hypertension; AF, atrial fibrillation; IHD, ischemic heart disease; CHF, congestive heart failure; CRF, chronic renal failure

Table 2. Logistic regression of predictive factors for PCCRC-3y

	Univariate analysis			Multivariable analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Patient factors						
Age (in yearly increments)	1.07	1.07 – 1.08	<**0.001**	1.07	1.06 – 1.08	<**0.001**
Male sex	1.57	1.37 – 1.81	<**0.001**	1.45	1.26 – 1.67	<**0.001**
History of colonic polyps	2.14	1.85 – 2.46	<**0.001**	1.31	1.13 – 1.51	<**0.001**
Polypectomy / biopsy at index colonoscopy	4.45	3.88 – 5.09	<**0.001**	3.97	3.46 – 4.56	<**0.001**
Smoking	2.60	1.89 – 3.48	<**0.001**	1.10	0.79 – 1.49	0.550
Alcohol	0.41	0.07 – 1.27	0.209			
Diabetes mellitus	*1.10*	*0.88 – 1.37*	*0.383*			
Hypertension	1.50	1.27 – 1.76	<**0.001**	0.87	0.71 – 1.03	0.079
Dyslipidemia	0.77	0.54 – 1.07	0.142			
Atrial fibrillation	2.22	1.67 – 2.90	<**0.001**	1.18	0.86 – 1.58	0.282
Ischemic heart disease	1.23	0.96 – 1.55	0.090			
Congestive heart failure	2.23	1.70 – 2.87	<**0.001**	1.09	0.81 – 1.45	0.561
Stroke	1.73	1.31 – 2.23	<**0.001**	0.97	0.73 – 1.28	0.854
Chronic renal failure	1.12	0.70 – 1.70	0.604			
Cirrhosis	0.35	0.07 – 1.08	0.137			
Dementia	3.04	1.80 – 4.77	<**0.001**	1.16	0.68 – 1.84	0.562
Parkinsonism	1.99	0.85 – 3.89	0.070			
Center performance						
Specialty						
Medical	Ref	-	-			-
Surgical	1.50	1.29 – 1.75	<**0.001**	1.53	1.31 – 1.78	<**0.001**
Center annual endoscopy volume						

Quartile 1 (< 2033)	Ref	-	-	Ref	-	-
Quartile 2 (2033 – 2923)	1.06	0.86 – 1.30	0.613	1.09	0.89 – 1.35	0.409
Quartile 3 (2924 – 3363)	1.42	1.17 – 1.73	**<0.001**	1.50	1.22 – 1.85	**<0.001**
Quartile 4 (> 3363)	1.49	1.23 – 1.81	**<0.001**	1.83	1.50 – 2.24	**<0.001**
Center annual polypectomy rate						
Quartile 1 (< 21.3%)	Ref	-	-	Ref	-	-
Quartile 2 (21.3% - 24.0%)	0.94	0.79 – 1.13	0.535	0.94	0.77 – 1.14	0.504
Quartile 3 (24.1% – 27.7%)	0.81	0.66 – 0.98	**0.031**	0.85	0.70 – 1.05	0.128
Quartile 4 (> 27.8%)	0.78	0.64 – 0.95	**0.012**	0.92	0.76 – 1.11	0.386

Significant p-values were bolded

* Distal colon included splenic flexure and descending colon. Proximal colon included cecum, ascending colon, hepatic flexure and transverse colon

Abbreviations: PCCRC-3y, postcolonoscopy colorectal cancer at for an interval of 3 years; CRC, colorectal cancer; OR, odds ratio; 95% CI, 95% confidence interval

Table 3. Cox Proportional hazards regression showing predictive factors for cancer-specific mortality after CRC diagnosis

	Univariate analysis			Multivariable analysis		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age at CRC diagnosis	1.016	1.013 – 1.019	**<0.001**	1.013	1.009 – 1.016	**<0.001**
Male sex	1.01	0.94 – 1.08	0.813			
History of colonic polyp	1.03	0.95 – 1.11	0.450			
Smoking	1.20	1.01 – 1.24	**0.036**	1.03	0.87 – 1.23	0.701
Alcohol	1.80	1.22 – 2.64	**0.003**	1.80	1.23 – 2.66	**0.003**
Detected vs PCCRC-3y						
Detected CRC	Ref	-	-	Ref	-	-
PCCRC-3y	1.47	1.31 – 1.65	**<0.001**	1.32	1.18 – 1.49	**<0.001**
Site of CRC						
Distal colon	Ref	-	-	Ref	-	-
Proximal colon	1.98	1.80 – 2.18	**<0.001**	1.80	1.63 – 1.98	**<0.001**
Other comorbidities						
Obesity	0.16	0.02 – 1.11	0.063			
Diabetes mellitus	1.18	1.06 – 1.20	**0.002**	1.06	0.95 – 1.18	0.294
Hypertension	1.13	1.03 – 1.23	**0.006**	0.93	0.84 – 1.02	0.115
Dyslipidemia	1.09	0.93 – 1.28	0.276			
Atrial fibrillation	1.11	0.94 – 1.32	0.222			
Ischemic heart disease	1.03	0.90 – 1.17	0.717			
Congestive heart failure	1.41	1.22 – 1.63	**<0.001**	1.14	0.98 – 1.33	0.097
Stroke	1.36	1.19 – 1.56	**<0.001**	1.20	1.04 – 1.38	**0.014**
Chronic renal failure	1.18	0.92 – 1.51	0.197			
Cirrhosis	1.37	0.88 – 2.13	0.159			
Dementia	1.42	1.09 – 1.86	**0.010**	1.03	0.78 – 1.35	0.845
Parkinsonism	1.24	0.81 – 1.90	0.332			

Significant p-values were bolded

* Distal colon included splenic flexure and descending colon. Proximal colon included cecum, ascending colon, hepatic flexure and transverse colon

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; CRC, colorectal cancer; PCCRC-3y, postcolonoscopy colorectal cancer at for an interval of 3 years

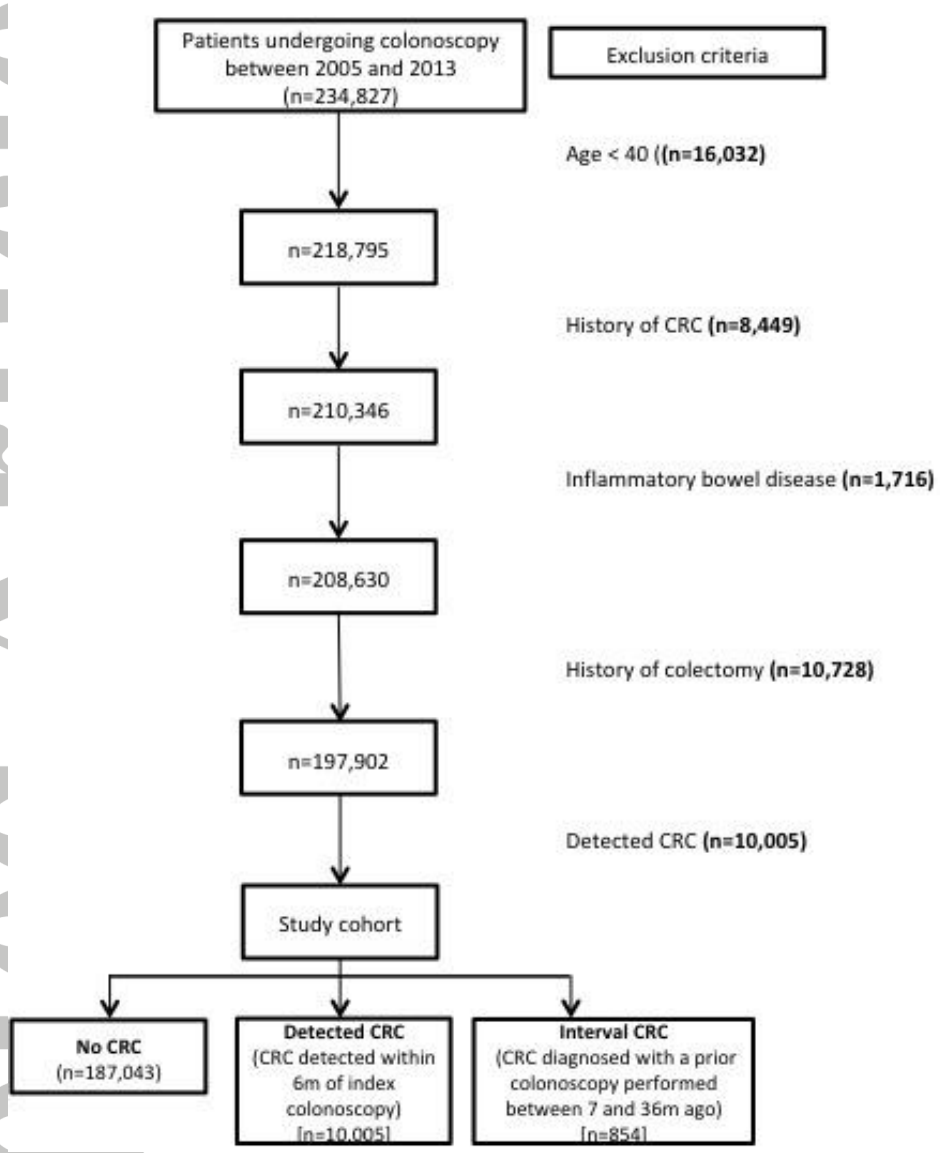
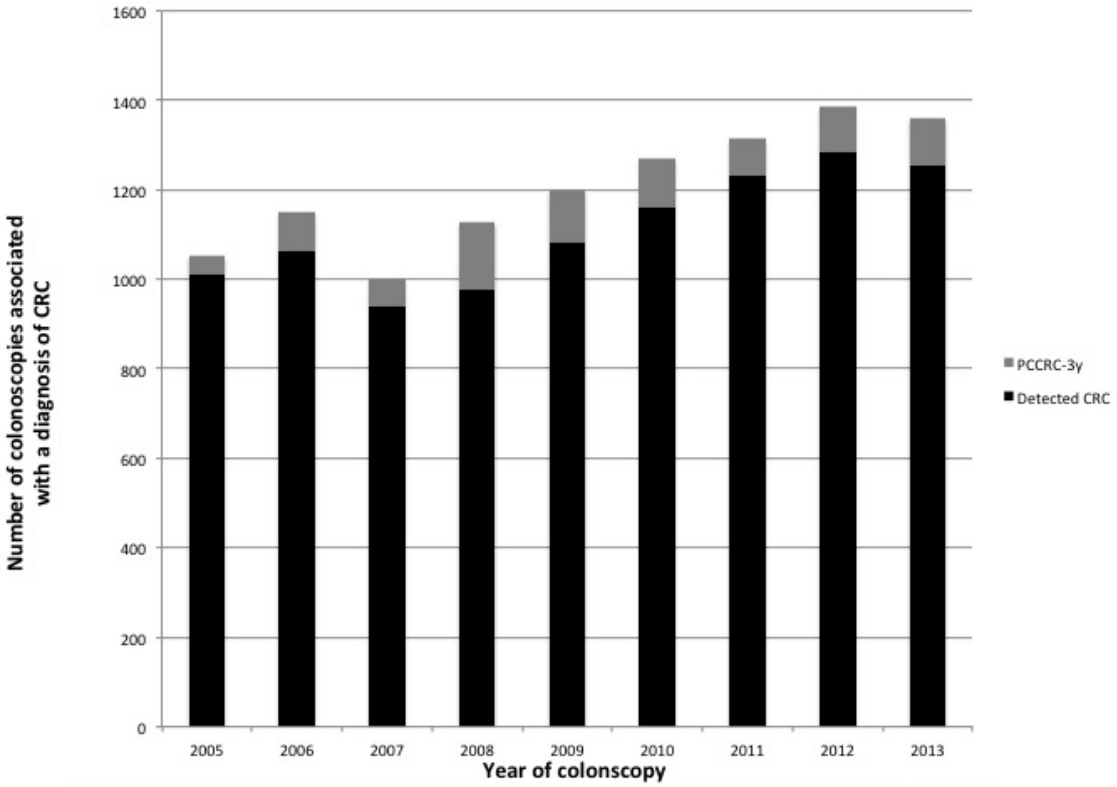


Figure 1. Patient selection flow diagram
Abbreviations: CRC, colorectal cancer



Detected CRC	1010	1063	941	977	1083	1160	1232	1285	1254
PCCRC-3y	43	87	61	149	116	109	82	102	105
PCCRC-3y rate	4.1	7.6	6.1	13.2	9.7	8.6	6.2	7.4	7.7

Figure 2. Number of cases of detected CRC and PCCRC-3y between 2005 and 2013
Abbreviations: CRC, colorectal cancer; PCCRC-3y, post-colonoscopy colorectal cancer for an interval of 3 years

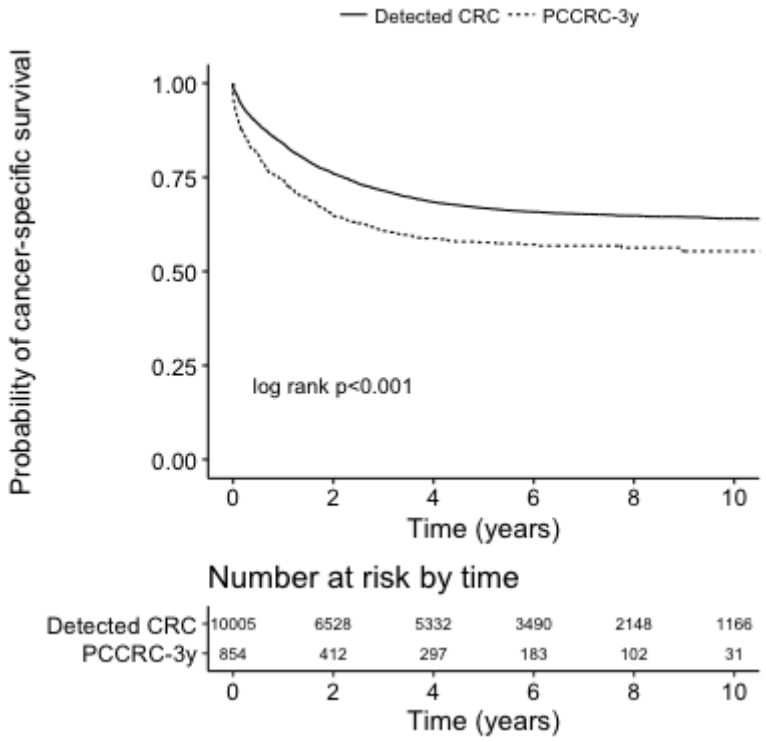


Figure 3. Kaplan Meier plot of patients with detected CRC and PCCRC-3y
Abbreviations: CRC, colorectal cancer; PCCRC-3y, post-colonoscopy colorectal cancer for an interval of 3 years