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Index Colonoscopy-Related Risk Factors for Post-Colonoscopy Colorectal Cancers

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Abstract

Background and Aims: Post-colonoscopy colorectal cancers (PCCRCs) are those detected ≤10 years after an index colonoscopy negative for cancer, but modifiable risk factors are not well established in large, community-based populations.

Methods: We evaluated risk factors from the index colonoscopy for PCCRCs diagnosed 1–10 years after an index colonoscopy using a case-control design. Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for potential confounders.

Results: A ≥10 mm proximal polyp (OR 8.18; 95%CI 4.59, 14.60); ≥10 mm distal polyp (OR 3.30; 95% CI 1.65, 6.58); adenoma with (OR 3.23; 95% CI 1.83, 5.68) and without advanced histology (OR 1.87; 95% CI 1.37, 2.55); and an incomplete colonoscopy (OR 5.52; 95% CI 2.98, 10.21) were associated with PCCRC. Among cases, risk factors for early vs. late cancers (12–36 months vs. >36 months-10 years post-examination) included incomplete polyp excision in the colonic segment of the subsequent cancer (OR 4.76; 95% CI 2.35, 9.65); failure to examine the segment (OR 2.42; 95% CI 1.27, 4.60); and a ≥10 mm polyp in the segment (OR 2.38; 95% CI 1.53, 3.70). A total of 559 of 1206 PCCRC patients (46.4%) had 1 or more risk factors that were significant for PCCRC (incomplete examination, large polyp, or any adenoma).

Conclusions: In a large community-based study with comprehensive capture of PCCRCs, almost half of PCCRCs had potentially modifiable factors related to polyp surveillance or removal

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and exam completeness. These represent potential high-yield targets for further increasing the effectiveness of colorectal cancer screening.

Introduction

Colorectal cancer (CRC) is the second leading cause of death from cancer in the United States.[1] Screening reduces mortality through detection and treatment of early-stage CRC and removal of precancerous adenomatous polyps (adenomas).[2] The United States Preventive Services Task Force endorses multiple CRC screening approaches;[2,3] however, the effectiveness of each hinges on colonoscopy since it is either the follow-up or primary test. Yet colonoscopy has limitations. *Post-colonoscopy CRCs (PCCRCs)* are those diagnosed after a colonoscopy in which no cancer is detected;[4] the term is sometimes used interchangeably with *interval cancer*, although the proposed definition for the latter has evolved to CRC diagnosed after a screening or surveillance examination in which no cancer is detected and before the date of the next recommended examination.[5,6]

PCCRC frequency estimates vary based on the length of follow-up after colonoscopy.[4–9] Among prior studies evaluating an interval of 6 to 36 months after colonoscopy, PCCRCs comprised 3.7% (95% confidence interval (CI) 2.8% to 4.9%) of all CRCs diagnosed,[8] and among studies of cancers diagnosed 6 months to 10 years after colonoscopy, 1.8% to 9.0% were PCCRCs.[7]

There are three plausible explanations for PCCRC: neoplasia missed at colonoscopy due to factors such as poor bowel preparation, incomplete examination, and difficult-to-see flat polyps or polyps behind folds; incomplete colonoscopic resection of detected neoplasia which progress to cancer; and development of new neoplasia after colonoscopy.[7] Risk from the first two proposed mechanisms could be reduced by improving colonoscopy quality. Consistent with this hypothesis, *physician adenoma detection rate*, a colonoscopy quality metric reflecting the percentage of a physician's screening colonoscopies in which an adenoma is detected, has been shown to be inversely related to the risk of PCCRC and PCCRC-related mortality.[10–14]

Several risk factors for PCCRC, including procedure-related factors, have been suggested,[4,5,7,8] including incomplete resection of pre-cancerous polyps and missed lesions at the index colonoscopy.[15–22] However, most studies had few cancer cases (<200 cases);[15–18,20–22] were conducted only in patients with prior adenomas or polypectomy;[15,16,18,19] or only included cancers detected within 5 years after colonoscopy, potentially missing slower developing lesions.[15–19,21,22] To our knowledge, no studies have comprehensively examined factors specific to the quality and findings of the index colonoscopy in a large community-based population in an integrated healthcare setting with long-term follow-up.

This study examined the index colonoscopy predictors of PCCRC diagnosed >1 year and up to 10 years post-examination.

Methods

Study Setting

The study was performed among health plan members of 2 large, integrated healthcare delivery organizations: Kaiser Permanente Northern California (KPNC) and Southern California (KPSC). These systems serve over 7 million people in urban, suburban, and semi-rural regions throughout California. Health plan membership is diverse and similar in socioeconomic characteristics to the underlying demographics of the region.[23–25]

The study was approved by the institutional review boards of KPNC and KPSC. The listed authors had sole responsibility for the study design, data collection, decision to submit the manuscript for publication, and drafting of the manuscript. This study was conducted within the National Cancer Institute-funded *Population-based Research Optimizing Screening through Personalized Regimens* (PROSPR) consortium (U54 CA163262) which conducts multisite, coordinated, transdisciplinary research to evaluate and improve cancer-screening processes. The funding source had no role in the conception, design, analysis, decision to publish, or conduct of the study.

Study Design

A case-control study design was used to examine the association between factors related to a colonoscopy that was negative for colorectal cancer (*index colonoscopy*) and the risk of PCCRC in the >1 to 10 years that followed. A secondary analysis examined, among patients with PCCRC, factors associated with early (arising >12 months and ≤36 months post-examination) versus late PCCRCs (arising >36 months to 10 years after). This analysis allowed for the evaluation of index colonoscopy-related factors specific to the colonic segment where the PCCRC was subsequently diagnosed (i.e., whether the colonic segment was examined, a polyp was found in the segment, and the polyp was completely excised).

Exposure Variables

Index colonoscopy-related factors included bowel preparation adequacy; extent of the examination; polyp presence, largest size, location, and completeness of excision; and adenoma presence and advanced histology status. *Inadequate bowel preparations* were those described as fair, poor, suboptimal, inadequate or unsatisfactory; *adequate bowel preparations* were those described as satisfactory, good, very good, excellent, or optimal. An *incomplete colonoscopy* was defined as a colonoscopy that did not reach the cecum. If the adequacy of the bowel preparation or extent of the examination was not described, it was assumed the preparation was adequate and the examination was complete for the main analyses. An *index colonoscopy with any polyp* included those with 1 or more polyps removed; the size of the largest polyp and its colonic segment location were noted if recorded. A *proximal polyp* was a polyp in the cecum, ascending colon, hepatic flexure, or transverse colon; a *distal polyp* was a polyp in the splenic flexure, descending colon, sigmoid colon, or rectum. *Incomplete polyp excision* was a polyp described as incompletely excised. A PCCRC was considered to have arisen in a colonic segment in which a previous polyp had been removed if the segment matched the segment of the subsequently diagnosed PCCRC. The presence of an adenoma and its *advanced histology status* (defined as a villous

or tubulovillous adenoma) were identified using Systematized Nomenclature of Medicine (SNOMED) codes from pathology reports. Adenoma data were inconsistently available at KPSC associated with the transition from paper to electronic medical records during the study interval; therefore, we elected not to use KPSC adenoma data. Validation studies have confirmed high levels of sensitivity for capture of colonoscopies compared with manual procedure logs (99%) and assignment of adenoma status (100%).[26]

Case and Control Definitions

PCCRC cases (n=1206) were KPNC (n=827) and KPSC (n=379) health plan members who had an index colonoscopy negative for CRC and were subsequently diagnosed with CRC (colorectal adenocarcinoma) between 1998 and 2010 for KPNC and between 2005 and 2012 for KPSC, with the diagnosis occurring >12 months and up to 10 years after the colonoscopy. CRCs diagnosed within 12 months after the colonoscopy were considered detected cancers and not included in the PCCRC definition.

Controls (n=634) were KPNC (n=488) and KPSC (n=146) health plan members who had an index colonoscopy negative for CRC and were without a CRC diagnosis at the time of their selection as controls between 2002 and 2012, which was >1 year and up to 10 years after their colonoscopy. For efficiency, controls were derived from cancer-free patients who were controls in a concurrent large case-control study examining the impact of screening colonoscopy on CRC mortality.[27,28] In that study, controls were matched to fatal cases on birth year (±1 year), sex, health plan enrollment duration prior to diagnosis (±1 year), and geographical region; controls were assigned their original matched case's CRC diagnosis date as their own reference date.[28] For the current study, risk estimates were adjusted for age, sex, and time from index colonoscopy to cancer diagnosis/reference date, among other factors, as detailed in the analysis.

Exclusion criteria included receipt of the index colonoscopy before age 50 or after age 90; a history of CRC, other gastrointestinal cancers, inflammatory bowel disease, Lynch Syndrome, or familial adenomatous polyposis; or a missing index colonoscopy report.

Data Sources

Electronic records were sourced for patient sex, age, race/ethnicity, colonoscopy procedures and pathology findings, family history of CRC, and prior diagnoses of CRC, inflammatory bowel disease, other gastrointestinal cancers, Lynch syndrome, and familial adenomatous polyposis. Endoscopy procedures were identified using Current Procedural Terminology codes.[29] Cancer diagnoses were obtained from the KPNC and KPSC cancer registries, which report to the Surveillance, Epidemiology and End Results (SEER) registry, and maintain a >97% population-based completeness standard as verified by random audits. Additional retrospective audits and death clearance processes have historically captured approximately 1–2% additional cases. Electronic data sources were complemented by manual chart abstractions of all colonoscopy reports in the 10-year interval prior to PCCRC diagnosis for cases, and for controls, a comparable 10-year look-back period before their reference date (date of diagnosis in the matching case from the prior case-control study).

Data Analysis

Population characteristics and the frequency of index colonoscopy-related factors were compared using chi-squared tests and t-tests. Multivariable logistic regression was used to evaluate the association between colonoscopy-related factors and PCCRC. For the base model, odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age (50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–90 years), sex (male, female), race/ethnicity (non-Hispanic white, Hispanic, black, Asian/Pacific Islander, other/unknown), family history of colorectal cancer (yes, no), year of index colonoscopy (1993–1998, 1999–2001, 2002–2004, 2005–2007, 2008–2012), time from index colonoscopy to the cancer diagnosis/reference date, medical region (KPNC, KPSC), extent of examination (complete or incomplete), and adequacy of the bowel preparation (adequate or inadequate). Because of the strong collinearity between the polyp- and adenoma-related factors, these were evaluated in separate multivariable models. Model 1 added polyp detection to the base model as a 2-level variable (yes, no). Model 2 added polyp detection/size/location to the base model as a 5-level variable (no polyp, distal polyp <10 mm, distal polyp ≥10 mm, proximal polyp <10 mm, and proximal polyp ≥10 mm). Model 3 added adenoma/histology to the base model as a 3-level variable (no adenoma, adenoma without advanced histology, and adenoma with advanced histology), and only KPNC data were utilized for Model 3. For extent of examination, we examined the potential modifying effect of sex by including an interaction term in the model. In sensitivity analyses, we evaluated the influence of excluding 75 patients who had >1 colonoscopy in the year before the index colonoscopy, and separately, 295 patients whose colonoscopy report was missing bowel preparation data (n=258) and/or extent of the examination (n=105). Also, in an analysis restricted to KPNC data, we separately added to the base model (described above), index colonoscopy indication (i.e., screening, surveillance, or diagnostic) ascertained using a validated algorithm,[30] physician adenoma detection rate (quartiles) for the year of the index colonoscopy, and physician experience defined as years from medical school graduation to the index colonoscopy.

Multivariable logistic regression was performed to evaluate the association between colonoscopy-related factors specific to the colonic segment in which the PCCRC was subsequently diagnosed, and early PCCRC (case-only analysis); late PCCRC served as the reference group. The risk factors evaluated included whether the colonic segment in which the PCCRC was subsequently diagnosed was examined at the index colonoscopy, whether a polyp was found in the segment (no polyp, polyp <10 mm, or polyp ≥10 mm), and whether the polyp was completely excised. The base model adjusted for age, sex, race/ethnicity, family history of colorectal cancer, year of the index colonoscopy, and medical region. All analyses were performed using SAS version 9.3 and Stata version 14.2 for Windows (StataCorp, College Station, Texas).

Results

Participant Characteristics

The mean (±standard deviation [SD]) age of study participants was 68.9±9.0 years, 52.0% were male, 68.9% were non-Hispanic white, and 71.5% were KPNC health plan members (Table 1). Cases and controls had similar ages (mean±SD: 68.5±9.1 vs. 69.9±8.6,

respectively) and average time intervals from index colonoscopy to cancer diagnosis or reference date (mean±SD: 4.1±2.1 vs. 4.3±2.5 years, respectively) (Table 1). Among cases, 36.6% of PCCRC's arose >12 months to ≤36 months after the index colonoscopy.

Quality and Finding Characteristics of the Index Colonoscopy Examinations

Inadequate bowel preparation was noted in 11.4% of cases and 10.6% of controls; 14.0% of procedures did not report the adequacy of the bowel preparation. Incomplete colonoscopies were reported in 8.9% of cases and 2.2% of controls; 5.7% of procedures did not report the extent of the examination. The detection of any polyp was more common among cases than controls (64.0% vs. 43.5%), as well as any polyp ≥10 mm (22.2% vs. 5.1%; 7.6% unknown size). Adenomas were also more common among KPNC cases compared to controls (47.8% vs. 43.4%), and 12.8% of cases had adenomas with advanced histology compared to 4.1% for controls, with 7.8% having unknown histology (Table 2).

Index Colonoscopy-Related Risk Factors for PCCRC

In adjusted analyses (Table 3), the detection of any polyp (OR 2.68; 95% CI 2.15, 3.34) and an incomplete colonoscopy (OR 5.52 95% CI 2.98, 10.21) were both significantly associated with PCCRC, whereas inadequate bowel preparation was not (OR 1.11; 95% CI 0.78, 1.57) (Model 1). ORs for incomplete examination and inadequate bowel preparation were comparable for Models 2 and 3, and therefore are not reported. There was no significant difference between women (OR 6.22; 95% CI 2.77, 13.96) and men (OR 4.89; 95% CI 1.87, 12.77) (p-interaction=0.82) in the association between an incomplete colonoscopy and PCCRC.

Compared to no polyps, a proximal polyp ≥10mm (OR 8.18; 95% CI 4.59, 14.60) and a distal polyp ≥10mm (OR 3.30; 95% CI 1.65, 6.58) were significantly associated with PCCRC (Model 2). A proximal polyp <10 mm (OR 1.32; 95% CI 0.97, 1.81) and a distal polyp <10 mm (OR 1.06; 95% CI 0.73, 1.53) were not significantly associated with PCCRC.

Compared to no adenoma, an adenoma with advanced histology (OR 3.23; 95% CI 1.83, 5.68) and without advanced histology (OR 1.87; 95% CI 1.37, 2.55) were both significantly associated with PCCRC (Model 3, Table 3).

Among 1206 cases, 559 (46.4%) had 1 or more of the risk factors that were significant for PCCRC (incomplete examination, large polyp, or any adenoma); among 634 controls, 155 (24.5%) had 1 or more risk factors.

In sensitivity analyses, the main risk estimates were not substantially changed by excluding 75 cases with one or more colonoscopies in the year before the index colonoscopy (Supplemental Table S1), or by excluding 295 patients with missing information on the adequacy of bowel preparation and/or completeness of the examination (Supplemental Table S2). Also, compared with screening colonoscopies, diagnostic colonoscopies were associated with a higher risk of PCCRC, physician adenoma detection rates were inversely associated with PCCRC, and physician experience was not a significant factor (Supplemental Table S3).

Index Colonoscopy-Related Risk Factors for Early vs. Late PCCRCs

In comparison to cases with a late PCCRC, an incomplete polyp excision in the colonic segment where the PCCRC was found (OR 4.76; 95% CI 2.35, 9.65), a polyp ≥10 mm in the segment (OR 2.38; 95% CI 1.53, 3.70), and failure to examine the segment (OR 2.42; 95% CI 1.27, 4.60) during the index colonoscopy were all significantly associated with early PCCRC (Table 4). A polyp <10 mm at the segment was not significantly associated with PCCRC (OR 0.85; 95% CI 0.59, 1.24). Among 48 cases who had an incomplete polyp excision at the colonic segment where cancer was subsequently diagnosed, 4 (8.3%) were re-examined within 12 months to evaluate the post-polypectomy site; 2 (4.2%) refused recommended surgical follow-up; 12 (25.0%) had follow-up at or shortly after recommended intervals, but the intervals ranged between >1 and 5 years post examination; and 30 (62.5%) did not follow-up until the time of cancer diagnosis.

Discussion

In a large community-based integrated healthcare setting with up to 10 years of follow-up, index colonoscopy-related factors significantly associated with PCCRC were any colonic polyp ≥10 mm in size, an incomplete examination, and any adenoma. Inadequate bowel preparation and polyps <10 mm in size were not significantly associated with PCCRC. Also, incomplete polyp excision in the colonic segment where the PCCRC was subsequently found, a polyp ≥10 mm in the segment, and failure to examine the segment were significantly associated with early PCCRC, whereas a polyp <10 mm in that segment was not significantly associated with early PCCRC.

Several potential clinical and endoscopy-related risk factors for PCCRC and interval cancer have been suggested,[4,5,8] including higher and lower comorbidity score;[31–34] older age;[31,32,35] female sex;[20,31,33] colonoscopy as follow-up to a positive fecal test;[20] prior diverticular disease or history of abdominal/pelvic surgery;[32,33,35] tumor molecular characteristics such as microsatellite instability and CpG island methylator positive phenotype;[36] family history of colorectal cancer;[22] colonoscopy performed by a non-gastroenterologist[31,34,35,37] or in a non-academic or non-inpatient setting;[31,32] and colonoscopy performed by an examiner with a high incomplete colonoscopy rate,[31] low polypectomy rate,[31,32] or low annual colonoscopy volume.[32] Also, some prior studies have implicated incomplete resection and missed lesions at colonoscopy as risk factors,[15–18] while case-control and cohort studies have implicated incomplete resection and incomplete examinations.[19–22] The current study extends the findings of prior studies by demonstrating an association between factors related to missed and incompletely excised lesions at the index colonoscopy and PCCRC and early PCCRC in an extremely large community-based population, including >2% of the United States population, in an integrated healthcare setting with comprehensive capture of cancers and detailed medical records, with non-cancer controls, and among patients followed for up to 10 years post-examination.

The presence of a large polyp at the index colonoscopy was strongly associated with PCCRC. Large polyps are more likely to require piecemeal excision, increasing the chance of incomplete resection, which can result in progression of the residual lesion to cancer. In a study of 269 patients who had 346 neoplastic polyps removed, 10.1% were incompletely

resected, and the incomplete resection rate was higher for polyps 10–20 mm in size than smaller polyps (17.3% vs. 6.8%).[38] Moreover, 20.4% of polyps removed piecemeal were incompletely resected.[38] In another study, following piecemeal excision of sessile adenomas >20 mm in size in which all adenomatous tissue was believed to have been removed, the adenoma recurrence rate 6 months after excision was 46.0%.[39] Lesion location was also a significant predictor of PCCRC. A large lesion in the proximal colon was a stronger risk factor than a large lesion in the distal colon. Proximal lesions are more likely to be flat or depressed, making them harder to detect, potentially more difficult to resect, and some of them may progress more rapidly to colorectal cancer.[4,7]

Another factor strongly associated with PCCRC was incomplete colonoscopy. Failure to intubate the cecum and complete a full structural examination contributes to PCCRC through the mechanism of missed lesions.[7] In a prior study, patients whose colonoscopy was performed by endoscopists with cecal intubation rates of ≥95% had a 27% lower risk of PCCRC than patients whose examiners had cecal intubation rates of <80%.[31] The current study's findings are consistent with a smaller German study of 78 patients with PCCRCs vs. 433 patients with CRC detected at screening, in which incomplete examination was associated with a 2.6-fold higher odds of PCCRC.[20] The German study noted the PCCRC risk varied by sex; women with an incomplete examination had a >4-fold increased odds of PCCRC, whereas for men, incomplete examination was not significantly associated with PCCRC.[20] Other studies have suggested female sex is a risk factor for PCCRC,[20,31,33] and incomplete examination may be a contributing factor.[7,40] However, the current, much larger study did not find a significantly stronger association in women compared to men.

Adenomas with and without advanced histology at the index colonoscopy were also significantly associated with PCCRC. These findings are consistent with a previous study in which patients with an adenoma at colonoscopy had higher odds of PCCRC (OR 1.89; 1.29, 2.77), compared to patients without an adenoma, while those with a villous adenoma had >8-fold higher odds (OR 8.40; 95% CI 5.57, 12.66).[22]

We also found that failing to completely excise a polyp in the colonic segment where the PCCRC was subsequently diagnosed conferred a more than 4-fold increase in the odds of an early-arising PCCRC, compared to a late-arising PCCRC, while failure to examine the relevant colonic segment, and having a polyp ≥10 mm in size in the relevant segment, each conferred over a 2-fold increase in odds. These findings are consistent with the assumption that missed or incompletely excised lesions are more likely to progress to cancer faster than new lesions developing de-novo.

Study strengths include the large number of PCCRC cases, the use of non-cancer controls from the same underlying population to minimize selection bias, adjustment of OR estimates for important potential confounders, and the integrated healthcare setting provided a stable community-based population with comprehensive clinical information in linked databases which enabled accurate exposure and outcome ascertainment that eliminated potential bias associated with differential recall between cases and controls.

Study limitations include the possibility of residual confounding inherent in observational studies. The use of controls selected for another concurrent study increased feasibility/efficiency, but precluded matching on time from index colonoscopy to cancer diagnosis/reference date; however, the time distributions among cases and controls were similar, and inclusion as a covariate did not alter the main estimates and conclusions. The lack of adenoma data from KPSC limited the extent to which we were able to examine physician adenoma detection rate as a risk factor. The study design precluded calculations of exact attributable risk estimates, although the 46.4% of PCCRC cases with at least 1 significant risk factor supports the stated conclusions. In future studies, evaluating PCCRC by adherence to surveillance interval recommendations would be informative.

Conclusions

In a large community-based integrated healthcare setting, factors related to missed and incompletely resected neoplasia at the index colonoscopy were significantly associated with PCCRC and early PCCRC. These findings suggest that improvements in the performance of colonoscopy, particularly related to ensuring complete examinations and excision of polyps, may substantially reduce the burden of PCCRC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CRC	colorectal cancer
CI	confidence interval
KPNC	Kaiser Permanente Northern California
KPSC	Kaiser Permanente Southern California; n, number
PROSPR	Population-based Research Optimizing Screening through Personalized Regimens
SNOMED	Systematized Nomenclature of Medicine
SEER	Surveillance Epidemiology and End Results
SD	standard deviation

References

1. Colorectal Cancer Statistics. http://www.cdc.gov/cancer/colorectal/statistics/index.htm. Accessed 3/29/16.
2. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149(9):627–637. [PubMed: 18838716]
3. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23):2564–2575. [PubMed: 27304597]
4. le Clercq CM, Sanduleanu S. Interval colorectal cancers: what and why. Curr Gastroenterol Rep. 2014;16(3):375. [PubMed: 24532192]
5. Sanduleanu S, le Clercq CM, Dekker E, et al. Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. Gut. 2015;64(8):1257–1267. [PubMed: 25193802]
6. Rutter MD, Beintaris I, Valori R, et al. World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer. Gastroenterology. 2018;6 26 pii: S0016–5085(18)34571–2..
7. Adler J, Robertson DJ. Interval Colorectal Cancer After Colonoscopy: Exploring Explanations and Solutions. Am J Gastroenterol. 2015;110(12):1657–1664; quiz 1665. [PubMed: 26553207]
8. Singh S, Singh PP, Murad MH, Singh H, Samadder NJ. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. Am J Gastroenterol. 2014;109(9):1375–1389. [PubMed: 24957158]
9. Rex DK, Bond JH, Feld AD. Medical-legal risks of incident cancers after clearing colonoscopy. Am J Gastroenterol. 2001;96(4):952–957. [PubMed: 11316211]
10. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. The New England journal of medicine. 2014;370(14):1298–1306. [PubMed: 24693890]
11. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. The New England journal of medicine. 2010;362(19):1795–1803. [PubMed: 20463339]
12. Rogal SS, Pinsky PF, Schoen RE. Relationship between detection of adenomas by flexible sigmoidoscopy and interval distal colorectal cancer. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013;11(1):73–78. [PubMed: 22902761]
13. Kaminski MF, Anderson J, Valori R, et al. Leadership training to improve adenoma detection rate in screening colonoscopy: a randomised trial. Gut. 2016;65(4):616–624. [PubMed: 25670810]
14. Kaminski MF, Wieszczy P, Rupinski M, et al. Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death. Gastroenterology. 2017.
15. Pabby A, Schoen RE, Weissfeld JL, et al. Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. Gastrointest Endosc. 2005;61(3):385–391. [PubMed: 15758908]
16. Robertson DJ, Lieberman DA, Winawer SJ, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut. 2014;63(6):949–956. [PubMed: 23793224]
17. le Clercq CM, Bouwens MW, Rondagh EJ, et al. Postcolonoscopy colorectal cancers are preventable: a population-based study. Gut. 2014;63(6):957–963. [PubMed: 23744612]
18. Huang Y, Gong W, Su B, Zhi F, Liu S, Jiang B. Risk and cause of interval colorectal cancer after colonoscopic polypectomy. Digestion. 2012;86(2):148–154. [PubMed: 22889865]
19. Belderbos TD, Pullens HJ, Leenders M, Schipper ME, Siersema PD, van Oijen MG. Risk of post-colonoscopy colorectal cancer due to incomplete adenoma resection: A nationwide, population-based cohort study. United European Gastroenterol J. 2017;5(3):440–447.
20. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Interval cancers after negative colonoscopy: population-based case-control study. Gut. 2012;61(11):1576–1582. [PubMed: 22200840]

21. Farrar WD, Sawhney MS, Nelson DB, Lederle FA, Bond JH. Colorectal cancers found after a complete colonoscopy. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2006;4(10):1259–1264. [PubMed: 16996804]
22. Samadder NJ, Curtin K, Tuohy TM, et al. Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. Gastroenterology. 2014;146(4):950–960. [PubMed: 24417818]
23. Krieger N Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health. 1992;82(5):703–710. [PubMed: 1566949]
24. Gordon NP. How Does the Adult Kaiser Permanente Membership in Northern California Compare with the Larger Community? 2006 http://www.dor.kaiser.org/dor/mhsnet/public/kpnc_community.htm. Accessed March 10, 2017.
25. Koebnick C, Langer-Gould AM, Gould MK, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. Perm J. 2012;16(3):37–41.
26. Corley DA, Jensen CD, Marks AR, Zhao W, Lee JK, Quesenberry C, Levin TR, Doubeni CA, Ballegooijen M, Zauber AG, Schottinger JE, Quinn VP, Ghai NR Physician adenoma detection rate variability and subsequent colorectal cancer risk following a negative colonoscopy. Gastroenterology. 2013;144(5 (supplement 1)):S-2–S-3.
27. Goodman M, Fletcher RH, Doria-Rose VP, et al. Observational methods to assess the effectiveness of screening colonoscopy in reducing right colon cancer mortality risk: SCOLAR. J Comp Eff Res. 2015;4(6):541–551. [PubMed: 26201973]
28. Doubeni CA, Corley DA, Quinn VP, et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. Gut. 2016.
29. CPT 2011 Professional Edition. American Medical Association Press; 2010.
30. Lee JK, Jensen CD, Lee A, et al. Development and validation of an algorithm for classifying colonoscopy indication. Gastrointestinal Endoscopy. 2015;81(3):575–582 e574. [PubMed: 25577596]
31. Baxter NN, Sutradhar R, Forbes SS, Paszat LF, Saskin R, Rabeneck L. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. Gastroenterology. 2011;140(1):65–72. [PubMed: 20854818]
32. Cooper GS, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. Cancer. 2012;118(12):3044–3052. [PubMed: 21989586]
33. Erichsen R, Baron JA, Stoffel EM, Laurberg S, Sandler RS, Sorensen HT. Characteristics and survival of interval and sporadic colorectal cancer patients: a nationwide population-based cohort study. Am J Gastroenterol. 2013;108(8):1332–1340. [PubMed: 23774154]
34. Singh H, Nugent Z, Demers AA, Bernstein CN. Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. The American journal of gastroenterology. 2010;105(12):2588–2596. [PubMed: 20877348]
35. Bressler B, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology. 2007;132(1):96–102. [PubMed: 17241863]
36. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369(12):1095–1105. [PubMed: 24047059]
37. Haseman JH, Lemmel GT, Rahmani EY, Rex DK. Failure of colonoscopy to detect colorectal cancer: evaluation of 47 cases in 20 hospitals. Gastrointest Endosc. 1997;45(6):451–455. [PubMed: 9199899]
38. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology. 2013;144(1):74–80 e71. [PubMed: 23022496]

39. Zlatanic J, Waye JD, Kim PS, Baiocco PJ, Gleim GW. Large sessile colonic adenomas: use of argon plasma coagulator to supplement piecemeal snare polypectomy. Gastrointest Endosc. 1999;49(6):731–735. [PubMed: 10343218]

40. Chutkan R Colonoscopy issues related to women. Gastrointest Endosc Clin N Am. 2006;16(1):153–163. [PubMed: 16546030]

Table 1.

Characteristics of cases and controls.

	Cases n (%)		Controls n (%)		Total n (%)	
Total	1,206		634		1,840	
Age at index colonoscopy						
50 to 64 years	407	(33.8)	176	(27.8)	583	(31.7)
65 to 90 years	799	(66.3)	458	(72.2)	1,257	(68.3)
Mean (SD), years	68.5	(9.1)	69.9	(8.6)	68.9	(9.0)
Sex						
Female	590	(48.9)	293	(46.2)	883	(48.0)
Male	616	(51.1)	341	(53.8)	957	(52.0)
Race/ethnicity						
Non-Hispanic White	824	(68.3)	444	(70.0)	1,268	(68.9)
Hispanic	125	(10.4)	68	(10.7)	193	(10.5)
Black	118	(9.8)	53	(8.4)	171	(9.3)
Asian/Pacific Islander	80	(6.6)	60	(9.5)	140	(7.6)
Other/Unknown	59	(4.9)	9	(1.4)	68	(3.7)
Family history of colorectal cancer						
No	991	(82.2)	512	(80.8)	1,503	(81.7)
Yes	215	(17.8)	122	(19.2)	337	(18.3)
Index colonoscopy time interval						
1993–1998	213	(17.7)	32	(5.1)	245	(13.3)
1999–2001	221	(18.3)	96	(15.1)	317	(17.2)
2002–2004	280	(23.2)	145	(22.9)	425	(23.1)
2005–2007	356	(29.5)	239	(37.7)	595	(32.3)
2008–2012	136	(11.3)	122	(19.2)	258	(14.0)
Median year	2004		2005		2004	
Time from index colonoscopy to diagnosis/reference date						
>12 months to ≤36 months	441	(36.6)	247	(39.0)	688	(37.4)
>36 months to 10 years	765	(63.4)	387	(61.0)	1,152	(62.6)
Mean (SD) (years)	4.1	(2.1)	4.3	(2.5)	4.2	(2.2)
Health plan region						
KPNC	827	(68.6)	488	(77.0)	1,315	(71.5)
KPSC	379	(31.4)	146	(23.0)	525	(28.5)

n, number; SD, standard deviation; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California.

Table 2.

Characteristics of the index colonoscopy examinations for cases and controls.

	Cases n (%)		Controls n (%)		Total n (%)		P-value
Total	1,206		634		1,840		
Adequacy of bowel preparation							
Adequate	851	(70.6)	526	(83.0)	1,377	(74.8)	
Inadequate	138	(11.4)	67	(10.6)	205	(11.1)	
Unknown	217	(18.0)	41	(6.5)	258	(14.0)	<0.001
Extent of examination							
Complete	1,049	(87.0)	565	(89.1)	1,614	(87.7)	
Incomplete	107	(8.9)	14	(2.2)	121	(6.6)	
Unknown	50	(4.2)	55	(8.7)	105	(5.7)	<0.001
Polyp, by size							
No polyp	434	(36.0)	358	(56.5)	792	(43.0)	
<10mm	393	(32.6)	215	(33.9)	608	(33.0)	
≥10mm	268	(22.2)	32	(5.1)	300	(16.3)	
Unknown size	111	(9.2)	29	(4.6)	140	(7.6)	<0.001
Polyp, by location							
No polyp	434	(36.0)	358	(56.5)	792	(43.0)	
Proximal	132	(11.0)	74	(11.7)	206	(11.2)	
Distal	170	(14.1)	102	(16.1)	272	(14.8)	
Proximal and distal	221	(18.3)	73	(11.5)	294	(16.0)	
Unknown location	249	(20.7)	27	(4.3)	276	(15.0)	<0.001
KPNC data only	827		488		1315		
Adenoma, by histology							
No adenoma	432	(52.2)	276	(56.6)	708	(53.8)	
No advanced histology	267	(32.3)	111	(22.8)	378	(28.8)	
Advanced histology	106	(12.8)	20	(4.1)	126	(9.6)	
Unknown histology	22	(2.7)	81	(16.6)	103	(7.8)	<0.001
Index Colonoscopy Indication							
Screening	202	(24.4)	111	(22.8)	313	(23.8)	
Surveillance	153	(18.5)	70	(14.3)	223	(17.0)	
Diagnostic	452	(54.7)	229	(46.9)	681	(51.8)	
Unknown	20	(2.4)	78	(16.0)	98	(7.5)	<0.001
Physician Adenoma Detection Rate, %							
Quartile 1: <19	177	(21.4)	97	(19.9)	274	(20.8)	
Quartile 2: 19 to <25	168	(20.3)	95	(19.5)	263	(20.0)	
Quartile 3: 25 to <32	172	(20.8)	105	(21.5)	277	(21.1)	
Quartile 4: 32 to 61	190	(23.0)	91	(18.7)	281	(21.4)	
Unknown	120	(14.5)	100	(20.5)	220	(16.7)	0.04
Median	*0.257*		*0.253*		*0.255*		

	Cases n (%)		Controls n (%)		Total n (%)		P-value
Physician experience, years							
Quartile 1: <14	206	(24.9)	108	(22.1)	314	(23.9)	
Quartile 2: 14 to <20	177	(21.4)	91	(18.7)	268	(20.4)	
Quartile 3: 20 to <28	195	(23.6)	109	(22.3)	304	(23.1)	
Quartile 4: 28 to 47	178	(21.5)	96	(19.7)	274	(20.8)	
Unknown	71	(8.6)	84	(17.2)	155	(11.8)	<0.001
Median	*19*		*20*		*19*		

n, number; SD, standard deviation; KPNC, Kaiser Permanente Northern California.

Adequate bowel preparation was defined as a preparation listed in the index colonoscopy report as satisfactory, good, very good, excellent, or optimal. *Inadequate bowel preparation* was defined as a preparation listed in the index colonoscopy procedure report as fair, poor, suboptimal, inadequate or unsatisfactory. *Complete colonoscopy* was defined as to the cecum or terminal ileum.

Index colonoscopy indication (screening, surveillance, or diagnostic) was ascertained using a validated algorithm, physician adenoma detection rate was for the year of the index colonoscopy, and physician experience was defined as years from medical school graduation to the index colonoscopy.

Table 3.

Association between index colonoscopy quality and examination findings and post-colonoscopy colorectal cancer (PCCRC).

		Cases		Controls			
Model	**At Index Colonoscopy**	**n**	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**
	Total	*1,206*		*634*			
1	No polyp	434	(36.0)	358	(56.5)	1.00	(reference)
	Polyp	772	(64.0)	276	(43.5)	2.68	(2.15, 3.34)
	Complete examination	1,099	(91.1)	620	(97.8)	1.00	(reference)
	Incomplete examination	107	(8.9)	14	(2.2)	5.52	(2.98, 10.21)
	Adequate bowel preparation	1,068	(88.6)	567	(89.4)	1.00	(reference)
	Inadequate bowel preparation	138	(11.4)	67	(10.6)	1.11	(0.78, 1.57)
	Total	*917*		*581*			
2	No polyp	434	(47.3)	358	(61.2)	1.00	(reference)
	Distal polyp, <10 mm	97	(10.6)	80	(13.8)	1.06	(0.73, 1.53)
	Distal polyp, ≥10 mm	59	(6.4)	12	(2.1)	3.30	(1.65, 6.58)
	Proximal polyp, <10 mm	176	(19.2)	115	(19.8)	1.32	(0.97, 1.81)
	Proximal polyp, ≥10 mm	151	(16.5)	16	(2.8)	8.18	(4.59, 14.60)
	Total (KPNC only)	*805*		*407*			
3	No adenoma	432	(53.7)	276	(67.8)	1.00	(reference)
	Adenoma, no advanced histology	267	(33.2)	111	(27.3)	1.87	(1.37, 2.55)
	Adenoma, advanced histology	106	(13.2)	20	(4.9)	3.23	(1.83, 5.68)

n, number.

Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age, sex, race/ethnicity, family history of colorectal cancer, year of index colonoscopy, time from index colonoscopy to the cancer diagnosis/reference date, medical region, extent of examination, and adequacy of the bowel preparation (base model).

In Model 1, polyp detection was added to the base model. In Model 2, polyp detection/size/location was added to the base model. In Model 3, adenoma/histology was added to the base model and only Kaiser Permanente Northern California (KPNC) data were utilized because histology status was not available from Kaiser Permanente Southern California.

Adequate bowel preparation was defined as a preparation listed in the index colonoscopy report as satisfactory, good, very good, excellent, or optimal. *Inadequate bowel preparation* was defined as a preparation listed in the index colonoscopy procedure report as fair, poor, suboptimal, inadequate or unsatisfactory. *Complete colonoscopy* was defined as to the cecum or terminal ileum. *Adenoma with advanced histology* was defined as a villous or tubulovillous adenoma.

Colonoscopies detecting both proximal and distal polyps were categorized as proximal for these analyses.

Table 4.

Association between early vs. late post-colonoscopy colorectal cancer (PCCRC) and index colonoscopy quality and examination findings.

		Early PCCRC		Late PCCRC			
Model	**At Index Colonoscopy**	**n**	**(%)**	**n**	**(%)**	**OR**	**(95% CI)**
	Total	441		765			
1	Colonic segment * examined						
	Yes	401	(93.5)	720	(97.0)	1.00	(reference)
	No	28	(6.5)	22	(3.0)	2.42	(1.27, 4.60)
2	Polyp detected at colonic segment *						
	No	314	(71.2)	579	(75.7)	1.00	(reference)
	Yes	127	(28.8)	186	(24.3)	1.27	(0.94, 1.72)
3	Polyp detected at colonic segment *						
	No	314	(71.2)	579	(75.7)	1.00	(reference)
	Yes, <10 mm	61	(13.8)	133	(17.4)	0.85	(0.59, 1.24)
	Yes, ≥10 mm	66	(15.0)	53	(6.9)	2.38	(1.53, 3.70)
4	Polyp excision at colonic segment *						
	No polyp	303	(73.0)	558	(77.0)	1.00	(reference)
	Complete excision	77	(18.6)	154	(21.2)	0.95	(0.67, 1.34)
	Incomplete excision	35	(8.4)	13	(1.8)	4.76	(2.35, 9.65)

n, number.

Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age, sex, race/ethnicity, family history of colorectal cancer, year of index colonoscopy, and medical region.

*Colonic segment refers to the segment of the colon where the PCCRC was subsequently found.