

BMJ Open Post-colonoscopy colorectal cancers identified by probabilistic and deterministic linkage: results in an Australian prospective cohort

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ABSTRACT

Objective Post-colonoscopy colorectal cancers (PCCRCs) are recognised as a critical quality indicator. Benchmarking of PCCRC rate has been hampered by the strong influence of different definitions and methodologies. We adopted a rigorous methodology with high-detail individual data to determine PCCRC rates in a prospective cohort representing a single jurisdiction.

Setting We performed a cohort study of individuals who underwent colonoscopy between 2001 and 2008 at a single centre serving Australian Capital Territory (ACT) and enclaving New South Wales (NSW) region. These individuals were linked to subsequent colorectal cancer (CRC) diagnosis, within 5 years of a negative colonoscopy, through regional cancer registries and hospital records using probabilistic and deterministic record linkage. All cases were verified by pathology review. Predictors of PCCRCs were extracted.

Participants 7818 individuals had a colonoscopy in the cohort. Linkage to cancer registries detected 384 and 98 CRCs for notification dates of 2001–2013 (ACT) and 2001–2010 (NSW). A further 55 CRCs were identified from a search of electronic medical records using International Classification of Diseases-10 diagnosis codes. After verification and exclusions, 385/537 CRCs (58% male) were included.

Primary outcome measure PCCRC rates.

Results There were 15 PCCRCs in our cohort. The PCCRC incidence rate was 0.384/1000 person-years and the 5-year PCCRC risk was estimated as 0.192% (95% CI 0.095 to 0.289). The index colonoscopy prior to PCCRC was more likely to show diverticulosis ($p=0.017$ for association, OR 3.56, $p=0.014$) and have poor bowel preparation ($p=0.017$ for association, OR 4.19, $p=0.009$).

Conclusion In this population-based cohort study, the PCCRC incidence rate was 0.384/1000 person-years and the 5-year PCCRC risk was 0.192%. These data show the 'real world' accuracy of colonoscopy for CRC exclusion.

INTRODUCTION

Colonoscopy is a recommended,¹ preferred² and cost-effective screening modality for colorectal cancer (CRC) screening, with large observational demonstrating its effectiveness in reducing CRC incidence and mortality.^{3–5}

Strengths and limitations of this study

- The post-colonoscopy colorectal cancer (PCCRC) rate is a quality standard for colonoscopy, but may be markedly affected by the detail available in large datasets and the methodology used to link them.
- We used a prospective colonoscopy cohort linked to state cancer registries and the electronic medical record, a combination of probabilistic and deterministic linkage, and individual case review to derive the incidence of PCCRC.
- For benchmarking of PCCRC incidence, the cohort having index colonoscopy should be followed prospectively to ensure that the same population is assessed.
- Our approach was affected by a lag to registration in each cancer registry, limiting the cohort size with a minimum of 5 years' follow-up.

As with other forms of cancer screening, interval cancers, defined as CRC diagnosed after a screening or surveillance examination in which no cancer is detected, and before the date of the next recommended examination,⁶ can occur. The Asia Pacific CRC Working Group have published recommendations on minimising interval cancers, recognising that interval cancers are a reflection of quality in colonoscopy practice.⁷ More recently, these events have been termed post-colonoscopy colorectal cancers (PCCRC), with the term interval cancer applied only to CRC arising within a defined period after a negative examination performed primarily for screening⁸ and to differentiate those screened by another means. Expert opinion is that PCCRCs are potentially the most important markers of colonoscopy quality.⁹

CRC is the second most common cancer in Australia.¹⁰ As a result, even a low-frequency event such as PCCRC may yield a substantial number of cases. Internationally, the reported proportion of new CRC cases that are PCCRC varies widely, with rates up



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to 9%,¹¹ possibly because of differing methodology and quality. Methodological issues that impact most severely on rates of PCCRC have been addressed.^{6 12}

One theoretically accurate way to determine PCCRC incidence is to measure its occurrence prospectively in a cohort of patients with colonoscopies negative for cancer. As detection of PCCRCs requires case matching between at least two datasets (such as Procedure or Claims Databases with a Cancer Registry), the relative completeness of data and quality of data linkage must also determine the apparent PCCRC incidence. The aim of this study was to accurately determine the PCCRC incidence in our geographically small but populous Australian jurisdiction, by exploiting the availability of three separate database sources—a Prospective Colonoscopy Database, a Hospital Records System and a Regional Cancer Registry. We sought to maximise one-to-one linkage and enable benchmarking in our jurisdiction and other regional jurisdictions.

METHODS

Study design

We performed a cohort study of individuals who underwent outpatient colonoscopy at the Canberra Hospital, Australia Capital Territory (ACT), Australia from 1 January 2001 to 31 December 2008, who were residents of the ACT at the time. We then identified individuals from this cohort subsequently diagnosed with CRC anywhere in ACT or New South Wales (NSW).

The ACT is a self-governing jurisdiction, with a population 390 800 and land area 2358 km², in the south-east of Australia. It is unique geographically in being enclaved by the larger and more populous NSW, with a population 7 618 200 and 800 641 km². In addition, its major hospital, the Canberra Hospital, is also the major public hospital for the surrounding region, supporting a population of 540 000. While migration to other states occurs, the majority of residents leaving the ACT take up residence in NSW.¹³

The Canberra Hospital performs the majority of publicly funded colonoscopies performed in the ACT. All colonoscopies performed in the ACT are performed in accredited facilities. Approximately 30% of colonoscopies performed at the Canberra Hospital are completed by trainees under supervision by accredited endoscopists.

CRC data were available from the ACT Cancer Registry (2403 CRC records for the study period including minimum 5 years' follow-up, see [table 1](#)) and the NSW Cancer Registry (46 200 CRC records for the period, [table 1](#)). The principal outcome measure of this study was PCCRCs, defined as CRC diagnosed anywhere in ACT or NSW within 5 years following a complete colonoscopy at Canberra Hospital. All colonoscopies performed at the Canberra Hospital between January 2001 and December 2008 that met inclusion criteria were used to report the incidence rate for PCCRC. In order to determine the incidence rate, we calculated the total person-years

Table 1 Baseline characteristics of the cohort between 2001 and 2008 (9383 procedures in 7818 individuals)

| Case characteristics | n | % |
|----------------------------------|------|------|
| Sex | | |
| Male | 3610 | 46.2 |
| Female | 4208 | 53.8 |
| Age (years) | | |
| <40 | 1474 | 18.9 |
| 40–49 | 1585 | 20.3 |
| 50–59 | 1855 | 23.7 |
| 60–69 | 1542 | 19.7 |
| >70 | 1360 | 17.4 |
| Year of first colonoscopy | | |
| 2001 | 543 | 6.9 |
| 2002 | 1026 | 13.1 |
| 2003 | 1042 | 13.3 |
| 2004 | 929 | 11.9 |
| 2005 | 1061 | 13.6 |
| 2006 | 1048 | 13.4 |
| 2007 | 1047 | 13.4 |
| 2008 | 1122 | 14.3 |
| Findings | | |
| Normal | 3702 | 39.5 |
| Diverticular disease | 1855 | 19.8 |
| Haemorrhoids | 1659 | 17.7 |
| IBD/colitis | 693 | 7.4 |
| Colonic polyps | 3113 | 33.2 |
| First endoscopist | | |
| Non-trainee | 6165 | 65.7 |
| Trainee | 3209 | 34.2 |
| Unknown | 9 | 0.1 |

IBD, Inflammatory bowel disease.

of observation for each patient based on the interval between the date of the colonoscopy and the earliest of the following: the diagnosis date of CRC, date of death or the study census date (census date 10 February 2016). The incidence of PCCRC was computed as the observed number of PCCRC divided by the total person-years of observation.

Patient and public involvement

We included all patients at our centre who had a complete colonoscopy during the recruitment period. The PCCRC incidence rate in a cohort undergoing colonoscopy is a fact that can be shared in the informed consent process with patients undergoing diagnostic colonoscopy.

Data sources

All colonoscopies were reported through proprietary reporting software into a relational database. Patient

identifiers for all procedures were populated from The Canberra Hospital patient administration system (CareSys, Advanced Health and Care, Ashford, UK, until September 2006; thereafter iPM, Healthcare Group, CSC, Banbury, UK).

The ACT Cancer Registry records all cases of cancer diagnosed in ACT residents since 1994 except basal cell carcinomas and squamous cell carcinomas. Pathology laboratories, hospitals and nursing homes in the ACT are required by law to notify the Registry of Cancer in people or human tissues. The NSW Central Cancer Registry maintains records of all cases of cancer diagnosed in NSW residents. The Centre for Health Record Linkage (CHeReL)¹⁴ is a collaboration of partner institutions in ACT and NSW creating a record linkage infrastructure for the health sectors covered by the collaboration and links over 69 million records representing more than 9 million individuals. Record identifiers are included in the Master Linkage Key,¹⁵ which has a false positive rate of 0.3%.¹⁴

To identify CRC cases missed by linkage between the colonoscopy database and the Cancer Registry, we also extracted CRC cases (adenocarcinomas only) for the same period from the Canberra Hospital electronic medical record by search of diagnostic codes C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20 from the International Classification of Diseases (ICD-10) code set. These cases were matched using the hospital patient identification number (PID) as the primary linkage and verified by first name, last name and date of birth. All matches were manually reviewed to ensure that the PID had not been previously assigned.

Cohort at risk

The cohort at risk included all patients who had a complete colonoscopy during the recruitment period between January 2001 and December 2008. The colonoscopy performed before the diagnosis of PCCRC was termed the index colonoscopy. A colonoscopy was considered complete if the proceduralist reported caecal landmarks or intubated the terminal ileum of an intact colon. Cases were excluded after manual record review if the colonoscopy was incomplete and the reason for incompleteness was recorded. We included patients with elevated risk of CRC, such as Lynch syndrome, familial adenomatous polyposis and inflammatory bowel disease, in the cohort.

Case linkage

The ACT and NSW Central Cancer Registry custodians provided record identification numbers for CRC cases for the recruitment period 1 January 2001 to 31 December 2008. ACT and NSW Cancer Registry records matching the CRC subset were then extracted from the Master Linkage Key for the periods of interest. This extract was linked to the colonoscopy records using probabilistic record linkage methods and *ChoiceMaker* software.¹⁶

Data collection

Data were extracted from colonoscopy reports, the electronic medical record and pathology reports. Case characteristics examined were age, gender and indication for colonoscopy. Colonoscopy characteristics examined included date of colonoscopy, the identity of first and (where applicable) second proceduralists, the sedation drug and dose, quality of bowel preparation, caecal and terminal ileal intubation rate (completion rate), the presence of postsurgical anatomy and all diagnoses made. The CRC site was classified as the proximal colon where this was the caecum to the transverse colon. The database was checked for internal validity by individual case review of all cases using the source medical record. Histopathological classification and staging were in accordance with the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC).¹⁷

Determination of mismatch repair defective CRC including Lynch syndrome

Mismatch repair (MMR) deficiency was determined by immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 proteins in the relevant formalin-fixed paraffin-embedded (FFPE) sections, using commercial antibodies (Ventana Medical Systems, Tucson, Arizona, USA). MMR expression status was available for all CRC diagnosed from 1 January 2004 in colon resection specimens but not where biopsy material only was available. BRAF V600E mutation status was determined retrospectively on MLH1-deficient cases from FFPE-extracted tumour DNA by single nucleotide primer extension assay.¹⁸

Statistical methods

Descriptive statistics were used to summarise the data. Fisher exact tests were carried out to explore the differences between groups. ORs for occurrence of PCCRC and non-PCCRC were calculated where indicated.

Kaplan-Meier estimates were used to estimate the 5-year PCCRC risk in this cohort. The time to PCCRC for patients diagnosed with PCCRC was calculated as the time from their last colonoscopy to the time of diagnosis. The time to last follow-up for all other patients was calculated as the time from their last colonoscopy to the census date 10 February 2016, when the linkage with the Cancer Registries was completed.

RESULTS

Cohort characteristics

There were 10 640 colonoscopy procedures carried out at the Canberra Hospital between January 2001 and December 2008. Of these, 3209 were performed by a trainee (first proceduralist) under supervision of an experienced second proceduralist. Sedation for the majority of procedures was administered by a nurse sedationist under direction of the endoscopist with a combination of fentanyl, midazolam and propofol (endoscopist-directed nurse administered propofol sedation). Specialist

anaesthetists provided sedation for patients classed as American Society of Anesthesiologists (ASA) Physical Status III.

Detailed case review of the entire patient group submitted for linkage was performed. A total of 465 procedures in 465 cases with a diagnosis of CRC at the initial colonoscopy were excluded from the cohort for the purposes of survival analysis. After line-by-line analysis of the database for internal agreement, agreement against the source medical record, and inclusion and exclusion criteria, another 792 procedures were excluded from further analysis. These included 166 incomplete procedures due to instrument looping, patient discomfort or bowel redundancy. A total of 101 procedures were excluded due to findings of a shortened postsurgical colon (ileostomy, rectal stump, neoterminal ileum or subtotal colectomy, but not anterior resection). A further 134 procedures were excluded due to incomplete colonoscopy arising from the pathology encountered, including obstructing cancer or other colonic stricture. In 133 cases, an elective short colonoscopy was performed and these cases were also excluded. Another 210 procedures were excluded due to bowel preparation classed by the reporting proceduralist as 'poor', 'unsatisfactory' or 'inadequate' that precluded caecal intubation. Cases were not excluded for poor bowel preparation if caecal intubation was achieved. A further 36 procedures were excluded where difficulties with patient sedation caused incompleteness.

Characteristics of the overall cohort at risk (7818 individuals; 9383 procedures) are summarised in [table 1](#). The average age at the time of the index colonoscopy was 53.6 years (SD 15.7) and 53.3% of the cohort was female. Follow-up ranged from 5 to 13 years (median follow-up, 7.9 years). At colonoscopy, 39.5% (n=3702) were reported as normal, while 33.2% (n=3113) involved polypectomy. Other findings included diverticulosis in 19.8%, haemorrhoids in 17.7% and inflammatory bowel disease in 7.4%.

Results of data linkage

The datasets for linkage are shown in [table 2](#). We submitted a total of 10 854 individuals who had one or more colonoscopy at our centre during the period 1 January 2001 to 31 December 2010 for linkage. This group contained individuals who were later excluded from the final cohort after detailed case review. Total CRC notifications to the ACT Cancer Registry and NSW Central Cancer Registry were 2403 records (notification date 1 January 2001 to 31 December 2013) and 46 200 records (notification date 1 January 2001 to 31 December 2010), respectively ([table 2](#)). Linkage from submitted records to these ACT and NSW CRC notifications detected 384 and 98 CRCs for notification dates of 2001–2013 (ACT) and 2001–2010 (NSW; online supplementary table 1).

Next, cases retrieved from a search of The Canberra Hospital electronic medical records using the relevant ICD-10 diagnosis codes were matched to the colonoscopy database according to a complete match of PID,

Table 2 Datasets used in this study for data linkage

| Data source | Description | Number |
|---|---|----------------------------------|
| Canberra Hospital Gastroenterology and Hepatology Unit colonoscopy cohort | Procedure dates: 1 Jan 2001 to 31 Dec 2013 Subset: Procedure dates 1 Jan 2001 to 31 Dec 2010 | 19 803 records 13 746 records |
| ACT Cancer Registry colorectal cancer subset (ACT CCR) | ACT Cancer notifications: Notification date: 1 Jan 2001 to 31 Dec 2013 Subset: Colorectal cancer notifications: Notification date: 1 Jan 2001 to 31 Dec 2013 | 19 931 records 2 403 records |
| NSW Cancer Registry colorectal cancer subset | NSW cancer notifications: Notification date: 1 Jan 2001 to 31 Dec 2010 Subset: Colorectal cancer notifications: Notification date: 1 Jan 2001 to 31 Dec 2010 | 38 321 records 46 200 records |

ACT, Australian Capital Territory; NSW, New South Wales.

first name, last name and date of birth. A further 55 CRCs were linked that had not been returned from linkage to the ACT or NSW Cancer Registries.

From the total of 537 CRCs, 384 returned from the ACT Cancer Registry, 98 from the NSW Cancer Registry and 55 from the Canberra Hospital electronic medical record, 385 were included in this study after excluding cases that did not have a colonoscopy during the recruitment period 2001–2008, those with a diagnosis of malignant polyp, carcinoid tumour, metastatic malignancy of unknown primary, CRC diagnosed outside NSW or ACT, and cases that could not be verified by pathological or clinical records. A summary of the results of linkage in the study is presented in [figure 1](#).

Reasons for linkage failure

There were 55 cases not returned from linkage to the cancer registries, which were subsequently returned from the Canberra Hospital electronic medical record. Of these 55 cases, 21 cases were included in this study after case review. The principal reasons for linkage failure were migration from the ACT to states other than NSW (n=15), missing identifiers (n=5) and one-to-many links (n=1).

PCCRC incidence

Of the 385 CRC cases returned from database linkage, 15 cases had a colonoscopy at our centre during the recruitment period and were diagnosed 0–60 months after the index colonoscopy, and these cases were defined as PCCRC. There were an additional 19 CRC that met some but not all criteria for PCCRC. In one case, case review revealed that the index colonoscopy failed to reach the

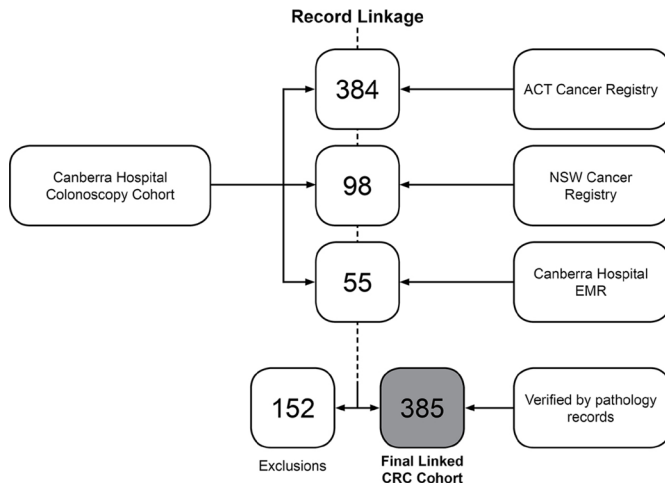


Figure 1 Results of data linkage. Primary linkage between the colonoscopy cohort and the ACT and NSW Cancer Registries by the Centre for Health Record Linkage (CHeReL) yielded 384 and 98 CRCs for notification dates of 2001–2013 (ACT) and 2001–2010 (NSW). An independent match of the colonoscopy database and The Canberra Hospital electronic medical record (EMR) matched 55 CRC to that had not been returned from linkage to the Cancer Registries. From this total of 537 CRCs, 152 were excluded where first colonoscopy fell outside the recruitment period, the CRC was diagnosed outside NSW/ACT or diagnosis of malignant polyp or carcinoid tumour or metastatic malignancy of unknown primary and cases that could not be verified. ACT, Australian Capital Territory; CRC, colorectal cancer; NSW, New South Wales.

caecum. In one case, the index colonoscopy occurred prior to the recruitment period. In seven cases, the diagnosis of CRC was made more than 5 years but less than 10 years after the previous index colonoscopy.¹⁹ There were 10 cases with multiple exclusion criteria.

The total exposure period of 81879 person-years in our cohort resulted in a CRC incidence rate of 4.70/1000 person-years. For PCCRC, the first 5 years following a colonoscopy contributed to total exposure and the PCCRC incidence was 0.384/1000 person-years.

Kaplan-Meier estimates were used to estimate the 5-year PCCRC risk in this cohort. The 5-year PCCRC risk was estimated as 0.192% (95% CI 0.095 to 0.289) (figure 2).

Factors associated with increased risk of PCCRC

Univariate analysis was performed to identify characteristics associated with PCCRC cases (table 3). The presence of diverticulosis at index colonoscopy ($p=0.017$, Fisher's exact test) was associated with PCCRC (table 3). The OR for the presence of diverticulosis and subsequent diagnosis of PCCRC was 3.56 (95% CI 1.29–9.83, $p=0.014$). The number needed to treat (NNT) for the presence of diverticulosis and subsequent PCCRC was 333.

The presence of poor bowel preparation was associated with PCCRC ($p=0.017$, Fisher's exact test). OR for the presence of poor bowel preparation and subsequent diagnosis of PCCRC was 4.19 (95% CI 1.43 to 12.3, $p=0.009$).

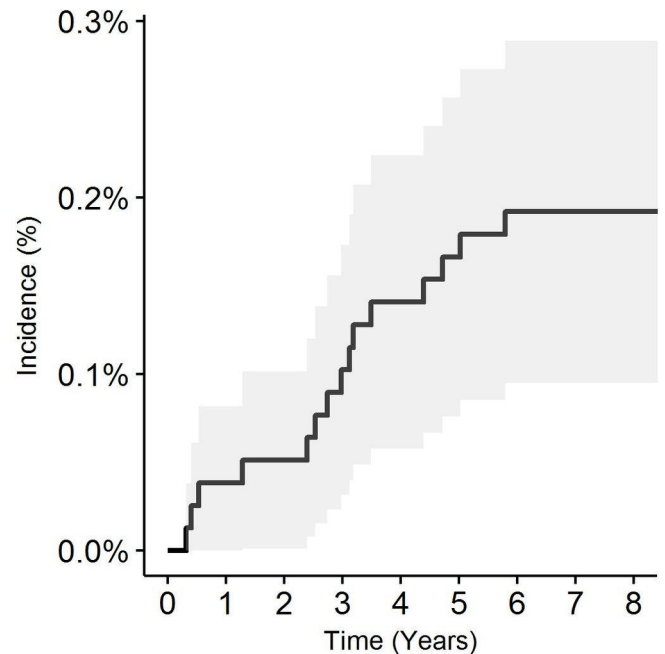


Figure 2 Kaplan-Meier incidence plot (solid line) and 25% CIs (shaded area) of post-colonoscopy colorectal cancer arising in the cohort. The solid line represents patients having colonoscopy at the Canberra Hospital during 2001–2008. Each increment in the Kaplan-Meier plot is an occurrence of post-colonoscopy colorectal cancer.

The NNT for the presence of poor bowel preparation and subsequent PCCRC was 250.

Trainee endoscopists were listed as the first endoscopists of index colonoscopies associated with 53.3% (8/15) PCCRC compared with 46.7% of the rest of the cohort, where the first listed endoscopist was not a trainee ($p=0.170$, Fisher's exact test).

PCCRC characteristics compared with incident colorectal cancers

There were a total of 385 CRC returned from linkage and comprised 258 incident CRC diagnosed at the index colonoscopy. A further 93 CRC cases underwent index

Table 3 Association between index colonoscopy characteristics and occurrence of PCCRC

| Characteristics | OR* | 95% CI | P value | Number needed to treat |
|---|-------|--------------|---------------|------------------------|
| Diverticulosis at colonoscopy and PCCRC | 3.56† | 1.29 to 9.83 | 0.0143 | 333 |
| 'Poor' bowel preparation at colonoscopy and PCCRC | 4.19* | 1.43 to 12.3 | 0.0091 | 250 |

*Compared with group with 'good' bowel preparation.
 †Compared with group with no finding of diverticulosis.
 Bold values highlight significance.
 PCCRC, post-colonoscopy colorectal cancer.

Table 4 Characteristics of PCCRCs compared with incident CRC (n=273)

| Characteristic | PCCRC cases, N (%) | Incident CRC, n (%) | P value |
|--------------------------|--------------------|---------------------|---------------|
| Gender | | | |
| Male | 5 (33.3) | 153 (59.3) | |
| Female | 10 (66.7) | 105 (40.7) | 0.048 |
| Age (years) | | | |
| ≤60 | 5 (33.3) | 74 (28.7) | |
| >60 | 10 (66.7) | 184 (71.3) | 0.699 |
| Unknown | | 5 (1.30) | |
| Indication | | | |
| Diagnostic | 7 (46.7) | 215 (83.3) | |
| Surveillance | 6 (40) | 24 (9.3) | 0.0005 |
| Screening | 2 (13.3) | 16 (6.2) | |
| Unknown | 0 (0) | 3 (0.12) | |
| Diverticulosis | | | |
| Yes | 6 (40) | 43 (16.7) | |
| No | 9 (60) | 215 (83.3) | 0.022 |
| First endoscopist | | | |
| Non-trainee | 7 (46.7) | 176 (68.2) | |
| Trainee | 8 (53.3) | 82 (31.8) | 0.084 |
| Bowel preparation | | | |
| Good | 5 (33.3) | 71 (27.5) | |
| Satisfactory | 5 (33.3) | 123 (47.7) | |
| Poor | 5 (33.3) | 62 (24) | 0.526 |
| Unknown | 0 (0) | 2 (0.78) | |

CRC, colorectal cancer; PCCRC, post-colonoscopy colorectal cancer.

Bold values highlight significance.

colonoscopy after the diagnosis of CRC. There were 34 provisional PCCRC diagnosed after the index colonoscopy and before the study census date. Of these 34 provisional PCCRC, 7 cases were diagnosed 5 years after the colonoscopy and 12 cases did not meet inclusion criteria. A total of 15 cases meeting our criteria for PCCRC were further analysed.

In the overall cohort, 66.7% of cases with PCCRCs were females compared with 40.7% of incident CRCs diagnosed ($p=0.048$, table 4). The mean age of PCCRC cases was 65 years and that of incident CRCs was 68 years. Clinicopathological characteristics of all CRC are summarised in online supplementary table 2. Among the 370 CRC that were not PCCRC, there was one case with mutation-proven Lynch syndrome and one case with mutation-proven familial adenomatous polyposis. There were two cases of Lynch syndrome in the 15 PCCRC cases; however, these were ascertained after the diagnosis of CRC.

CRC were located in the proximal colon in 8 (53.3%) PCCRC compared with 80 (31%) of incident CRC

($p=0.48$). There was no association of PCCRC with histological subtype ($p=0.17$) or with CRC stage ($p=0.57$; online supplementary table 2). Of 15 PCCRC, 7 were detected in individuals who had prior polypectomy; in 2 of these cases, a polyp was removed in the same region of the colon.

One hundred fifty-one CRC cases overall had available MMR expression status during the period (online supplementary table 3). There were no statistically significant differences between PCCRC and incident CRC with respect to abnormal MMR status (30% vs 20.6%; $p=0.48$). BRAF V600E mutation status was assessed in both cases of MLH1-negative PCCRC and 22/29 of other CRCs with absent MLH1 expression. The BRAF V600E mutation was detected in 50% (1/2) of the MLH1-negative PCCRCs and in 82% (18/22) of the MLH1-negative CRCs that were not PCCRCs.

DISCUSSION

Since a comprehensive study reported in 2007 the 'miss rates' for CRC in subjects having colonoscopy,²⁰ it has been accepted that PCCRC comprise a measurable and significant proportion of CRC cases. A recent consensus statement holds that PCCRC is the preferred term for cancers appearing after a colonoscopy in which no cancer is diagnosed.¹⁹ As a quality assurance term, PCCRC refers to CRC detected after any such complete prior colonoscopy. The term 'interval cancer' was recommended for CRC (or other cancer) arising before the next recommended screening or surveillance procedure.

In our study, we followed a cohort of 7818 individuals who underwent 10640 colonoscopy procedures at our centre over the period 1 January 2001 to 31 December 2008, for a minimum of 5 years following the index colonoscopy. We then performed linkage for the detection of subsequent CRC. In this prospective, population-based cohort study, 15 individuals developed PCCRC, resulting in an incidence rate of 0.384/1000 person-years. The 5-year probability of PCCRC was 0.192%.

A significant factor that arose in the study was the number of index colonoscopies that were excluded because of incompleteness, previous surgery, pathology or technical factors. The effect of exclusions was to reduce the overall cohort size and thereby increase the apparent incidence rate. Making these exclusions required line-by-line verification of the endoscopy database and access to source documents. This process is unavailable to studies that use larger volume retrospective data sources.

We also audited case linkage by a search of the electronic medical record for unlinked cases of CRC. We found 21 additional cases of CRC (5% of the total), which had escaped the linkage process, predominantly because the individual had migrated from the jurisdiction during the follow-up period. These cases did however present with CRC to our centre within the jurisdiction. We suspect these 21 cases to be a minority of the occasions of linkage failure in this study. While our study benefited from the

| Author, Year, (reference) | Period & Country | Design | Definition of interval CRC | Data Sources | Primary Data set | Methods of Record linkage | Interval CRC rate |
|---------------------------|--|---|--|--|--|---|--|
| Baxter 2011 | 2000-2005 Ontario, Canada | Retrospective cohort, administrative database record linkage | CRC diagnosis 6-36 months after colonoscopy | Ontario Health Insurance Plan (OHIP) Database (physician claims database to identify colonoscopy) Canadian Institute for Health Information (ICD-9 diagnosis codes) Ontario Cancer Registry | Ontario Cancer Registry | OHIP number is used to match Ontario Cancer Registry to other records. | 9% |
| Brenner 2012 | 2003-2007, Rhine-Neckar region, Germany | Prospective, case-control, 22 hospitals participated | CRC diagnosis 1-36 months after negative colonoscopy | 1) Screen-detected CRC database 2) Incident cancer database: mostly surgical patients Group 1 and 2 interviewed in hospital. For any history and date of previous colonoscopy, some validation done with physician records | Screen-detected and incident CRC database | N/A | 1.8% |
| Brenner 2012 | 2003-2007, Rhine-Neckar region, Germany | Prospective, case-control, 22 hospitals participated | CRC diagnosis 1-36 months after colonoscopy and polypectomy | 1) Screen-detected CRC database 2) Incident cancer database: mostly surgical patients Group 1 and 2 interviewed in hospital. For any history and date of previous colonoscopy, some validation done with physician records | Screen-detected and incident CRC database | N/A | 2.3% |
| Bressler 2007 | 1997-2002 Ontario, Canada | Retrospective cohort, administrative database record linkage | CRC diagnosis 6-36 months after colonoscopy | Ontario Health Insurance Plan Claims Database Canadian Institute for Health Information Ontario Cancer Registry | Ontario Cancer Registry | Health Care Number from Ontario Cancer Registry used to match OHIP cases | 3.4% |
| Cooper 2011 | 1994-2005, USA | Retrospective cohort, administrative database record linkage; Age limited to >69 | CRC diagnosis 6-36 months after colonoscopy | SEER/Medicare database (contains separate data from files of providers, outpatients and inpatient facilities) | SEER | Shared identifier | 7.2% |
| Erichsen 2013 | 2000-2009, Denmark | Retrospective cohort; population-based with record linkage | CRC diagnosis 12-60 months after colonoscopy | Danish National Registry of Patients (tracks hospitalisations and outpatient visits) to get colonoscopy exams Danish Cancer Registry | Danish Cancer Registry | Same Civil Registration Number (10 digit unique ID number) in both data sets | 2.8% |
| Farrar 2006 | 1991-2004, Minneapolis, Minnesota, USA | Retrospective cohort; population-based; Veterans only | CRC diagnosis 60 months after complete colonoscopy | Minneapolis Veterans Affairs Medical Centre Cancer Registry Minneapolis Veterans Affairs Medical Centre Medical Records Department | Minneapolis Veterans Affairs Medical Centre Cancer Registry | Manual lookup of medical records | 5.4% |
| Ferrandez 2010 | 2000-2005, Hospital Clinic Lozano Blesa Zaragoza, Spain | Retrospective cohort | CRC diagnosis 36 months after colonoscopy | Colonoscopy reports at a single centre | Colonoscopy reports (Electronically generated reports not used; open boxes generate nonstandardized reports – some data lacking) | N/A | 7% (27/386) |
| Horiuchi 2011 | 2005-2009, Showa Inan General Hospital, Japan | Retrospective cohort | CRC diagnosis 60 months after negative colonoscopy | Endoscopy database at a single centre (2500 colonoscopies/year performed) | Endoscopy database | N/A | 4.3% (9/211) |
| Huang 2012 | May 1976 - June 2008, Nanfang Hospital, Guangzhou and Affiliated Hospital of Inner Mongolia Medical College, Huhhot, China | Retrospective cohort | CRC diagnosis 60 months after complete colonoscopy and polypectomy | Patient record system and medical records at two hospitals | patient record system and medical records | N/A | Among 1,794 patients, 14 had interval CRC before scheduled colonoscopy |
| Kaminski 2010 | Oct 2000- Dec 2004, Poland | Retrospective cohort; population-based; 40-66 years old | CRC diagnosis before scheduled colonoscopy | National Colorectal Cancer Screening Program Database (40-66 yrs old average risk) Regional and National Cancer Registries | National Colorectal Cancer Screening Program Database | Used personal identifiers from CRC Screening Database to search Cancer Registries | 42 interval CRC during 188,788 person-year |
| Le Clercq 2014 | 2001-2010; South Limburg, the Netherlands | Retrospective cohort; population-based with record linkage; 3 hospitals covers for 650000 inhabitants | CRC diagnosis 12-60 months after colonoscopy | PALGA Database (pathology database); Medical record review at each of the 3 hospitals | PALGA Database verified by Cancer Registry | N/A | 2.9% |
| Samadder 2014 | 1995-2009; Utah, United States | Retrospective cohort; population-based with record linkage | CRC diagnosis 6-60 months after colonoscopy | Univ of Utah Healthcare and Intermountain Healthcare EMR procedure codes Utah Cancer Registry | Univ of Utah Healthcare and Intermountain Healthcare EMR procedure codes | Probabilistic record linkage | 3.4% (6-36m) 6% (6-60m) |
| Singh 2010 | 1992-2008; Manitoba, Canada; | Retrospective cohort; population-based with record linkage; 50-80 years old | CRC diagnosis 6-36 months after colonoscopy | Manitoba Health Databases: (1) MH Physicians Billing Claim Database (to identify colonoscopy; colonoscopy reports not visualised) (2) MH Population Registry (migration status of individuals) (3) MH Hospital Discharge Database (hosp discharges) | Manitoba Health Databases | Deterministic using Patient Health Identification Number to Manitoba Health Cancer Registry | 7.9% |

Figure 3 Interval cancer rates expressed as a proportion of all colorectal cancer (CRC) from published studies

Table 5 Incidence rates per 1000 patient-years of PCCRC from eight published articles during 2000–2017 and the present study

| Study | Total number of subjects | Follow-up (years) | Cases of PCCRC | Incidence per 1000 person-years |
|--------------------------------------|--------------------------|--------------------|----------------|---------------------------------|
| Alberts <i>et al</i> ³³ | 1303 | 35 months (median) | 9 | 2.4 |
| Citarda <i>et al</i> ³⁴ | 1693 | 10.5 (mean) | 6 | 0.4 |
| Robertson <i>et al</i> ³⁵ | 2915 | 3.7 (mean) | 19 | 1.7 |
| Pabby <i>et al</i> ³⁶ | 2079 | 2.79 (mean) | 13 | 2.2 |
| Lieberman <i>et al</i> ³⁷ | 1171 | 5.5 (mean) | | 1.7 |
| Leung <i>et al</i> ³⁸ | 1297 | 10 (median) | 9 | 1.2 |
| Belderbos <i>et al</i> ³⁹ | 107 744 | 5.1 (mean) | 1031 | 1.88 |
| Samadder <i>et al</i> ⁴⁰ | 131 349 | | 171 | 0.55 |
| Present study | 7818 | 10.52 (mean) | 15 | 0.38 |

PCCRC, post-colonoscopy colorectal cancer.

peculiarities of the ACT's geography, we have no information as to whether unlinked cases of CRC are more or less likely to be PCCRC.

A remarkable feature of interval CRC and PCCRC studies is the variation between PCCRC rates expressed as a proportion of all CRC, in different studies, from as low as 0.8%²¹ to as high as 9%.¹¹ Among studies that used a single identifier to link two databases (figure 3),^{11 20 22–32} the rate of PCCRC ranged from 2.8% to 9%.^{11 20 23 25 28} Two studies reporting from the same jurisdiction yielded different PCCRC rates of 3.4% and 9%.^{11 20} It follows that these variations are due less to differences in CRC biology or technical excellence in colonoscopy than to methodological issues. In some retrospective studies,^{26 27} where the PCCRC rate appears to be lower (1.8%–2.3%), ascertainment of a prior colonoscopy was based on self-reporting by participants with recently diagnosed CRC. One study reporting a PCCRC rate of 2.9%²² was performed by retrieving regional CRC records from a national pathology database and matching these to records from three regional hospitals to obtain a history of colonoscopy in the 5 years prior to diagnosis. The method of data linkage was not reported.

Alternatively, PCCRC have also been reported in cohort studies with the incidence rates expressed as a survival function; typically, 1.7–2.4 cancers per 1000 person-years of observation (table 5).^{33–40} Most have been interval CRC studies including only subjects with adenoma at index colonoscopy, which would be expected to yield a higher incidence rate of PCCRC than we found in our cohort.

Since we were limited to Cancer Registry notifications to the end of 2013 (for ACT cases), and the end of 2010 (for the smaller cohort of NSW cases), the follow-up period in the study population was 5–13 years, with a median follow-up period of 7.9 years. Cancer Registry data (online supplementary table 1) were available until 32 months prior to the linkage date (ACT Registry) and 68 months prior to the linkage date (NSW Registry). This

limited the size of the cohort that could be assessed for PCCRC with a follow-up of 5 years.

We report that linkage failure can be detected and should be addressed in PCCRC studies. We identified 21 cases of CRC that were not returned from data linkage, although none of these cases were PCCRC. Possible causes of linkage failure include missing or ambiguous identifiers, returning 'one-to-many' outputs. In order to identify linkage failure, we also matched CRC cases from our hospital medical record system.

We confirm the finding of others^{20 23 25 28} that a characteristic strongly associated with PCCRC was a finding of diverticular disease at index colonoscopy. On the contrary, the OR for patients with diverticular disease and a subsequent diagnosis of PCCRC was 3.56. The NNT for the presence of diverticulosis and subsequent PCCRC was 333. In order to achieve a halving of the PCCRC ratio, for example, through 3 yearly surveillance colonoscopy, 666 patients would be required to undergo enhanced screening for each PCCRC avoided. Our study also found that poor bowel preparation increased the risk of PCCRC with an OR of 4.2.

We also confirmed the reported associations of PCCRC with female gender,^{11 19 22 27} but not with age,^{20 23–25} proximal tumour location^{20 24–26 28} or family history of CRC.^{22 24} There was a non-significant association between index colonoscopies performed by a trainee and subsequent PCCRC. These negative findings may be due to type II error.

The reported higher frequency of right-sided PCCRC may arise from these CRC being more biologically aggressive or alternatively from right-sided precursor lesions being more likely to be undetected or incompletely removed at prior examinations. The former explanation is supported by the observation of a higher frequency of abnormal MMR expression in PCCRC.⁴¹ However, recently Soong and colleagues performed analysis of cancer gene mutations and copy number variation by

targeted exon capture and deep sequencing in interval CRC detected at a single institution.⁴² When interval CRC were compared with incident CRC matched to age, gender and tumour location, there were no appreciable differences in any classifying molecular alteration in interval CRCs, pointing to a similar biological behaviour of interval and incident CRC. Soong *et al* concluded that interval PCCRC were therefore likely to result from missed or recurrent lesions. We did not find a significant difference in abnormal expression of MMR proteins between PCCRC and incident cancers. We found 2 of 15 PCCRC were detected in individuals who had prior polypectomy in the same region of the colon.

We note that our study design optimises detection of PCCRC arising in our cohort. We did not detect all PCCRC occurring during the period. Some CRC diagnosed during the period of this study may have been PCCRC if an index colonoscopy had been performed elsewhere within the previous 10 years. All these cases were excluded from our cohort but were used as a comparator group for analysis of factors associated with PCCRC. The degree to which this influences our comparisons was not ascertained.

Our institution performs the majority of publicly funded colonoscopies performed in the region. We have no data comparing our patient population with the overall regional population. The ACT population is comparable to the broader Australian population, but to a significant degree is more affluent and more likely to hold tertiary education qualifications, and is somewhat less linguistically and culturally diverse.⁴³ With these caveats, we believe our results to broadly reflect the Australian population.

One factor distinguishing our facility from other local facilities was that trainees completed 34% of index colonoscopies in the cohort. There was a non-significant trend for these cases to be associated with PCCRC.

We conclude that in the Australian setting, in a cohort undergoing colonoscopy, using probabilistic record linkage and individually curated cases: the 5-year incidence rate for PCCRC was estimated as 0.4 per 1000 person-years. These data show the 'real world' accuracy of colonoscopy for CRC exclusion. These data should be shared with patients in the informed consent process before screening and diagnostic colonoscopy.

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