Factors associated with colorectal cancer occurrence after colonoscopy that did not diagnose colorectal cancer

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Abstract: Background and Aims: Up to 6% of colorectal cancers (CRC) are diagnosed within 5 years of a colonoscopy that did not diagnose CRC (post-colonoscopy colorectal cancer, PCCRC). PCCRC and associated risk factors were examined within a national hospital episode database.

Methods: A retrospective case-control study of all adult colonoscopies recorded in Hospital Episode Statistics (HES) between 2003-2009 in England. PCCRC cases underwent colonoscopy 6-60 months before diagnosis; controls had not undergone colonoscopy 6-60 months before diagnosis. Multivariate logistic regression analysis examined associations with PCCRC.

Results: 1,439,684 colonoscopies were analysed, including 67,202 CRC and 8147 (12.1%) PCCRC cases. Multivariate analysis revealed that female gender (odds ratio 1.13 (95% CI 1.08-1.19), p<0.001), older age (70-74 years) (1.09 (1.00-1.18), p=0.039), increased co-morbidity (Charlson index 5+) (1.16 (1.05-1.28), p<0.003) and right sided CRC (1.17 (1.11-1.23), p<0.0001) were associated with PCCRC. Emergency colonoscopy (0.54 (0.59-0.69), p<0.0001) was negatively associated with PCCRC. More PCCRC subjects developed metastases within 12 months and less underwent surgery (0.33 (0.32-0.35), p<0.0001) or chemotherapy (0.66 (0.62-0.69), p<0.0001). PCCRC rates varied twofold between providers, and was associated with medium volume providers compared with high volume (1.13 (1.01-1.27), p=0.035). The PCCRC rate fell from 13.8% in 2003 to 11.9% in 2009.

Conclusions: PCCRC occurred in 12.1% of CRC patients between 2003 and 2009. PCCRC was associated with female gender, older age, increased co-morbidity, right sided CRC, elective procedures and colonoscopy volume. PCCRC was associated with worse outcomes.

Cover Page (Title, all author names, affiliations, and degrees, corresp author contact information)

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Abstract

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Methods: A retrospective case-control study of all adult colonoscopies recorded in Hospital Episode Statistics (HES) between 2003 and 2009 in England. PCCRC cases underwent colonoscopy 6 to 60 months before diagnosis; controls had not undergone colonoscopy 6 to 60 months before diagnosis. Multivariate logistic regression analysis examined associations with PCCRC.

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Conclusions: PCCRC occurred in 12.1% of CRC patients between 2003 and 2009. PCCRC was associated with female gender, older age, increased co-morbidity, right-sided CRC, elective procedures, and colonoscopy volume. PCCRC was associated with worse outcomes.

Introduction

Colonoscopy is the criterion standard for diagnosing, screening and surveillance for CRC. In England, the setting of national standards for colonoscopy and accreditation of endoscopy units has resulted in an improvement in auditable colonoscopy standards over the last decade.[1] The same period has also coincided with an increase in 5-year survival after CRC diagnosis from 47.8% to 53.6%.[2] However, 2.6% to 6.0% of CRC patients have previously been reported to be diagnosed within 5 years of a colonoscopy that did not detect cancer. These events are termed post-colonoscopy colorectal cancer (PCCRC).[3, 4, 5] It has been proposed that PCCRC may have a different cell biology from other CRC with more aggressive and rapidly growing tumors.[6, 7] However, 2 recently published North American studies concluded that this did not apply to the majority of PCCRC, with around two-thirds of PCCRC a result of missed lesions or incomplete polypectomy.[4, 8]

Given the improvements in colonoscopy over the past decade in England, we have examined the impact on PCCRC in a national hospital episode database and associated risk factors for these events.

Methods

Data sources

Hospital Episode Statistics (HES) is an administrative database that records information on all elective and emergency care episodes in National Health Service (NHS) hospitals in England.[9] Each care episode record includes demographic, admission, diagnoses and procedures data. Diagnoses are coded using International Classification of Diseases version 10 (ICD-10) and procedures are coded using Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision (OPCS-4). HES is linked to Office for National Statistics (ONS) mortality records, which include date of death and causes of death recorded on death certificates. The NHS provides comprehensive healthcare coverage for the UK population, with the vast majority of colonoscopies performed in the UK by a NHS provider.[1]

Subject definitions

All subjects over the age of 18 years undergoing colonoscopy between April 2003 and March 2009 were identified from HES. Colonoscopy and CRC were defined by OPCS-4 *(appendix 1)* and ICD-10 codes *(appendix 2)* respectively. Subjects with a CRC diagnosis before the first episode of colonoscopy and subjects with a diagnosis of inflammatory bowel disease (IBD) were excluded from the analysis to avoid confounding through surveillance.

Recording of a CRC diagnosis in HES records may be delayed by a few weeks from the date of the diagnostic colonoscopy code.[10, 11] For the purpose of this study, the diagnosis date was therefore defined as the first colonoscopy code during the 6 months before the first CRC coding episode in HES or mortality records[10, 12], or the first CRC episode for those subjects who did not have a colonoscopy during this 6-month period due to being diagnosed through an alternative method, eg, barium enema, CT colonography or flexible sigmoidoscopy. Subjects undergoing colonoscopy 6 to 60 months before subsequent CRC diagnosis were identified as PCCRC cases. These cases were further classified as PCCRC 6 to 12 months (colonoscopy 6 to 12 months before CRC diagnosis); PCCRC 12 to 36 months (colonoscopy 12 to 36 months before CRC diagnosis) and PCCRC 36 to 60 months (colonoscopy 36 to 60 months before CRC diagnosis). For patients who had more than one colonoscopy 6 to 60 months before CRC diagnosis, data from the most recent colonoscopy was used for analysis. Controls were subjects who had not undergone colonoscopy in the period 6 to 60 months before CRC diagnosis. Colonoscopies from 2003 to 2009 were studied to ensure all subjects had at least 5 years of follow-up within HES. The PCCRC rate was calculated from the number of PCCRC subjects divided by the sum of PCCRC subjects and controls.[13]

Validation of colonoscopy and colorectal cancer populations

To assess the validity of the HES colonoscopy population, the number of colonoscopies between 2007 and 2010 at University Hospital Birmingham (UHB) was extracted from endoscopy records (Unisoft Medical Systems, Enfield, Middlesex, UK) and compared with the number of colonoscopies recorded in HES for UHB. To assess the validity of a CRC

diagnosis in HES using the study methodology, the number of HES CRC cases was compared with the number of CRC cases diagnosed in England from the National Cancer Intelligence Network (NCIN)[14] from 2002 to 2011. Finally, the rate of surgery in the HES CRC population was compared with rate of surgery in the National Bowel Cancer Audit between 2008 and 2011.[15, 16, 17]

Study variables

Subject demographics

Study variables were extracted from coding at the time of PCCRC colonoscopy in cases and diagnostic colonoscopy or first CRC episode in controls. Ethnicity was identified from HES demographic fields and grouped into White or White British, Asian or Asian British, Black or Black British, Chinese, Mixed and other ethnic groups.

Co-morbidity

The Charlson co-morbidity index was calculated using ICD-10 codes for secondary diagnoses, excluding metastatic disease, and divided into 3 categories: 0 (no co-morbidity), 1 to 4 (low co-morbidity) and 5 or greater (high co-morbidity).[18]

Socio-economic status

Deprivation was assessed using the Index of Multiple Deprivations 2007, which is an aggregate score for each English catchment area. Subjects were linked to their corresponding catchment area by postcode of residence and associations with deprivation were analyzed in quintiles, with quintile 1 being the most deprived.

Colorectal cancer variables

CRC site was classified based on the first CRC coding episode into right sided, left sided, and unspecified *(appendix 3)*. Coding records of initially unspecified site CRC were examined and if a more specific code had been used subsequently, this was used to determine the CRC site. Colonic polyps were identified from ICD-10 codes *(appendix 4)*.

Distant metastases were identified by ICD-10 codes (*appendix 5*) up to 12 months from diagnosis date and were used as a surrogate marker of CRC stage at diagnosis, as Dukes' staging is not recorded in HES. Codes for metastases can occasionally be miscoded as a primary neoplasm (eg, lung), and therefore primary malignancy codes were also used, provided that they were recorded in the 12 months subsequent to CRC diagnosis *(appendix 5)*. Surgery and chemotherapy were identified by respective OPCS-4 codes (*appendix 6*).

Survival analysis

Survival analysis adjusted for gender, age, deprivation, and co-morbidity was calculated from the CRC diagnosis date of PCCRC cases and controls using date of death from ONS. Subjects who were not diagnosed by colonoscopy were not included to avoid potential lead time bias due to the method of determining date of diagnosis from HES.

Provider variables

For the purpose of this study, all endoscopy units operating within the same NHS organisation were analysed as a single provider. Individual providers were stratified by colonoscopy volume, bowel cancer screening program (BCSP) status and the percentage of CRCs diagnosed during an emergency rather than an elective episode to determine if there was an association with PCCRC. Colonoscopy volume was determined from the total number of colonoscopies performed during the study period at each provider and separated into tertiles. A BCSP accredited provider had at least one endoscopy unit accredited with BCSP status by the end of the study period. The percentage of CRCs diagnosed as an emergency at a provider was the ratio of CRCs diagnosed during an acute (unplanned) admission divided by all CRCs, including CRCs diagnosed during an elective episode.

Ethics

As only pseduonymized information was used in this study, ethics approval was not necessary. HES data are available under a data-sharing agreement for the purposes of service evaluation.

Statistical methodology

Statistical analysis was carried out with STATA SE v13.1 (Statacorp LP, Tex, USA). Analysis of variance and χ^2 tests were used to compare differences in continuous and categorical variables respectively. Associations with PCCRC were examined by univariate and multivariate logistic regression. A multivariate model was constructed to determine associations with PCCRC after adjusting for gender, age, Charlson co-morbidity index, procedure type (emergency or elective), CRC site (left side of colon or right side of colon), metastases, and procedure year. For tests of significance, p values <0.05 were considered significant. All odds ratios, 95% confidence intervals, and associated p values are the result of multivariate analysis unless stated otherwise. Unadjusted Kaplan-Meier analysis and Cox proportional hazards modeling after adjustment for gender, age, deprivation, and co-morbidity were used to compare survival in PCCRC cases and controls.

Results

Study cohort

Between April 2003 and March 2009, 1,439,684 colonoscopies were identified and 67,202 subjects were diagnosed with CRC during this period. Out of the 67,202 CRC subjects, there were 8147 (12.1%) PCCRC subjects: 1796 (2.7%) PCCRC 6 to 12 months; 3772 (5.6%) PCCRC 12 to 36 months, and 2579 (3.8%) PCCRC 36 to 60 months. A total of 59,055 CRC subjects had not had a colonoscopy between 6 and 60 months before CRC diagnosis and served as controls. Overall, 0.66% or 1 in every 150 subjects developed PCCRC after a colonoscopy that did not diagnose CRC.

Validation of colonoscopy and colorectal cancer populations

The total number of colonoscopies carried out between 2007 and 2010 at UHB was 8708 and 8292 colonoscopies (95.2%) were coded in HES for UHB for the equivalent 4-year period. The CRC population was validated by comparing CRC cases recorded in HES (315,515) to CRC cases reported from 2002 to 2011 by NCIN (312,984)[14], showing a concordance of over 99%. The CRC population was further validated by comparing the 70.4% surgical rate for CRC from HES with the National Bowel Cancer Audit, which reported that 75.7% of CRC patients enrolled in the audit underwent surgery between 2008 and

2011.[15, 16, 17] All of the validation processes showed a good correlation between HES data and independent data sources, suggesting the study methodology was valid.

Subject characteristics

The characteristics of cases with PCCRC and CRC controls are shown in Table 1. PCCRC subjects (mean age 70.7 ± 11.4 years) were older than controls (mean age 70.2 ± 11.4 years)($p<0.001$). The risk of PCCRC appeared to increase with age on univariate analysis, but only subjects aged 70 to 74 were associated with PCCRC compared with subjects under 60, after adjusting for confounding factors. PCCRC subjects were more likely to be female. Subjects with the most co-morbidities (Charlson co-morbidity index of 5 or greater) were associated with PCCRC. PCCRC was not associated with differences in ethnicity or deprivation.

Colonoscopy variables and findings

The influence of colonoscopy variables and findings on PCCRC are shown in Table 2. The majority of CRC were diagnosed during an elective colonoscopy. However, being diagnosed during an emergency colonoscopy reduced the risk of PCCRC nearly by half. There was minor increased risk of PCCRC on univariate analysis in colonoscopies carried out at the weekend compared with during the week.

PCCRC was more likely to be associated with CRC in the right side of the colon. Colonic polyps were coded in 21.6% of the colonoscopies that did not detect CRC in the PCCRC group. Polypectomy was coded in a further 18.9%. On univariate analysis, this was higher than both the recorded polyp rate of 9.8% (2.52 (95% CI, 2.39-2.65), $p<0.0001$) and polypectomy rate of 11.3% (1.82 (95% CI, 1.72-1.92), $p<0.0001$) from all colonoscopies during the study period. Furthermore, the polyp and polypectomy rates were both higher in the PCCRC 6 to 12 months group on univariate analysis, than in the PCCRC 12 to 36 months ($p<0.0001$), and PCCRC 36 to 60 months ($p<0.0001$) groups.

Colorectal outcomes and survival

The prevalence of metastatic disease within 12 months of CRC diagnosis in PCCRC cases and controls are shown in Table 3. PCCRC cases were up to twice as likely to be diagnosed with

lung, peritoneal, and bone metastases within 12 months of CRC diagnosis. However, lymph node metastases were more prevalent in controls than PCCRC cases, suggesting coding bias related to the increased rate of surgery in control subjects described later.

On univariate analysis, PCCRC cases were less likely to undergo surgery compared with controls (0.33 (95% CI, 0.32-0.35), p<0.0001) or chemotherapy (0.66 (95% CI, 0.62-0.69), p<0.0001). Overall survival was also worse in PCCRC subjects compared with controls, with a median survival of 5.8 years in controls compared with 2.1 years in the PCCRC 6- to 12-month group, 2.0 years in the PCCRC 12- to 36-month group, and 3.5 years in the PCCRC 36- to 60-month group (figure 1). after adjusting for age, gender, co-morbidity, and deprivation, survival outcomes remained worse for PCCRC subjects with a hazard ratio of 1.17 (95% CI, 1.10- 1.24)(p<0.0001), 1.26 (95% CI, 1.20-1.31)(p<0.0001) and 1.20 (95% CI, 1.13-1.27)(p<0.0001) for the PCCRC 6 to 12 months, PCCRC 12 to 36 months, and PCCRC 36 to 60 months respectively when compared with controls.

Individual provider variables

The influence of provider variables on PCCRC are shown in Table 4. There was a more than twofold variation in PCCRC rates between individual providers in England during the study period (figure 2). On univariate analysis, medium colonoscopy volume providers and low volume providers were both more likely to be associated with PCCRC than high volume providers. after adjusting for other variables in the multivariate model an association with medium volume providers remained. BCSP accreditation status and the percentage of CRC diagnosed as an emergency were not associated with an increased risk of PCCRC.

PCCRC rates over time

The number of colonoscopies recorded in HES has increased by almost 2-fold over the study period. Despite the increase in colonoscopy numbers performed year on year, the annual rate of PCCRC has steadily fallen over the study period (p<0.0001)(figure 3). The annual PCCRC rate decreased from 13.8% in 2003 to 2004 to 11.9% by the end of study period in 2008 to 2009 with the reduction seen mainly in the PCCRC 6- to 12-month and PCCRC 12- to 36-month groups.

Discussion

The overall PCCRC rate of 12.1% in 67,202 subjects in England between 2003 and 2009 appears higher than previously published figures. However, some previous studies have calculated the PCCRC rate by only including CRC subjects with a colonoscopy up to 36 months before diagnosis and the comparable figure from the present study is 8.3%. A Canadian study of 14,064 CRC subjects reported a PCCRC rate of 9.0% between 2000 and 2005.[12] Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database in the USA, a PCCRC rate of 7.2% was reported between 1994 to 2005 from a study of 57,839 CRC subjects.[19] A further population based study from Utah, USA, with 2659 CRC subjects between 1995 and 2009 described a PCCRC rate of 6% when subjects with a colonoscopy up to 60 months before CRC diagnosis were included.[4] In Europe, 2 recent studies have reported much lower PCCRC rates. A Danish population based study between 2000 to 2009 included 37,044 CRC subjects and concluded that only 2.7% of CRC subjects have had a colonoscopy that failed to diagnose CRC 1 to 5 years before diagnosis.[5] A second study from the Netherlands analyzed 5107 CRC subjects between 2001 to 2010 from three providers and found a PCCRC rate of only 2.9% for subjects with a colonoscopy up to 60 months before CRC diagnosis.[20] In addition to potential variations in subject and colonoscopy factors between the difference studies, the wide range of reported PCCRC rates are likely to be contributed to by methodological differences.[13]

In the present study, PCCRC was associated with older subjects, female gender, an increased number of co-morbidities and right-sided CRC, which is in keeping with findings from other studies of PCCRC. [3, 12, 19, 21] The association between increasing age and PCCRC was less marked on multivariate analysis and this may relate to confounding from increasing co-morbidity in the elderly. Elderly patients are more likely to have inadequate bowel preparation, thus reducing mucosal visualisation and detection of polyps and early CRC.[22, 23] Female patients are more likely to have had previous abdominal and pelvic surgery, which may increase the technical difficulty of colonoscopy and impair patient tolerance, reducing the cecal intubation rate.[24] In addition to factors that have an adverse effect on cecal intubation rate, right-sided CRC are more likely to arise from flat, non-polypoid

adenomatous lesions[20, 25] that poor bowel preparation may make difficult to detect. This will contribute to the association of right-sided CRC with PCCRC.

Over a fifth of PCCRC subjects had colonic polyps or polypectomy coded during the most recent colonoscopy before CRC diagnosis. This is higher than the average polypectomy rate in all colonoscopy procedures during the same period. Furthermore, polyp and polypectomy coding rates were highest in the PCCRC 12- to 36-month group. Prior polypectomy has been reported to double the risk of PCCRC[19], with up to 19% of CRCs occurring in the same anatomic segment as a previously resected adenoma.[8] Paradoxically, colonoscopists with higher polypectomy rates have been reported to be associated with a lower risk of PCCRC[12, 19], presumably as they detect more polyps and remove them more completely than other colonoscopists. Incomplete polypectomy, or inadequate biopsy sampling of polyps, is therefore a key modifiable risk factor for PCCRC and ensuring adequate follow-up and assessment after polypectomy may reduce PCCRC rates.

PCCRC subjects appeared to have worse outcomes in terms of both treatment after diagnosis (surgery and chemotherapy) and overall survival. Previous studies have reported no survival difference between PCCRC subjects and controls[5, 21] with one recent study even reporting a survival benefit in the PCCRC subjects, which was likely to be due to earlier CRC stage at diagnosis in the PCCRC subjects.[4] In the current study, PCCRC subjects were older, had greater co-morbidities and were more likely to present with distant metastases within 12 months of diagnosis compared with controls. All these factors contributed to the reduced rates of curative surgery or palliative chemotherapy for PCCRC subjects and will have contributed to worse survival. Adjusting the survival analyses for differences in ages, gender, co-morbidity and deprivation still revealed worse survival for PCCRC subjects and, at least in England, PCCRC is clearly associated with worse survival. Survival in PCCRC subjects would have been potentially better if earlier opportunities to diagnose their CRC had been taken.

Previous studies have reported that PCCRC was not associated with endoscopist procedure volume[12] and that higher colonoscopy volumes may even be positively associated with PCCRC surprisingly.[19] In the current study, there was a large variation in PCCRC rates

between individual providers across England but PCCRC appeared to be associated with lower colonoscopy volume providers. This result should be interpreted with caution. We did not have access to colonoscopy quality indicators such as cecal intubation and adenoma detection rates that are likely to be potentially more important factors in PCCRC incidence.

Colonoscopy undertaken during an emergency admission covered 10% of procedures examined and was associated with a lower risk of PCCRC at 9% compared with 14% for elective procedures. Patients presenting as an emergency may have more advanced colorectal cancer and therefore a lower chance of PCCRC.

The annual PCCRC rate in England has fallen steadily over the study period from 13.8% to 11.9%, at least partly due to improving colonoscopy standards over the corresponding time period. In 2003, a multi-regional audit in England including 9223 colonoscopies reported that mean cecal intubation rate was only 76.9%.[26] A subsequent national audit in 2011 of 20085 colonoscopies found that the cecal intubation rate had improved to 92.3%.[1] The PCCRC rate is likely to continue to improve in recent years given changes in colonoscopy practice, including the recognition of the importance of minimum withdrawal times [27], bowel preparation improvements[28], and better endoscopic recognition of sessile serrated polyps[25], subsequent to the study period.

The use of a national hospital dataset enabled us to undertake one of the largest PCCRC studies to date, including the vast majority of colonoscopies performed during a period of rising colonoscopy standards. The quality of diagnostic and procedural coding in HES has been previously investigated and there was a high concordance when compared with independent national data sources.[1, 10, 29] However, we did not have the opportunity to link our HES dataset directly to cancer registry data due to restrictions under which the data is held and therefore, in order to validate the methodology chosen, colonoscopy and CRC populations were compared with national cancer databases and a local data sample and revealed a good correlation. The completeness and accuracy of coding in HES is still a potential source of concern. For example, the diagnosis date may not be recorded accurately in HES due to the need for histological confirmation before CRC coding and therefore a colonoscopy within 6 months of CRC coding had to be considered the diagnostic

procedure. There are also limitations in HES concerning coding of colonoscopy procedures, polyps, polypectomy, presence of metastases, surgery and chemotherapy and the figures included may be an over or under estimate, though this is likely to affect PCCRC cases and controls equally. A further limitation is that key procedure information such as the bowel preparation quality, sedation doses, colonoscopist grade and specialty, extent of examination, completeness of polypectomy, and number of biopsy specimens taken are not recorded in HES and all may influence the PCCRC risk. Furthermore, due to the HES coding hierarchy, indication, presence of diverticular disease and history of abdominal or pelvic surgery may not be coded, partly due to under-reporting by colonoscopists when significant pathology or CRC are found and again each may be important risk factors for PCCRC. As HES does not record polyp histology or the International Classification of Diseases for Oncology (ICD-O) codes, the lack of data on polyp and CRC histology and Duke's staging further limits analysis of potential causes of PCCRC (de novo CRC, incomplete adenoma resection, missed lesion or biopsy failed to detect CRC), and survival in PCCRC subjects.

In conclusion, the PCCRC rate was 12.1% in England between 2003 and 2009. PCCRC was associated with older age, female gender, increasing co-morbidity, procedure related factors (elective procedures and right-sided CRC), and provider colonoscopy volume. Despite the encouraging fall in annual PCCRC rate over the study period, the PCCRC rate should be a routinely measured endoscopy unit colonoscopy quality marker, and potentially avoidable risk factors for PCCRC should be addressed.

Table 1. The characteristics of post-colonoscopy colorectal cancer cases and controls

	PCCRC 6-12 months	PCCRC 12-36 months	PCCRC 36-60 months	All PCCRC	Controls	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Total subjects (number)						Univariate			Multivariate		
	1796 (2.7)	3772 (5.6)	2579 (3.8)	8147 (12.1)	59055 (87.9)	-	-	-	-	-	-
Mean age ±SD (years)											
	71.5±11.4	70.9±11.7	69.8±10.8	70.7±11.4	70.2±11.4	-	-	**<0.001**			
Age group (number (%))											
Under 60	263 (3.2)	598 (7.3)	415 (5.1)	1276 (15.7)	9849 (16.7)	Ref					
60-64	167 (2.0)	367 (4.5)	288 (3.5)	822 (10.1)	6749 (11.4)	0.94	0.86-1.03	0.1928	0.95	0.86-1.04	0.277
65-69	217 (2.7)	531 (6.5)	435 (5.3)	1183 (14.5)	8810 (14.9)	1.04	0.95-1.13	0.4044	1.03	0.94-1.12	0.537
70-74	344 (4.2)	648 (8.0)	488 (6.0)	1480 (18.2)	10229 (17.3)	**1.12**	**1.03-1.21**	**0.0067**	**1.09**	**1.00-1.18**	**0.039**
75-79	359 (4.4)	678 (8.3)	499 (6.1)	1536 (18.9)	10698 (18.1)	**1.11**	**1.02-1.20**	**0.0109**	1.07	0.98-1.16	0.159
80+	446 (5.5)	950 (11.7)	454 (5.6)	1850 (22.7)	12720 (21.5)	**1.12**	**1.04-1.21**	**0.0029**	1.08	1.00-1.17	0.065
Gender (number (%))											
Male	974 (12.0)	1974 (24.2)	1340 (16.4)	4288 (52.6)	33057 (56.0)	Ref	-	-	Ref	-	-
Female	822 (10.1)	1798 (22.1)	1239 (15.2)	3859 (47.4)	25998 (44.0)	**1.14**	**1.09-1.20**	**<0.0001**	**1.13**	**1.08-1.19**	**<0.001**
Charlson co-morbidity index (number (%))											
0	1514 (18.6)	3210 (39.4)	2235 (27.4)	6959 (85.4)	50663 (85.8)	Ref	-	-	Ref	-	-
1-4	154 (1.9)	298 (3.7)	210 (2.6)	662 (8.1)	4764 (8.1)	1.01	0.93-1.10	0.7896	1.06	0.97-1.16	0.195
5+	128 (1.6)	264 (3.2)	134 (1.6)	526 (6.5)	3628 (6.1)	1.06	0.96-1.16	0.2641	**1.16**	**1.05-1.28**	**0.003**
Deprivation quintile (number (%))											
1 (most)	329 (4.0)	637 (7.8)	393 (4.8)	1359 (16.7)	10015 (17.0)	Ref	-	-	-	-	-
2	365 (4.5)	740 (9.1)	499 (6.1)	1604 (19.7)	11258 (19.1)	1.05	0.97-1.13	0.2153	-	-	-
3	333 (4.1)	782 (9.6)	551 (6.8)	1666 (20.4)	12399 (21.0)	0.99	0.91-1.07	0.8002	-	-	-
4	387 (4.8)	784 (9.6)	568 (7.0)	1739 (21.3)	12642 (21.4)	1.01	0.94-1.09	0.7242	-	-	-
5 (least)	381 (4.7)	823 (10.1)	566 (6.9)	1770 (21.7)	12620 (21.4)	1.03	0.96-1.11	0.3905	-	-	-
Ethnicity (number (%))											
White	1656 (20.3)	3536 (43.4)	2467 (30.3)	7659 (94.0)	54512 (92.3)	Ref	-	-	-	-	-
Asian	21 (0.3)	55 (0.7)	36 (0.4)	112 (1.4)	788 (1.3)	1.01	0.83-1.23	0.9097	-	-	-

Afro-Caribbean	25 (0.3)	53 (0.7)	27 (0.3)	105 (1.3)	823 (1.4)	0.91	0.74-1.11	0.3553	-	-	-
Chinese	0	0	0	12 (0.1)	118 (0.2)	0.72	0.40-1.30	0.2865	-	-	-
Mixed	0	0	0	18 (0.2)	160 (0.3)	0.80	0.49-1.30	0.3719	-	-	-
Others	12 (0.1)	21 (0.3)	21 (0.3)	54 (0.7)	341 (0.6)	1.13	0.85-1.50	0.4156	-	-	-
Unknown	74 (0.9)	95 (1.2)	18 (0.2)	187 (2.3)	2313 (3.9)	**0.58**	**0.49-0.67**	**<0.0001**	-	-	-

Odds ratios with 95% confidence intervals and p values for PCCRC (all) compared with controls

PCCRC – post-colonoscopy colorectal cancer

Table 2. The colonoscopy characteristics and findings of post-colonoscopy colorectal cancer cases and controls

	PCCRC 6-12 months	PCCRC 12-36 months	PCCRC 36-60 months	All PCCRC	Controls	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Procedure day (number (%))						Univariate			Multivariate		
Weekday	1736 (21.3)	3628 (44.5)	2486 (30.5)	7850 (96.4)	57249 (96.9)	Ref	-	-	-	-	-
Weekend	60 (0.7)	144 (1.8)	93 (1.1)	297 (3.6)	1806 (3.1)	**1.19**	**1.06-1.36**	**0.0044**	-	-	-
Procedure type (number (%))											
Elective	1622 (19.9)	3473 (42.6)	2455 (30.1)	7550 (92.7)	52605 (89.1)	Ref	-	-	Ref	-	-
Emergency	174 (2.1)	299 (3.7)	124 (1.5)	597 (7.3)	6450 (10.9)	**0.64**	**0.59-0.70**	**<0.0001**	**0.54**	**0.59-0.69**	**<0.0001**
Colorectal cancer location (number (%))											
Left sided	897 (11.0)	1754 (21.5)	1260 (15.5)	3911 (48.0)	34703 (58.8)	Ref	-	-	Ref	-	-
Right sided	535 (6.6)	1242 (15.2)	919 (11.3)	2696 (33.1)	20751 (35.1)	**1.15**	**1.09-1.21**	**<0.0001**	**1.17**	**1.11-1.23**	**<0.0001**
Unknown/ overlapping sites	364 (4.5)	776 (9.5)	400 (4.9)	1540 (18.9)	3601 (6.1)	**3.79**	**3.54-4.06**	**<0.0001**	**3.72**	**3.46-3.99**	**<0.0001**
Polyp/ polypectomy coded (number (%))											
Polyp coded	491 (6.0)	742 (9.1)	523 (6.4)	1756 (21.6)	141799* (9.8)	**2.52**+	**2.39-2.65**+	**<0.0001**+	-	-	-
No polyp coded	1305 (16.0)	3030 (37.2)	2056 (25.2)	6391 (78.4)	1300714* (90.2)	Ref	-	-	-	-	-
Polypectomy coded	348 (4.3)	669 (8.2)	523 (6.4)	1540 (18.9)	162364* (11.3)	**1.82**+	**1.72-1.92**+	**<0.0001**+	-	-	-
No polypectomy coded	1448 (17.8)	3103 (38.1)	2056 (25.2)	6607 (81.1)	1280150* (89.7)	Ref	-	-	-	-	-

Odds ratios with 95% confidence intervals and p values for all PCCRC compared with controls
PCCRC – post-colonoscopy colorectal cancer
*** From all colonoscopies**
+ Univariate analysis comparing all PCCRC with all colonoscopies during study period.

Table 3. The prevalence of metastases within 12 months of colorectal cancer diagnosis in post-colonoscopy colorectal cancer cases and controls

	PCCRC 6-12 months	PCCRC 12-36 months	PCCRC 36-60 months	All PCCRC	Controls	Odds ratio	95% CI	p value	Odds ratio	95% CI	*P* value
Subjects with metastases within 12 months of diagnosis (number (%))						Univariate			Multivariate		
Liver metastases	276 (3.4)	619 (7.6)	365 (4.5)	1260 (15.5)	8545 (14.5)	**1.08**	**1.01-1.15**	**0.017**	0.97	0.91-1.05	0.486
Lung metastases	154 (1.9)	345 (4.2)	182 (2.2)	681 (8.4)	3104 (5.3)	**1.64**	**1.51-1.79**	**<0.0001**	**1.61**	**1.46-1.77**	**<0.0001**
Peritoneal metastases	75 (0.9)	166 (2.0)	102 (1.3)	343 (4.2)	1903 (3.2)	**1.32**	**1.17-1.48**	**<0.0001**	**1.27**	**1.12-1.44**	**<0.0001**
Bone metastases	45 (0.6)	106 (1.3)	78 (1.0)	229 (2.8)	678 (1.1)	**2.49**	**2.14-2.90**	**<0.0001**	**2.21**	**1.88-2.60**	**<0.0001**
Lymph node metastases	136 (1.7)	282 (3.5)	231 (2.8)	649 (8.0)	6459 (10.9)	**0.70**	**0.65-0.76**	**<0.0001**	**0.75**	**0.69-0.82**	**<0.0001**
Treatment outcome after diagnosis (number (%))											
Surgery	791 (9.7)	1661 (20.4)	1337 (16.4)	3789 (46.5)	42790 (72.5)	**0.33**	**0.32-0.35**	**<0.0001**	-	-	-
Chemotherapy	422 (5.2)	911 (11.2)	594 (7.3)	1927 (23.7)	18908 (32.0)	**0.66**	**0.62-0.69**	**<0.0001**	-	-	-

Odds ratios with 95% confidence intervals and *P* values for PCCRC (all) compared with controls.
PCCRC – post-colonoscopy colorectal cancer.

Table 4. The influence of provider variables on post-colonoscopy colorectal cancer

	PCCRC 6-12 months	PCCRC 12-36 months	PCCRC 36-60 months	All PCCRC	Controls	Odds ratio	95% CI	p value	Odds ratio	95% CI	*P* value
Colonoscopy volume by NHS provider (number (%))						Univariate			Multivariate		
High volume providers (>1680 pa)	955 (11.7)	1993 (24.5)	1415 (17.4)	4363 (53.6)	33353 (56.5)	Ref	-	-	Ref	-	-
Medium volume providers	704 (8.6)	1486 (18.2)	994 (12.2)	3184 (39.1)	21942 (37.2)	**1.11**	**1.06-1.16**	**<0.0001**	**1.13**	**1.01-1.27**	**0.035**
Low-volume providers (<747 pa)	137 (1.7)	293 (3.6)	170 (2.1)	600 (7.4)	3760 (6.4)	**1.22**	**1.11-1.34**	**<0.0001**	1.05	0.98-1.12	0.161
BCSP status (number (%))											
BCSP provider	959 (11.8)	2064 (25.3)	1396 (17.1)	4419 (54.2)	31780 (53.8)	Ref	-	-	-	-	-
Non-BCSP provider	837 (10.3)	1708 (21.0)	1183 (14.5)	3728 (45.8)	27275 (46.2)	0.98	0.94-1.03	0.4690	0.96	0.90-1.03	0.255
Percentage of CRC diagnosed during an emergency admission by NHS provider (number (%))											
Low-percentage providers (<27.3%)	408 (5.0)	848 (10.4)	629 (7.7)	1885 (23.1)	14270 (24.2)	**0.91**	**0.84-0.98**	**0.0115**	0.96	0.87- 1.06	0.443
Medium percentage providers	1068 (13.1)	2273 (27.9)	1530 (18.8)	4871 (59.8)	35211 (59.6)	0.95	0.89-1.01	0.1299	0.96	0.85-1.09	0.531
High-percentage providers (>33.9%)	320 (3.9)	651 (8.0)	420 (5.2)	1391 (17.1)	9572 (16.2)	Ref	-	-	Ref	-	-

Odds ratios with 95% confidence intervals and p values for PCCRC (all) compared with controls
PCCRC – post-colonoscopy colorectal cancer
BCSP – Bowel Cancer Screening Program

Figure 1. Post-colonoscopy colorectal cancer rates by individual provider in England between 2003 and 2009.

Figure 2. Unadjusted survival after colorectal cancer diagnosis in post-colonoscopy colorectal cancer cases and control subjects.

Figure 3 Post-colonoscopy colorectal cancer rates and colonoscopy volume in England by year.

Appendix 1 - OPCS-4 codes for colonoscopy

H20.1 Snare polypectomy

H20.6 Polypectomy with colonoscopy

H22.1 Diagnostic fibreoptic endoscopic examination of colon and biopsy of lesion of colon

H22.8 Other specified diagnostic endoscopic examination of colon

H22.9 Unspecified diagnostic endoscopic examination of colon

Appendix 2 - ICD-10 codes for colorectal cancers

C18 Malignant neoplasm of colon - excluding C18.1 (malignant neoplasm of appendix)

C19 Malignant neoplasm of rectosigmoid junction

C20 Malignant neoplasm of rectum

Appendix 3 – ICD-10 codes for colorectal cancer (CRC) sites

Right sided CRC

C18.0 Caecum, Ileocaecal valve

C18.2 Ascending colon

C18.3 Hepatic flexure

C18.4 Transverse colon

Left sided CRC

C18.5 Splenic flexure

C18.6 Descending colon

C18.7 Sigmoid colon

C19 Rectosigmoid junction

C20 Rectum

Unspecified CRC location

C18.8 Overlapping lesion of colon

C18.9 Colon, unspecified

Appendix 4 - ICD-10 codes for colorectal polyps

D12.0 Caecal polyp(s)

D12.2 Ascending colon polyp(s)

D12.3 Transverse colon, hepatic flexure, splenic flexure polyp(s)

D12.4 Descending colon polyp(s)

D12.5 Sigmoid colon polyp(s)

D12.6 Colon, site unspecified polyp(s)

D12.7 Rectosigmoid junction polyp(s)

D12.8 Rectal polyp(s)

Appendix 5 - ICD-10 codes for metastases

C77.1 Intrathoracic lymph nodes

C77.2 Intra-abdominal lymph nodes

C77.4 Inguinal and lower limb lymph nodes

C77.5 Intrapelvic lymph nodes

C78.0 Secondary malignant neoplasm of lung

C78.6 Secondary malignant neoplasm of retroperitoneum and peritoneum

C78.7 Secondary malignant neoplasm of liver and intrahepatic bile duct

C79.5 Secondary malignant neoplasm of bone and bone marrow

C34 Malignant neoplasm of bronchus and lung

C48 Malignant neoplasm of retroperitoneum and peritoneum

C22 Malignant neoplasm of liver

C40-C41 Malignant neoplasms of bone and articular cartilage

Appendix 6- OPCS-4 codes for surgical procedures

H04 Total excision of colon and rectum

H05 Total excision of colon

H06 Extended excision of right hemicolon

H07 Other excision of right hemicolon

H08 Excision of transverse colon

H09 Excision of left hemicolon

H10 Excision of sigmoid colon

H11 Other excision of colon

H29 Subtotal excision of colon

H33 Excision of rectum

H40 Operations on rectum through anal sphincter

H122 Excision of lesion of colon NEC

H123 Destruction of lesion of colon NEC

H128 Other specified extirpation of lesion of colon

H129 Unspecified extirpation of lesion of colon

H341 Open excision of lesion of rectum

H345 Open destruction of lesion of rectum

H348 Other specified open extirpation of lesion of rectum

H349 Unspecified open extirpation of lesion of rectum

H402 Trans-sphincteric excision of lesion of rectum

H403 Trans-sphincteric destruction of lesion of rectum

OPCS-4 codes for chemotherapy

X70 Procurement of drugs for chemotherapy for neoplasm in Bands 1-5

X71 Procurement of drugs for chemotherapy for neoplasm in Bands 6-10

X72 Delivery of Chemotherapy for neoplasm

X73 Delivery of oral chemotherapy for neoplasm

X352 Intravenous chemotherapy

X384 Subcutaneous chemotherapy

X373 Intramuscular chemotherapy

Z082 Follow up examination after chemotherapy for malignant neoplasm

Z511 Chemotherapy session for neoplasm

Z542 Convalescence following chemotherapy

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***Acronyms (list all acronyms used in paper with their spell-outs)**

Bowel cancer screening program (BCSP)

Colorectal cancers (CRC)

Hospital Episode Statistics (HES)

International Classification of Diseases version 10 (ICD-10)

National Cancer Intelligence Network (NCIN)

National Health Service (NHS)

Office for National Statistics (ONS)

Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision (OPCS-4)

Surveillance, Epidemiology, and End Results Medicare database (SEER)

Post-colonoscopy colorectal cancer (PCCRC)

University Hospital Birmingham (UHB)

Journal CME Conflict of Interest: Disclosure and Attestation

Lead Author: Dr Danny W F Cheung

Article: How often does colonoscopy fail to diagnose colorectal cancer (retrospective analysis of English Hospital Episode Statistics from 2003 to 2009)?

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***Revision point-by-points**

January 12th 2016

Michael B. Wallace, MD, MPH
Editor-in-Chief
Seth Andrew Gross, MD
Associate Editor
GIE Editorial Team

Dear Drs. Wallace and Gross,

Re – GIE-D-15-01290: How often does colonoscopy fail to diagnose colorectal cancer (retrospective analysis of English Hospital Episode Statistics from 2003 to 2009)?

Thank you very much for sending your further editorial comments and requesting review and resubmission of our manuscript. We have detailed below our responses to the editorial comments and related amendments to the paper.

Editorial comments

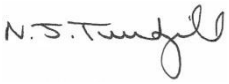
In the first paragraph of the discussion we explain the potential reasons for our reported PCCRC rate of 12.1% appearing higher than other published studies. The most important reason is that we chose to study PCCRC for five years after colonoscopy, rather than three years as some studies have done. Using a three year follow up period after colonoscopy, our PCCRC rate of 8.3% is consistent with other studies as we discuss.

Unfortunately, we are unable to provide the data requested for the period 2010 to 2014. This time period would not allow five years of follow up within the database to ascertain whether colorectal cancer developed following the colonoscopy.

However, the rate of PCCRC fell during the period we studied and we do accept the point made that there have been a number of advances in colonoscopy in recent years that should impact further on the rate of PCCRC in recent years when it is subsequently analysed. We have amended the discussion to acknowledge that the current PCCRC rate is likely to be even lower than the reported PCCRC rate in our study due to changes in colonoscopy practice. Text amended.

We hope our manuscript is now suitable for publication.

Yours sincerely,



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Factors associated with colorectal cancer occurrence after colonoscopy that did not diagnose colorectal cancer.

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Abstract

Background and Aims: Up to 6% of colorectal cancers (CRC) are diagnosed within 5 years of a colonoscopy that did not diagnose CRC (post-colonoscopy colorectal cancer, PCCRC). PCCRC and associated risk factors were examined within a national hospital episode database.

Methods: A retrospective case-control study of all adult colonoscopies recorded in Hospital Episode Statistics (HES) between 2003-2009 in England. PCCRC cases underwent colonoscopy 6-60 months before diagnosis; controls had not undergone colonoscopy 6-60 months before diagnosis. Multivariate logistic regression analysis examined associations with PCCRC.

Results: 1,439,684 colonoscopies were analysed, including 67,202 CRC and 8147 (12.1%) PCCRC cases. Multivariate analysis revealed that female gender (odds ratio 1.13 (95% CI 1.08-1.19), p<0.001), older age (70-74 years) (1.09 (1.00-1.18), p=0.039), increased co-morbidity (Charlson index 5+) (1.16 (1.05-1.28), p<0.003) and right sided CRC (1.17 (1.11-1.23), p<0.0001) were associated with PCCRC. Emergency colonoscopy (0.54 (0.59-0.69), p<0.0001) was negatively associated with PCCRC. More PCCRC subjects developed metastases within 12 months and less underwent surgery (0.33 (0.32-0.35), p<0.0001) or chemotherapy (0.66 (0.62-0.69), p<0.0001). PCCRC rates varied twofold between providers, and was associated with medium volume providers compared with high volume (1.13 (1.01-1.27), p=0.035). The PCCRC rate fell from 13.8% in 2003 to 11.9% in 2009.

Conclusions: PCCRC occurred in 12.1% of CRC patients between 2003 and 2009. PCCRC was associated with female gender, older age, increased co-morbidity, right sided CRC, elective procedures and colonoscopy volume. PCCRC was associated with worse outcomes.

Introduction

Colonoscopy is the gold standard for diagnosing, screening and surveillance for CRC. In England, the setting of national standards for colonoscopy and accreditation of endoscopy units has resulted in an improvement in auditable colonoscopy standards over the last decade.[1] The same period has also coincided with an increase in 5 year survival following CRC diagnosis from 47.8% to 53.6%.[2] However, 2.6 to 6.0% of CRC patients have previously been reported to be diagnosed within 5 years of a colonoscopy which did not detect cancer. These events are termed post-colonoscopy colorectal cancer (PCCRC).[3, 4, 5] It has been proposed that PCCRC may have a different cell biology from other CRC with more aggressive and rapidly growing tumours.[6, 7] However, two recently published North American studies concluded that this did not apply to the majority of PCCRC, with around two thirds of PCCRC a result of missed lesions or incomplete polypectomy.[4, 8]

Given the improvements in colonoscopy over the past decade in England, we have examined the impact on PCCRC in a national hospital episode database and associated risk factors for these events.

Methods

Data sources

Hospital Episode Statistics (HES) is an administrative database which records information on all elective and emergency care episodes in National Health Service (NHS) hospitals in England.[9] Each care episode record includes demographic, admission, diagnoses and procedures data. Diagnoses are coded using International Classification of Diseases version 10 (ICD-10) and procedures are coded using Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision (OPCS-4). HES is linked to Office for National Statistics (ONS) mortality records, which include date of death and causes of death recorded on death certificates. The NHS provides comprehensive healthcare coverage for the UK population, with the vast majority of colonoscopies performed in the UK by a NHS provider.[1]

Subject definitions

All subjects over the age of 18 years undergoing colonoscopy between April 2003 and March 2009 were identified from HES. Colonoscopy and CRC were defined by OPCS-4 *(appendix 1)* and ICD-10 codes *(appendix 2)* respectively. Subjects with a CRC diagnosis prior to the first episode of colonoscopy and subjects with a diagnosis of inflammatory bowel disease (IBD) were excluded from the analysis to avoid confounding through surveillance.

Recording of a CRC diagnosis in HES records may be delayed by a few weeks from the date of the diagnostic colonoscopy code.[10, 11] For the purpose of this study, the diagnosis date was therefore defined as the first colonoscopy code during the 6 months prior to the first CRC coding episode in HES or mortality records[10, 12], or the first CRC episode for those subjects who did not have a colonoscopy during this 6 month period due to being diagnosed through an alternative method, e.g. barium enema, CT colonography or flexible sigmoidoscopy. Subjects undergoing colonoscopy 6 to 60 months before subsequent CRC diagnosis were identified as PCCRC cases. These cases were further classified as PCCRC 6-12 months (colonoscopy 6 to 12 months prior to CRC diagnosis); PCCRC 12-36 months (colonoscopy 12 to 36 months prior to CRC diagnosis) and PCCRC 36-60 months

(colonoscopy 36 to 60 months prior to CRC diagnosis). For patients who had more than one colonoscopy 6 to 60 months prior to CRC diagnosis, data from the most recent colonoscopy was used for analysis. Controls were subjects who had not undergone colonoscopy in the period 6 to 60 months before CRC diagnosis. Colonoscopies from 2003 to 2009 were studied to ensure all subjects had at least 5 years of follow up within HES. The PCCRC rate was calculated from the number of PCCRC subjects divided by the sum of PCCRC subjects and controls.[13]

Validation of colonoscopy and colorectal cancer populations

To assess the validity of the HES colonoscopy population, the number of colonoscopies between 2007 and 2010 at University Hospital Birmingham (UHB) was extracted from endoscopy records (Unisoft Medical Systems, Enfield, Middlesex, UK) and compared with the number of colonoscopies recorded in HES for UHB. To assess the validity of a CRC diagnosis in HES using the study methodology, the number of HES CRC cases was compared with the number of CRC cases diagnosed in England from the National Cancer Intelligence Network (NCIN)[14] from 2002 to 2011. Finally, the rate of surgery in the HES CRC population was compared with rate of surgery in the National Bowel Cancer Audit between 2008 and 2011.[15, 16, 17]

Study variables

Subject demographics

Study variables were extracted from coding at the time of PCCRC colonoscopy in cases and diagnostic colonoscopy or first CRC episode in controls. Ethnicity was identified from HES demographic fields and grouped into White or White British, Asian or Asian British, Black or Black British, Chinese, Mixed and other ethnic groups.

Co-morbidity

The Charlson co-morbidity index was calculated using ICD-10 codes for secondary diagnoses, excluding metastatic disease, and divided into three categories: 0 (no co-morbidity), 1-4 (low co-morbidity) and 5 or greater (high co-morbidity).[18]

Socio-economic status

Deprivation was assessed using the Index of Multiple Deprivations 2007, which is an aggregate score for each English catchment area. Subjects were linked to their corresponding catchment area by postcode of residence and associations with deprivation were analysed in quintiles, with quintile 1 being the most deprived.

Colorectal cancer variables

CRC site was classified based on the first CRC coding episode into: right sided, left sided and unspecified *(appendix 3)*. Coding records of initially unspecified site CRC were examined and if a more specific code had been used subsequently, this was used to determine the CRC site. Colonic polyps were identified from ICD-10 codes *(appendix 4)*.

Distant metastases were identified by ICD-10 codes (*appendix 5*) up to 12 months from diagnosis date and were used as a surrogate marker of CRC stage at diagnosis, as Dukes' staging is not recorded in HES. Codes for metastases can occasionally be miscoded as a primary neoplasm (e.g. lung), and therefore primary malignancy codes were also used, provided that they were recorded in the 12 months subsequent to CRC diagnosis *(appendix 5)*. Surgery and chemotherapy were identified by respective OPCS-4 codes (*appendix 6*).

Survival analysis

Survival analysis adjusted for gender, age, deprivation and co-morbidity was calculated from the CRC diagnosis date of PCCRC cases and controls using date of death from ONS. Subjects who were not diagnosed by colonoscopy were not included to avoid potential lead time bias due to the method of determining date of diagnosis from HES.

Provider variables

For the purpose of this study, all endoscopy units operating within the same NHS organisation were analysed as a single provider. Individual providers were stratified by colonoscopy volume, bowel cancer screening program (BCSP) status and the percentage of CRC diagnosed during an emergency rather than an elective episode to determine if there was an association with PCCRC. Colonoscopy volume was determined from the total number of colonoscopies performed during the study period at each provider and separated into

tertiles. A BCSP accredited provider had at least one endoscopy unit accredited with BCSP status by the end of the study period. The percentage of CRC diagnosed as an emergency at a provider was the ratio of CRC diagnosed during an acute (unplanned) admission divided by all CRC, including CRC diagnosed during an elective episode.

Ethics

As only pseduonymised information was used in this study, ethics approval was not necessary. HES data is available under a data sharing agreement for the purposes of service evaluation.

Statistical methodology

Statistical analysis was carried out with STATA SE v13.1 (Statacorp LP, Texas, USA). Analysis of variance and χ^2 tests were used to compare differences in continuous and categorical variables respectively. Associations with PCCRC were examined by univariate and multivariate logistic regression. A multivariate model was constructed to determine associations with PCCRC following adjusting gender, age, Charlson co-morbidity index, procedure type (emergency or elective), CRC site (left colon or right colon), metastases and procedure year. For tests of significance, p values <0.05 were considered significant. All odds ratios, 95% confidence intervals and associated p values are the result of multivariate analysis unless stated otherwise. Unadjusted Kaplan-Meier analysis and Cox proportional hazards modelling following adjustment for gender, age, deprivation and co-morbidity were used to compare survival in PCCRC cases and controls.

Results

Study cohort

Between April 2003 and March 2009, 1,439,684 colonoscopies were identified and 67,202 subjects were diagnosed with CRC during this period. Out of the 67,202 CRC subjects, there were 8,147 (12.1%) PCCRC subjects: 1796 (2.7%) PCCRC 6-12 months; 3,772 (5.6%) PCCRC 12-36 months and 2,579 (3.8%) PCCRC 36-60 months. 59,055 CRC subjects had not had a colonoscopy between 6 and 60 months prior to CRC diagnosis and served as controls. Overall, 0.66% or 1 in every 150 subjects developed PCCRC after a colonoscopy that did not diagnose CRC.

Validation of colonoscopy and colorectal cancer populations

The total number of colonoscopies carried out between 2007 and 2010 at UHB was 8708 and 8292 colonoscopies (95.2%) were coded in HES for UHB for the equivalent four year period. The CRC population was validated by comparing CRC cases recorded in HES (315,515) to CRC cases reported from 2002 to 2011 by NCIN (312,984)[14], showing a concordance of over 99%. The CRC population was further validated by comparing the 70.4% surgical rate for CRC from HES with the National Bowel Cancer Audit, which reported that 75.7% of CRC patients enrolled in the audit underwent surgery between 2008 and 2011.[15, 16, 17] All of the validation processes showed a good correlation between HES data and independent data sources, suggesting the study methodology was valid.

Subject characteristics

The characteristics of cases with PCCRC and CRC controls are shown in Table 1. PCCRC subjects (mean age 70.7±11.4 years) were older than controls (mean age 70.2±11.4 years)($p<0.001$). The risk of PCCRC appeared to increase with age on univariate analysis, but only subjects aged 70 to 74 were associated with PCCRC compared with subjects under 60, following adjusting for confounding factors. PCCRC subjects were more likely to be female. Subjects with the most co-morbidities (Charlson co-morbidity index of 5 or greater) were associated with PCCRC. PCCRC was not associated with differences in ethnicity or deprivation.

Colonoscopy variables and findings

The influence of colonoscopy variables and findings on PCCRC are shown in Table 2. The majority of CRC were diagnosed during an elective colonoscopy. However, being diagnosed during an emergency colonoscopy reduced the risk of PCCRC nearly by half. There was minor increased risk of PCCRC on univariate analysis in colonoscopies carried out at the weekend compared with during the week.

PCCRC was more likely to be associated with CRC in the right colon. Colonic polyps were coded in 21.6% of the colonoscopies which did not detect CRC in the PCCRC group. Polypectomy was coded in a further 18.9%. On univariate analysis, this was higher than both the recorded polyp rate of 9.8% (2.52 (95% CI 2.39-2.65), p<0.0001) and polypectomy rate of 11.3% (1.82 (95% CI 1.72-1.92), p<0.0001) from all colonoscopies during the study period. Furthermore, the polyp and polypectomy rates were both higher in the PCCRC 6-12 months group on univariate analysis, than in the PCCRC 12-36 months (p<0.0001) and PCCRC 36-60 months (p<0.0001) groups.

Colorectal outcomes and survival

The prevalence of metastatic disease within 12 months of CRC diagnosis in PCCRC cases and controls are shown in Table 3. PCCRC cases were up to twice as likely to be diagnosed with lung, peritoneal and bone metastases within 12 months of CRC diagnosis. However, lymph node metastases were more prevalent in controls than PCCRC cases, suggesting coding bias related to the increased rate of surgery in control subjects described later.

On univariate analysis, PCCRC cases were less likely to undergo surgery compared with controls (0.33 (95% CI 0.32-0.35), p<0.0001) or chemotherapy (0.66 (95% CI 0.62-0.69), p<0.0001). Overall survival was also worse in PCCRC subjects compared with controls, with a median survival of 5.8 years in controls compared with 2.1 years in the PCCRC 6-12 months group, 2.0 years in the PCCRC 12-36 months group and 3.5 years in the PCCRC 36-60 months group (figure 1). Following adjusting for age, gender, co-morbidity and deprivation, survival outcomes remained worse for PCCRC subjects with a hazard ratio of 1.17 (95% CI 1.10-1.24)(p<0.0001), 1.26 (95% CI 1.20-1.31)(p<0.0001) and 1.20 (95% CI 1.13-1.27)(p<0.0001)

for the PCCRC 6-12 months, PCCRC 12-36 months and PCCRC 36-60 months respectively when compared with controls.

Individual provider variables

The influence of provider variables on PCCRC are shown in Table 4. There was a more than twofold variation in PCCRC rates between individual providers in England during the study period (figure 2). On univariate analysis, medium colonoscopy volume providers and low volume providers were both more likely to be associated with PCCRC than high volume providers. Following adjusting for other variables in the multivariate model an association with medium volume providers remained. BCSP accreditation status and the percentage of CRC diagnosed as an emergency were not associated with an increased risk of PCCRC.

PCCRC rates over time

The number of colonoscopies recorded in HES has increased by almost two fold over the study period. Despite the increase in colonoscopy numbers performed year on year, the annual rate of PCCRC has steadily fallen over the study period ($p<0.0001$)(figure 3). The annual PCCRC rate decreased from 13.8% in 2003-2004 to 11.9% by the end of study period in 2008-2009 with the reduction seen mainly in the PCCRC 6-12 months and PCCRC 12-36 months groups.

Discussion

The overall PCCRC rate of 12.1% in 67202 subjects in England between 2003 and 2009 appears higher than previously published figures. However, some previous studies have calculated the PCCRC rate by only including CRC subjects with a colonoscopy up to 36 months prior to diagnosis and the comparable figure from the present study is 8.3%. A Canadian study of 14,064 CRC subjects reported a PCCRC rate of 9.0% between 2000 and 2005.[12] Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database in the USA, a PCCRC rate of 7.2% was reported between 1994 to 2005 from a study of 57,839 CRC subjects.[19] A further population based study from Utah, USA with 2659 CRC subjects between 1995 and 2009 described a PCCRC rate of 6% when subjects with a colonoscopy up to 60 months prior to CRC diagnosis were included.[4] In Europe, two recent studies have reported much lower PCCRC rates. A Danish population based study between 2000 to 2009 included 37,044 CRC subjects and concluded that only 2.7% of CRC subjects have had a colonoscopy that failed to diagnose CRC 1 to 5 years prior to diagnosis.[5] A second study from the Netherlands analysed 5107 CRC subjects between 2001 to 2010 from three providers and found a PCCRC rate of only 2.9% for subjects with a colonoscopy up to 60 months prior to CRC diagnosis.[20] In addition to potential variations in subject and colonoscopy factors between the difference studies, the wide range of reported PCCRC rates are likely to be contributed to by methodological differences.[13]

In the present study, PCCRC was associated with older subjects, female gender, an increased number of co-morbidities and right-sided CRC, which is in keeping with findings from other studies of PCCRC. [3, 12, 19, 21] The association between increasing age and PCCRC was less marked on multivariate analysis and this may relate to confounding from increasing co-morbidity in the elderly. Elderly patients are more likely to have inadequate bowel preparation, thus reducing mucosal visualisation and detection of polyps and early CRC.[22, 23] Female patients are more likely to have had previous abdominal and pelvic surgery, which may increase the technical difficulty of colonoscopy and impair patient tolerance, reducing the caecal intubation rate.[24] In addition to factors that have an adverse effect on caecal intubation rate, right sided CRC are more likely to arise from flat, non-polypoid

adenomatous lesions[20, 25] that poor bowel preparation may make difficult to detect. This will contribute to the association of right sided CRC with PCCRC.

Over a fifth of PCCRC subjects had colonic polyps or polypectomy coded during the most recent colonoscopy prior to CRC diagnosis. This is higher than the average polypectomy rate in all colonoscopy procedures during the same period. Furthermore, polyp and polypectomy coding rates were highest in the PCCRC 12-36 months group. Prior polypectomy has been reported to double the risk of PCCRC[19], with up to 19% of CRC occurring in the same anatomic segment as a previously resected adenoma.[8] Paradoxically, colonoscopists with higher polypectomy rates have been reported to be associated with a lower risk of PCCRC[12, 19], presumably as they detect more polyps and remove them more completely than other colonoscopists. Incomplete polypectomy, or inadequate biopsy sampling of polyps, is therefore a key modifiable risk factor for PCCRC and ensuring adequate follow up and assessment following polypectomy may reduce PCCRC rates.

PCCRC subjects appeared to have worse outcomes in terms of both treatment following diagnosis (surgery and chemotherapy) and overall survival. Previous studies have reported no survival difference between PCCRC subjects and controls[5, 21] with one recent study even reporting a survival benefit in the PCCRC subjects, which was likely to be due to earlier CRC stage at diagnosis in the PCCRC subjects.[4] In the current study, PCCRC subjects were older, had greater co-morbidities and were more likely to present with distant metastases within 12 months of diagnosis compared with controls. All these factors contributed to the reduced rates of curative surgery or palliative chemotherapy for PCCRC subjects and will have contributed to worse survival. Adjusting the survival analyses for differences in ages, gender, co-morbidity and deprivation still revealed worse survival for PCCRC subjects and, at least in England, PCCRC is clearly associated with worse survival. Survival in PCCRC subjects would have been potentially better if earlier opportunities to diagnose their CRC had been taken.

Previous studies have reported that PCCRC was not associated with endoscopist procedure volume[12] and that higher colonoscopy volumes may even be positively associated with PCCRC surprisingly.[19] In the current study, there was a large variation in PCCRC rates

between individual providers across England but PCCRC appeared to be associated with lower colonoscopy volume providers. This result should be interpreted with caution. We did not have access to colonoscopy quality indicators such as caecal intubation and adenoma detection rates that are likely to be potentially more important factors in PCCRC incidence.

Colonoscopy undertaken during an emergency admission covered 10% of procedures examined and was associated with a lower risk of PCCRC at 9% compared with 14% for elective procedures. Patients presenting as an emergency may have more advanced colorectal cancer and therefore a lower chance of PCCRC.

The annual PCCRC rate in England has fallen steadily over the study period from 13.8% to 11.9%, at least partly due to improving colonoscopy standards over the corresponding time period. In 2003, a multi-regional audit in England including 9223 colonoscopies reported that mean caecal intubation rate was only 76.9%.[26] A subsequent national audit in 2011 of 20085 colonoscopies found that the caecal intubation rate had improved to 92.3%.[1] The PCCRC rate is likely to continue to improve in recent years given changes in colonoscopy practice, including the recognition of the importance of minimum withdrawal times [27], bowel preparation improvements[28] and better endoscopic recognition of sessile serrated polyps[25], subsequent to the study period.

The use of a national hospital dataset enabled us to undertake one of the largest PCCRC studies to date, including the vast majority of colonoscopies performed during a period of rising colonoscopy standards. The quality of diagnostic and procedural coding in HES has been previously investigated and there was a high concordance when compared with independent national data sources.[1, 10, 29] However, we did not have the opportunity to link our HES dataset directly to cancer registry data due to restrictions under which the data is held and therefore, in order to validate the methodology chosen, colonoscopy and CRC populations were compared with national cancer databases and a local data sample and revealed a good correlation. The completeness and accuracy of coding in HES is still a potential source of concern. For example, the diagnosis date may not be recorded accurately in HES due to the need for histological confirmation before CRC coding and therefore a colonoscopy within 6 months of CRC coding had to be considered the diagnostic

procedure. There are also limitations in HES concerning coding of colonoscopy procedures, polyps, polypectomy, presence of metastases, surgery and chemotherapy and the figures included may be an over or under estimate, though this is likely to affect PCCRC cases and controls equally. A further limitation is that key procedure information such as the bowel preparation quality, sedation doses, colonoscopist grade and specialty, extent of examination, completeness of polypectomy and number of biopsies taken are not recorded in HES and all may influence the PCCRC risk. Furthermore, due to the HES coding hierarchy, indication, presence of diverticular disease and history of abdominal or pelvic surgery may not be coded, partly due to under reporting by colonoscopists when significant pathology or CRC are found and again each may be important risk factors for PCCRC. As HES does not record polyp histology or the International Classification of Diseases for Oncology (ICD-O) codes, the lack of data on polyp and CRC histology and Duke's staging further limits analysis of potential causes of PCCRC (de novo CRC, incomplete adenoma resection, missed lesion or biopsy failed to detect CRC) and survival in PCCRC subjects.

In conclusion, the PCCRC rate was 12.1% in England between 2003 and 2009. PCCRC was associated with older age, female gender, increasing co-morbidity, procedure related factors (elective procedures and right sided CRC) and provider colonoscopy volume. Despite the encouraging fall in annual PCCRC rate over the study period, PCCRC rate should be a routinely measured endoscopy unit colonoscopy quality marker and potentially avoidable risk factors for PCCRC addressed.

Table 1. The characteristics of post-colonoscopy colorectal cancer cases and controls

	PCCRC 6-12 months	PCCRC 12-36 months	PCCRC 36-60 months	All PCCRC	Controls	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Total subjects (number)						Univariate			Multivariate		
	1796 (2.7)	3772 (5.6)	2579 (3.8)	8147 (12.1)	59055 (87.9)	-	-	-	-	-	-
Mean age ±SD (years)											
	71.5±11.4	70.9±11.7	69.8±10.8	70.7±11.4	70.2±11.4	-	-	**<0.001**			
Age group (number (%))											
Under 60	263 (3.2)	598 (7.3)	415 (5.1)	1276 (15.7)	9849 (16.7)	Ref					
60-64	167 (2.0)	367 (4.5)	288 (3.5)	822 (10.1)	6749 (11.4)	0.94	0.86-1.03	0.1928	0.95	0.86-1.04	0.277
65-69	217 (2.7)	531 (6.5)	435 (5.3)	1183 (14.5)	8810 (14.9)	1.04	0.95-1.13	0.4044	1.03	0.94-1.12	0.537
70-74	344 (4.2)	648 (8.0)	488 (6.0)	1480 (18.2)	10229 (17.3)	**1.12**	**1.03-1.21**	**0.0067**	**1.09**	**1.00-1.18**	**0.039**
75-79	359 (4.4)	678 (8.3)	499 (6.1)	1536 (18.9)	10698 (18.1)	**1.11**	**1.02-1.20**	**0.0109**	1.07	0.98-1.16	0.159
80+	446 (5.5)	950 (11.7)	454 (5.6)	1850 (22.7)	12720 (21.5)	**1.12**	**1.04-1.21**	**0.0029**	1.08	1.00-1.17	0.065
Gender (number (%))											
Male	974 (12.0)	1974 (24.2)	1340 (16.4)	4288 (52.6)	33057 (56.0)	Ref	-	-	Ref	-	-
Female	822 (10.1)	1798 (22.1)	1239 (15.2)	3859 (47.4)	25998 (44.0)	**1.14**	**1.09-1.20**	**<0.0001**	**1.13**	**1.08-1.19**	**<0.001**
Charlson co-morbidity index (number (%))											
0	1514 (18.6)	3210 (39.4)	2235 (27.4)	6959 (85.4)	50663 (85.8)	Ref	-	-	Ref	-	-
1-4	154 (1.9)	298 (3.7)	210 (2.6)	662 (8.1)	4764 (8.1)	1.01	0.93-1.10	0.7896	1.06	0.97-1.16	0.195
5+	128 (1.6)	264 (3.2)	134 (1.6)	526 (6.5)	3628 (6.1)	1.06	0.96-1.16	0.2641	**1.16**	**1.05-1.28**	**0.003**
Deprivation quintile (number (%))											
1 (most)	329 (4.0)	637 (7.8)	393 (4.8)	1359 (16.7)	10015 (17.0)	Ref	-	-	-	-	-
2	365 (4.5)	740 (9.1)	499 (6.1)	1604 (19.7)	11258 (19.1)	1.05	0.97-1.13	0.2153	-	-	-
3	333 (4.1)	782 (9.6)	551 (6.8)	1666 (20.4)	12399 (21.0)	0.99	0.91-1.07	0.8002	-	-	-
4	387 (4.8)	784 (9.6)	568 (7.0)	1739 (21.3)	12642 (21.4)	1.01	0.94-1.09	0.7242	-	-	-
5 (least)	381 (4.7)	823 (10.1)	566 (6.9)	1770 (21.7)	12620 (21.4)	1.03	0.96-1.11	0.3905	-	-	-
Ethnicity (number (%))											
Caucasian	1656 (20.3)	3536 (43.4)	2467 (30.3)	7659 (94.0)	54512 (92.3)	Ref	-	-	-	-	-
Asian	21 (0.3)	55 (0.7)	36 (0.4)	112 (1.4)	788 (1.3)	1.01	0.83-1.23	0.9097	-	-	-

Afro-Caribbean	25 (0.3)	53 (0.7)	27 (0.3)	105 (1.3)	823 (1.4)	0.91	0.74-1.11	0.3553	-	-	-
Chinese	0	0	0	12 (0.1)	118 (0.2)	0.72	0.40-1.30	0.2865	-	-	-
Mixed	0	0	0	18 (0.2)	160 (0.3)	0.80	0.49-1.30	0.3719	-	-	-
Others	12 (0.1)	21 (0.3)	21 (0.3)	54 (0.7)	341 (0.6)	1.13	0.85-1.50	0.4156	-	-	-
Unknown	74 (0.9)	95 (1.2)	18 (0.2)	187 (2.3)	2313 (3.9)	**0.58**	**0.49-0.67**	**<0.0001**	-	-	-

Odds ratios with 95% confidence intervals and p values for PCCRC (all) compared with controls

PCCRC – post-colonoscopy colorectal cancer

Table 2. The colonoscopy characteristics and findings of post-colonoscopy colorectal cancer cases and controls

	PCCRC 6-12 months	PCCRC 12-36 months	PCCRC 36-60 months	All PCCRC	Controls	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Procedure day (number (%))						Univariate			Multivariate		
Weekday	1736 (21.3)	3628 (44.5)	2486 (30.5)	7850 (96.4)	57249 (96.9)	Ref	-	-	-	-	-
Weekend	60 (0.7)	144 (1.8)	93 (1.1)	297 (3.6)	1806 (3.1)	**1.19**	**1.06-1.36**	**0.0044**	-	-	-
Procedure type (number (%))											
Elective	1622 (19.9)	3473 (42.6)	2455 (30.1)	7550 (92.7)	52605 (89.1)	Ref	-	-	Ref	-	-
Emergency	174 (2.1)	299 (3.7)	124 (1.5)	597 (7.3)	6450 (10.9)	**0.64**	**0.59-0.70**	**<0.0001**	**0.54**	**0.59-0.69**	**<0.0001**
Colorectal cancer location (number (%))											
Left sided	897 (11.0)	1754 (21.5)	1260 (15.5)	3911 (48.0)	34703 (58.8)	Ref	-	-	Ref	-	-
Right sided	535 (6.6)	1242 (15.2)	919 (11.3)	2696 (33.1)	20751 (35.1)	**1.15**	**1.09-1.21**	**<0.0001**	**1.17**	**1.11-1.23**	**<0.0001**
Unknown/ overlapping sites	364 (4.5)	776 (9.5)	400 (4.9)	1540 (18.9)	3601 (6.1)	**3.79**	**3.54-4.06**	**<0.0001**	**3.72**	**3.46-3.99**	**<0.0001**
Polyp/ polypectomy coded (number (%))											
Polyp coded	491 (6.0)	742 (9.1)	523 (6.4)	1756 (21.6)	141799* (9.8)	**2.52+**	**2.39-2.65+**	**<0.0001+**	-	-	-
No polyp coded	1305 (16.0)	3030 (37.2)	2056 (25.2)	6391 (78.4)	1300714* (90.2)	Ref	-	-	-	-	-
Polypectomy coded	348 (4.3)	669 (8.2)	523 (6.4)	1540 (18.9)	162364* (11.3)	**1.82+**	**1.72-1.92+**	**<0.0001+**	-	-	-
No polypectomy coded	1448 (17.8)	3103 (38.1)	2056 (25.2)	6607 (81.1)	1280150* (89.7)	Ref	-	-	-	-	-

Odds ratios with 95% confidence intervals and p values for all PCCRC compared with controls
PCCRC – post-colonoscopy colorectal cancer
*** From all colonoscopies**
+ Univariate analysis comparing all PCCRC with all colonoscopies during study period.

Table 3. The prevalence of metastases within 12 months of colorectal cancer diagnosis in post-colonoscopy colorectal cancer cases and controls

	PCCRC 6-12 months	PCCRC 12-36 months	PCCRC 36-60 months	All PCCRC	Controls	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Subjects with metastases within 12 months of diagnosis (number (%))						Univariate			Multivariate		
Liver metastases	276 (3.4)	619 (7.6)	365 (4.5)	1260 (15.5)	8545 (14.5)	**1.08**	**1.01-1.15**	**0.017**	0.97	0.91-1.05	0.486
Lung metastases	154 (1.9)	345 (4.2)	182 (2.2)	681 (8.4)	3104 (5.3)	**1.64**	**1.51-1.79**	**<0.0001**	**1.61**	**1.46-1.77**	**<0.0001**
Peritoneal metastases	75 (0.9)	166 (2.0)	102 (1.3)	343 (4.2)	1903 (3.2)	**1.32**	**1.17-1.48**	**<0.0001**	**1.27**	**1.12-1.44**	**<0.0001**
Bone metastases	45 (0.6)	106 (1.3)	78 (1.0)	229 (2.8)	678 (1.1)	**2.49**	**2.14-2.90**	**<0.0001**	**2.21**	**1.88-2.60**	**<0.0001**
Lymph node metastases	136 (1.7)	282 (3.5)	231 (2.8)	649 (8.0)	6459 (10.9)	**0.70**	**0.65-0.76**	**<0.0001**	**0.75**	**0.69-0.82**	**<0.0001**
Treatment outcome following diagnosis (number (%))											
Surgery	791 (9.7)	1661 (20.4)	1337 (16.4)	3789 (46.5)	42790 (72.5)	**0.33**	**0.32-0.35**	**<0.0001**	-	-	-
Chemotherapy	422 (5.2)	911 (11.2)	594 (7.3)	1927 (23.7)	18908 (32.0)	**0.66**	**0.62-0.69**	**<0.0001**	-	-	-

Odds ratios with 95% confidence intervals and p values for PCCRC (all) compared with controls
PCCRC – post-colonoscopy colorectal cancer

Table 4. The influence of provider variables on post-colonoscopy colorectal cancer

	PCCRC 6-12 months	PCCRC 12-36 months	PCCRC 36-60 months	All PCCRC	Controls	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Colonoscopy volume by NHS provider (number (%))						Univariate			Multivariate		
High volume providers (>1680 pa)	955 (11.7)	1993 (24.5)	1415 (17.4)	4363 (53.6)	33353 (56.5)	Ref	-	-	Ref	-	-
Medium volume providers	704 (8.6)	1486 (18.2)	994 (12.2)	3184 (39.1)	21942 (37.2)	**1.11**	**1.06-1.16**	**<0.0001**	**1.13**	**1.01-1.27**	**0.035**
Low volume providers (<747 pa)	137 (1.7)	293 (3.6)	170 (2.1)	600 (7.4)	3760 (6.4)	**1.22**	**1.11-1.34**	**<0.0001**	1.05	0.98-1.12	0.161
BCSP status (number (%))											
BCSP provider	959 (11.8)	2064 (25.3)	1396 (17.1)	4419 (54.2)	31780 (53.8)	Ref	-	-	-	-	-
Non-BCSP provider	837 (10.3)	1708 (21.0)	1183 (14.5)	3728 (45.8)	27275 (46.2)	0.98	0.94-1.03	0.4690	0.96	0.90-1.03	0.255
Percentage of CRC diagnosed during an emergency admission by NHS provider (number (%))											
Low percentage providers (<27.3%)	408 (5.0)	848 (10.4)	629 (7.7)	1885 (23.1)	14270 (24.2)	**0.91**	**0.84-0.98**	**0.0115**	0.96	0.87- 1.06	0.443
Medium percentage providers	1068 (13.1)	2273 (27.9)	1530 (18.8)	4871 (59.8)	35211 (59.6)	0.95	0.89-1.01	0.1299	0.96	0.85-1.09	0.531
High percentage providers (>33.9%)	320 (3.9)	651 (8.0)	420 (5.2)	1391 (17.1)	9572 (16.2)	Ref	-	-	Ref	-	-

Odds ratios with 95% confidence intervals and p values for PCCRC (all) compared with controls
PCCRC – post-colonoscopy colorectal cancer
BCSP – Bowel Cancer Screening Program

Figure 1. Post-colonoscopy colorectal cancer rates by individual provider in England between 2003 and 2009.

Figure 2. Unadjusted survival following colorectal cancer diagnosis in post-colonoscopy colorectal cancer cases and control subjects.

Figure 3 Post-colonoscopy colorectal cancer rates and colonoscopy volume in England by year.

Appendix 1 - OPCS-4 codes for colonoscopy

H20.1 Snare polypectomy

H20.6 Polypectomy with colonoscopy

H22.1 Diagnostic fibreoptic endoscopic examination of colon and biopsy of lesion of colon

H22.8 Other specified diagnostic endoscopic examination of colon

H22.9 Unspecified diagnostic endoscopic examination of colon

Appendix 2 - ICD-10 codes for colorectal cancers

C18 Malignant neoplasm of colon - excluding C18.1 (malignant neoplasm of appendix)

C19 Malignant neoplasm of rectosigmoid junction

C20 Malignant neoplasm of rectum

Appendix 3 – ICD-10 codes for colorectal cancer (CRC) sites

Right sided CRC

C18.0 Caecum, Ileocaecal valve

C18.2 Ascending colon

C18.3 Hepatic flexure

C18.4 Transverse colon

Left sided CRC

C18.5 Splenic flexure

C18.6 Descending colon

C18.7 Sigmoid colon

C19 Rectosigmoid junction

C20 Rectum

Unspecified CRC location

C18.8 Overlapping lesion of colon

C18.9 Colon, unspecified

Appendix 4 - ICD-10 codes for colorectal polyps

D12.0 Caecal polyp(s)

D12.2 Ascending colon polyp(s)

D12.3 Transverse colon, hepatic flexure, splenic flexure polyp(s)

D12.4 Descending colon polyp(s)

D12.5 Sigmoid colon polyp(s)

D12.6 Colon, site unspecified polyp(s)

D12.7 Rectosigmoid junction polyp(s)

D12.8 Rectal polyp(s)

Appendix 5 - ICD-10 codes for metastases

C77.1 Intrathoracic lymph nodes

C77.2 Intra-abdominal lymph nodes

C77.4 Inguinal and lower limb lymph nodes

C77.5 Intrapelvic lymph nodes

C78.0 Secondary malignant neoplasm of lung

C78.6 Secondary malignant neoplasm of retroperitoneum and peritoneum

C78.7 Secondary malignant neoplasm of liver and intrahepatic bile duct

C79.5 Secondary malignant neoplasm of bone and bone marrow

C34 Malignant neoplasm of bronchus and lung

C48 Malignant neoplasm of retroperitoneum and peritoneum

C22 Malignant neoplasm of liver

C40-C41 Malignant neoplasms of bone and articular cartilage

Appendix 6- OPCS-4 codes for surgical procedures

H04 Total excision of colon and rectum

H05 Total excision of colon

H06 Extended excision of right hemicolon

H07 Other excision of right hemicolon

H08 Excision of transverse colon

H09 Excision of left hemicolon

H10 Excision of sigmoid colon

H11 Other excision of colon

H29 Subtotal excision of colon

H33 Excision of rectum

H40 Operations on rectum through anal sphincter

H122 Excision of lesion of colon NEC

H123 Destruction of lesion of colon NEC

H128 Other specified extirpation of lesion of colon

H129 Unspecified extirpation of lesion of colon

H341 Open excision of lesion of rectum

H345 Open destruction of lesion of rectum

H348 Other specified open extirpation of lesion of rectum

H349 Unspecified open extirpation of lesion of rectum

H402 Trans-sphincteric excision of lesion of rectum

H403 Trans-sphincteric destruction of lesion of rectum

OPCS-4 codes for chemotherapy

X70 Procurement of drugs for chemotherapy for neoplasm in Bands 1-5

X71 Procurement of drugs for chemotherapy for neoplasm in Bands 6-10

X72 Delivery of Chemotherapy for neoplasm

X73 Delivery of oral chemotherapy for neoplasm

X352 Intravenous chemotherapy

X384 Subcutaneous chemotherapy

X373 Intramuscular chemotherapy

Z082 Follow up examination after chemotherapy for malignant neoplasm

Z511 Chemotherapy session for neoplasm

Z542 Convalescence following chemotherapy

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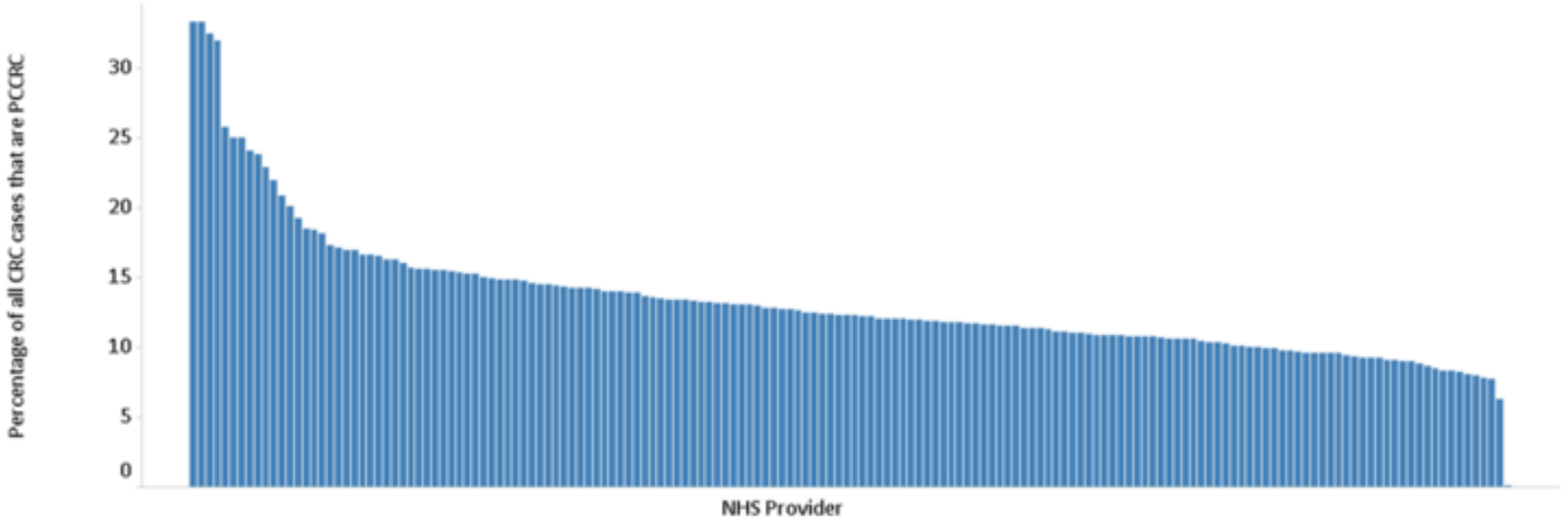

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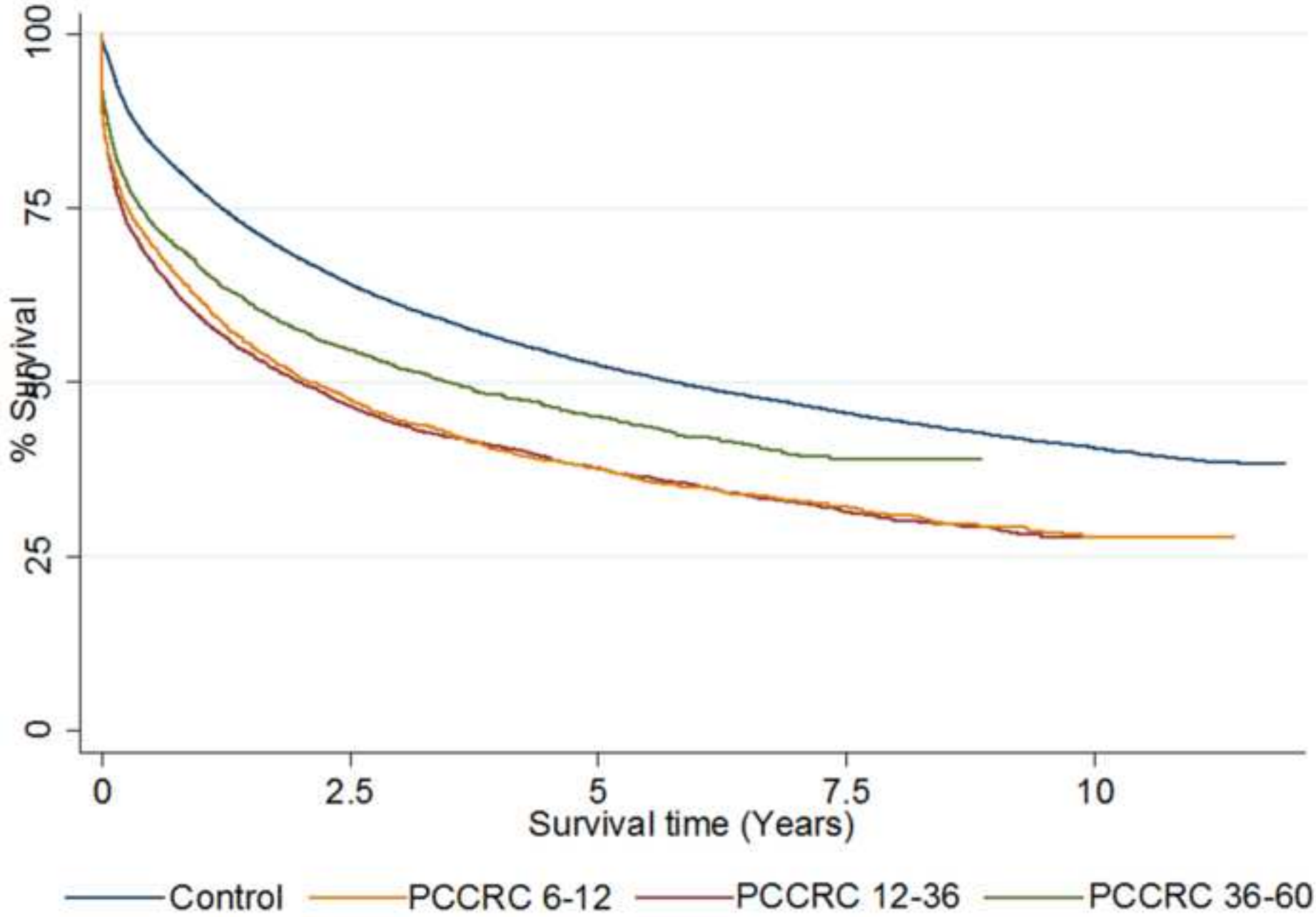

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