Epidemiology, prognosis, risk factors, and chemopreventive agents for post-colonoscopy colorectal cancer: abridged secondary publication

KS Cheung *, WK Leung †, EWY Chan, IOL Wong

KEY MESSAGES

1. In Hong Kong, post-colonoscopy colorectal cancer (PCCRC) is associated with higher prevalences of distal cancers (>80%) and cancer-specific mortality, compared with detected colorectal cancer. The rate of PCCRC at 3 years is 7.9%.
2. Predictive factors for PCCRC at 3 years are older age, male sex, history of colonic polyps, polypectomy/biopsy at index colonoscopy, index colonoscopy by a surgical endoscopist, and a higher centre annual colonoscopy volume.
3. Non-steroidal anti-inflammatory drugs have potential chemoprotective effects against PCCRC.
4. Statins are potential chemopreventive agents against PCCRC.

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[1] KS Cheung, [1] WK Leung, [2] EWY Chan, [3] IOL Wong

[1] *Department of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[2] *Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China*
[3] *School of Public Health, The University of Hong Kong, Hong Kong SAR, China*

* Principal applicant: cks634@hku.hk
† Corresponding author: waikleung@hku.hk

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women. In 2015, there were 1.65 million newly diagnosed cases of CRC and 835 000 CRC-related deaths. Colonoscopy screening is an effective means to reduce CRC incidence and mortality.[1] However, CRC can occur between colonoscopy screening procedures, a condition known as post-colonoscopy CRC (PCCRC).[2] The PCCRC rate is an indicator of colonoscopy service quality in CRC detection and prevention. Non-steroidal anti-inflammatory drugs (NSAIDs)[3] and statins[4] can decrease CRC risk, but no stratified analysis has been performed with a focus on interval PCCRC.

Methods

The Clinical Data Analysis and Reporting System was searched to retrieve relevant data from 2005 to 2016. The World Endoscopy Organization consensus was used to define the PCCRC rate at 3 years: CRC diagnosed between 6 and 36 months after a colonoscopy in which no CRC was detected. The definition of 'detected CRC' was CRC diagnosed within 6 months of the index colonoscopy, based on the assumption that CRC suspected at the index colonoscopy would be confirmed within this period.

Patients aged ≥40 years who underwent colonoscopy during 2005 to 2013 were identified. Patients with a history of CRC, inflammatory bowel disease, or previous colectomy were excluded. The CRC sites were categorised as distal colon (from rectum to splenic flexure) and proximal colon (from transverse colon to cecum).

Factors evaluated for associations with PCCRC development, relative to detected CRC, included patient characteristics, endoscopy centre polypectomy rate, and annual endoscopy volume. Endoscopy centre characteristics included the annual polypectomy rate (divided into four quartiles: <21.3%, 21.3%-24.0%, 24.1%-27.7%, >27.7%) and annual colonoscopy volume (divided into four quartiles: <2033, 2033-2923, 2924-3363, >3363). Patient characteristics included sex, age at index colonoscopy, presence of colonic polyps, biopsy/polypectomy at index colonoscopy, cigarette use, alcohol intake, and presence of comorbidities (obesity, hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease, atrial fibrillation, stroke, congestive heart failure, chronic renal failure, cirrhosis, parkinsonism, and dementia). These comorbidities increase PCCRC risk due to inadequate bowel preparation. Survival was calculated from CRC diagnosis until death or the end of the study (31 December 2017).

Outcome measures included use of NSAIDs, statins, and aspirin prior to index colonoscopy. Patient factors, endoscopy centre performance, and concurrent medication use were considered in analyses of PCCRC risk at 3 years.

All drug prescription and dispensing data were

tracked up to 5 years before the index colonoscopy. Medication use was defined as ≥90 days of usage.

Results

Of 234 827 patients, 197 902 who underwent colonoscopies during the 9-year study period were included in the analysis. The rate of detected CRC was 5.1% (n=10 005), and the PCCRC rate at 3 years was 0.4% (n=854). Among patients with PCCRC at 3 years, 82.8% (n=707) and 17.2% (n=147) exhibited CRC in the distal colon and proximal colon, respectively. The overall incidence was 15.2 per 10 000 person-years. The overall PCCRC rate at 3 years was 7.9% for the period 2005 to 2013. The PCCRC rate at 3 years increased from 4.1% in 2005 to 9.7% in 2009 (Poisson P<0.001) and then decreased from 9.7% in 2009 to 7.7% in 2013 (Poisson P=0.046).

Compared with patients with detected CRC, patients with PCCRC at 3 years 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). The median time from baseline to diagnosis of PCCRC was 1.2 (interquartile range, 0.8-1.9) years. Higher percentages of patients with PCCRC at 3 years had proximal involvement (17.2% vs 9.8%, P<0.001), a history of colonic polyps (35.8% vs 25.4%, P<0.001), and comorbidities including congestive heart failure and atrial fibrillation.

Multivariate analysis revealed that the diagnosis of PCCRC at 3 years was associated with older age (adjusted odds ratio [aOR]=1.07, 95% confidence interval [CI]=1.06-1.08), male sex (aOR=1.45, 95% CI=1.26-1.67), polypectomy/biopsy at index colonoscopy (aOR=3.97, 95% CI=3.46-4.56), a history of colonic polyps (aOR=1.31, 95% CI=1.13-1.51), index colonoscopy by a surgical endoscopist (aOR=1.53, 95% CI=1.31-1.78), and a higher annual centre colonoscopy volume (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).

Patients were followed up for up to 13 years; 6011 (55.4%) of all patients with CRC died, and 3413 (31.4%) of these deaths were cancer related. The 1-year, 3-year, 5-year, and 10-year cancer-specific survival probabilities were 83.2%, 70.6%, 66.1%, and 63.4%, respectively.

Cancer-specific survival was worse among patients with PCCRC at 3 years than among patients with detected CRC (log-rank P<0.001). The 1-year, 3-year, 5-year, and 10-year cancer-specific survival probabilities for PCCRC at 3 years were 74.3%, 60.8%, 57.7%, and 55.3%, respectively. The corresponding cancer-specific survival probabilities for detected CRC were 84.0%, 71.4%, 66.8%, and 64.0%, respectively.

Of 187 897 patients receiving NSAIDs, 91 961 (48.9%) were men. The follow-up duration was 560 471 person-years. In 5 years preceding the index colonoscopy, there were 21 757 NSAID users with a median use duration of 0.7 (interquartile range, 0.4-1.6) years. Among the NSAID users, 0.25% (n=55) were diagnosed with PCCRC at 3 years. The incidence rates for PCCRC at 3 years were 8.4 and 16.1 per 10 000 person-years among NSAID users and non-users, respectively.

Crude analysis showed that the hazard ratio (HR) for PCCRC at 3 years among NSAID users was 0.53 (95% CI=0.40-0.69) and the adjusted HR was 0.54 (95% CI=0.41-0.70). Stratified analysis indicated that NSAID use was associated with a reduced risk of PCCRC at 3 years in the proximal colon (adjusted HR=0.48, 95% CI=0.24-0.95) and distal colon (adjusted HR=0.55, 95% CI=0.40-0.74). The adjusted HR for PCCRC at 3 years among aspirin users was 1.01 (95% CI=0.80-1.28, P=0.92).

Statin users comprised 13.5% (n=25 447) of the cohort. The specific statins were simvastatin (69.7%, n=17 744), atorvastatin (7.3%, n=1847), and rosuvastatin (2.1%, n=542); 20.9% (n=5314) of patients switched between types. Among statin users, 0.5% (n=114) developed PCCRC at 3 years; the incidence rate was 15.0 per 10 000 person-years.

After propensity score matching, all covariates were balanced between statin users (n=17 662) and non-users (n=30 304) [absolute standardised difference <0.2]. Statin users had a decreased risk of PCCRC at 3 years (sub-distribution HR=0.72, 95% CI=0.55-0.95). Stratified analysis revealed that statin use was associated with a lower risk of PCCRC at 3 years in the proximal colon (sub-distribution HR=0.50, 95% CI=0.28-0.91) but not in the distal colon (sub-distribution HR=0.80, 95% CI=0.59-1.09).

Discussion

In Hong Kong, the PCCRC rate at 3 years was 7.9%, consistent with findings in Western populations that ranged from 0.8% of all colonoscopies to 9% of all diagnosed CRCs. The PCCRC rate at 3 years increased from 2005 to 2009 and then decreased from 2009 to 2013. The decrease may be related to the enhanced attention towards interval cancers, greater emphasis on adenoma detection, and adoption of high-definition endoscopes.

Patients with PCCRC at 3 years were older at cancer diagnosis, had a history of colonic polyps, and showed greater involvement of the proximal colon, compared with patients with detected CRC. Incomplete polypectomy was a risk factor for PCCRC development. A higher annual colonoscopy volume was associated with a greater risk of PCCRC at 3 years. Higher volume may result in a shorter procedure duration and thus a higher likelihood of missed lesions. However, we could not capture data regarding the duration of individual colonoscopy procedures.

Although proximal colon involvement was more prevalent in patients with PCCRC at 3 years than in patients with detected CRC, the distal colon was the predominant tumour site among patients with PCCRC at 3 years. This finding differs from previous findings, which indicated that proximal colon involvement was more common in PCCRC (50%-68%). The rate of PCCRC can exceed 15% among individuals with incomplete colonoscopy. In our latest colonoscopy registry, the rates of complete colonoscopy and caecal intubation are >95%. In 2017, distal CRC constituted 68.6% of all CRC cases. This percentage may explain the higher proportion of distal PCCRC at 3 years in the present study, considering that our centre predominantly serves Chinese patients, who reportedly have a higher prevalence of proximal cancer than distal cancer (56.5% vs 43.5%).

Patients with PCCRC at 3 years had a worse survival rate, compared with patients with detected CRC. This finding contrasts with a study conducted in Utah, which showed a better survival rate in patients with PCCRC. The discrepancy could be related to the earlier staging of PCCRC. Furthermore, the CRC site may play a role. The involvement of the proximal colon is commonly associated with aberrant methylation and microsatellite instability, implying distinct tumour biology associated with better survival, compared with microsatellite-stable CRC. Conversely, studies from Korea and Norway revealed no difference in cancer mortality between interval and detected CRC.

Regarding chemopreventive agents, NSAIDs were associated with a 47% reduction in the risk of PCCRC at 3 years in terms of both proximal and distal cancers. However, aspirin use did not show risk reduction. Cyclooxygenase-2 inhibition could play a crucial role in the chemopreventive effect of NSAIDs, but the inhibition is more selective in aspirin. Moreover, the chemopreventive effect of aspirin is evident only after >5 years of use with a latency period of at least 10 years, compared with a shorter period of time in NSAIDs. Statins demonstrated a dose-related chemopreventive effect on PCCRC at 3 years. Statins reduced the risk of PCCRC at 3 years by 28%, with a more pronounced effect on proximal CRC. Statins tend to act on later stages of the adenoma-carcinoma. Considering that pre-existing adenomas require approximately 10 years to progress to invasive cancer, we speculate that statins have the strongest effects on missed lesions (ie, those commonly located in the proximal colon) during the index colonoscopy, thereby impeding advanced adenoma progression to cancer.

Conclusion

In Hong Kong, the PCCRC rate at 3 years was 7.9%. Compared with Western populations, our cohort displayed lower cancer-specific survival and primarily distal colon involvement. NSAIDs and statins have potential chemopreventive effects on PCCRC development. Additional studies are needed to confirm our findings.

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Disclosure

The results of this research have been previously published in:

1. Cheung KS, Chen L, Seto WK, Leung WK. Epidemiology, characteristics, and survival of post-colonoscopy colorectal cancer in Asia: a population-based study. J Gastroenterol Hepatol 2019;34:1545-53.
2. Cheung KS, Chen L, Chan EW, Seto WK, Wong ICK, Leung WK. Nonsteroidal anti-inflammatory drugs but not aspirin are associated with a lower risk of post-colonoscopy colorectal cancer. Aliment Pharmacol Ther 2020;51:899-908.

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