Colonoscopy and colorectal cancer mortality within the Veterans Affairs Health System. A case-control study

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Abstract

Background: While colonoscopy is widely used in the Veterans Affairs (VA) system for colorectal cancer (CRC) prevention, its effect on CRC mortality is unknown.

Objective: To determine whether colonoscopy is associated with decreased CRC mortality in Veterans, and whether its effect differs by anatomic location.

Design: Case-control

Setting: Veterans Affairs-Medicare administrative data

Participants: Cases were Veterans aged 52 or older diagnosed with CRC between 2002 and 2008, and died of CRC by the end of 2010. Cases were age-, sex-, and facility-matched to 4 controls without prior CRC. Conditional logistic regression was performed to calculate odds ratios (OR) for exposure to colonoscopy, adjusted for race, Charlson comorbidity score, selected chronic conditions, NSAID use, and family history of CRC.

Measure: Exposure to colonoscopy was determined from 1997 to 6 months before CRC diagnosis in cases, and to a corresponding date in controls. Subgroup analysis was performed for patients who had undergone a colonoscopy for screening.

Results: 4,964 cases and 19,856 controls were identified. Cases were significantly less likely than controls to have undergone any colonoscopy (OR=0.39; 95% CI, 0.35-0.43). Colonoscopy was associated with reduced mortality for left-sided cancer (OR=0.28; 95% CI, 0.24-0.32) and right-sided cancer (OR=0.54; 95% CI, 0.47-0.63). The results were similar for the subgroup of patients who had undergone colonoscopy for screening (overall OR 0.30 (95% CI, 0.24-0.38). Sensitivity analysis varying the time interval before CRC diagnosis and colonoscopy exposure did not affect the primary findings.

Limitations: Unmeasured confounding

Conclusions: In this national VA-Medicare study, colonoscopy was associated with significant reductions in CRC mortality among Veterans. Colonoscopy was associated with greater benefit for left- than for right-sided cancers.

INTRODUCTION

In the United States, colonoscopy is the dominant modality for colorectal cancer (CRC) screening[1]. Colonoscopy was first endorsed for this indication in 1997 based on several observational studies, and the concept that it would extend the benefits of sigmoidoscopic screening to the entire colon. Screening colonoscopy became a Medicare benefit in 2001, and its use has increased exponentially, with annual volume estimates ranging from 11.5 to 14 million[2,3]. However, screening colonoscopy is not supported by randomized controlled trials, and recent studies have challenged whether colonoscopy offers incremental benefit over sigmoidoscopy in screening the proximal colon: case-control studies in Canadian populations showed that colonoscopy was associated with reduction in risk of death from left-sided CRC, but not right-sided cancer[4,5]. Conversely, studies from Germany[6-8] and the United States[9] reported that colonoscopy was associated with decreased incidence and mortality for both left-sided and right-sided CRC, although the benefit was less in the proximal colon. These inconsistent findings and variable degree of protection of colonoscopy against CRC have been partly attributed to operator-dependent quality factors[10].

The Veterans Health Administration (VHA) is the largest integrated health care provider in the United States. The VHA system includes 168 medical centers and 1,053 outpatient clinics which provide services to nearly 9 million Veterans each year. The use of colonoscopy for colorectal cancer (CRC) screening in the VHA has been expanding: a more than 2-fold increase in the use of screening colonoscopy and a decrease in the use of sigmoidoscopy and double-contrast barium enema was noted between 1997 and 2003[11], and the VHA endorsed colonoscopy as a primary CRC screening option for patients 50 years or older in 2007. Despite these trends, it is unknown whether colonoscopy decreases CRC mortality among Veterans, and whether there is a variable effect based on anatomic location of CRC. Estimating colonoscopy effectiveness is important from an individual perspective. Veterans differ from the general population with regards to colon neoplasia risk factors (male gender, cigarette smoking)

and have higher CRC and adenoma prevalence[12]. From a systems perspective, the VHA is centralized and less reliant on financial incentives for individual providers, and thus may provide a reference standard for other health care systems. In the context of increasing utilization of colonoscopy, and its dominance as a CRC screening modality in the US, knowledge of the impact on important patient outcomes is critical to guide health care resource utilization and policy, both within the VHA and in other health care settings.

We conducted a case-control study using national VA-Medicare administrative data to determine whether colonoscopy is associated with decreased CRC mortality in Veterans, and whether its effect differs by anatomic location.

METHODS

The study was approved by the Institutional Review Boards at Indiana University-Purdue University at Indianapolis and Dartmouth Institute Dartmouth-Hitchcock Medical Center, and the Research and Development Committees of the Richard L. Roudebush VA Medical Center (Indianapolis, Indiana), and the VA Medical Center at White River Junction (Vermont).

Study population

The sampling frame consisted of Veterans with inpatient and/or outpatient visits at any VA facility from 1997 to 2010. Case and control definitions are broadly similar to those employed in the studies by Baxter and colleagues[4,9]. To ensure that cases and controls are representative of Veterans who receive health care predominantly in the VHA system[13], we only included Veterans with at least 2 primary care visits at one VA facility in the 3 years preceding the diagnosis of cancer in cases and corresponding index date in controls.

Identification of cases

Cases were Veterans who received a diagnosis and died of CRC when they were 52 years or older. We chose 52 years, to allow inclusion of controls who were screen-eligible (50 years or older) during the study time frame.

Cases were identified from January 1, 2002 to December 31, 2008, and died of CRC between January 1, 2002 and December 31, 2010. Patients with a diagnosis of CRC and who died due to other causes were not counted as cases. Patients were excluded for a personal history of CRC or surgical resection of CRC prior to January 1, 2002.

Patients with Crohn's disease, ulcerative colitis, and familial polyposis were also excluded. Cancers were categorized as right-sided (cecum, ascending colon, hepatic flexure, transverse colon) and left-sided (splenic flexure, descending colon, sigmoid colon, rectum).

Identification of controls

Controls were assigned an index date that corresponds to the date of CRC diagnosis in their matched case subject. Controls were Veterans who did not receive a diagnosis of CRC prior to the index date, nor die of CRC prior to December 31, 2010. For each case, we matched 4 controls according to age (± 1 year), sex, and VA medical center. Similar to cases, controls with a history of Crohn's disease, ulcerative colitis, or familial polyposis were excluded. Similar to prior studies, controls were alive at the time of death of a matched case patient[4,9].

Exposure

The exposure was defined as undergoing colonoscopy from January 1, 1997 to a date 6 months before the diagnosis of CRC in a case patient or the corresponding index date in matched controls (Figure 1). If a case patient had undergone more than one colonoscopy during the exposure time frame, the first colonoscopy was counted as the exposure. We performed subgroup analysis to determine the exposure of cases and controls to screening colonoscopy, utilizing an algorithm developed and validated in VA administrative data by El-Serag and colleagues[11] for the classification of colonoscopy indication according to administrative codes. The algorithm defines screening colonoscopy based on the absence of prior codes associated

with gastrointestinal disorders (diagnostic indication) or history of polyps (surveillance indication). The algorithm has about 70% sensitivity and 72% specificity.

Confounding factors

For all cases and controls, we calculated a Charlson comorbidity score[14,15] based on one inpatient code or ≥ 2 outpatient codes separated by at least a 30-day period, within the 1-year before index date (date of diagnosis for cases, corresponding time point for matched controls)[16]. We measured duration of use, expressed as days of aspirin, NSAID, and statin prescription. This was divided into none, >0-3 years, 3-5 years, and ≥ 5 years. We adjusted for confounders which may affect CRC risk, including race, Charlson Comorbidity Score, socioeconomic status, diabetes mellitus, cigarette smoking, family history of CRC, ischemic heart disease, cholecystectomy, and use of aspirin, NSAIDs, and statins. We measured the number of PSA measurements (in men) during the study time frame, to assess health-care utilization propensity.

Data Sources

Data for this study were obtained from the following electronic sources:

1. VA Central Cancer Registry (VACCR) was used to ascertain the diagnosis of CRC for case patients and the exclusion of CRC among the controls. The VACCR has excellent sensitivity[17]. Cancer diagnoses within VHA are submitted to the VACCR every 6 months. This registry includes demographic information, date of diagnosis, pathologic confirmation, cancer location within the colon and rectum, previous cancer, and stage of cancer.

2. The VA Medical SAS datasets contain national administrative data on all VA inpatient stays and outpatient encounters. This dataset was used to abstract patient level information on performance of colonoscopy, dates, comorbidities, and primary care visits. Outpatient procedures are coded using the Current Procedural Terminology (CPT) codes and the Healthcare Common Procedure Coding System (HCPCS) codes. Inpatient procedures and

diagnoses are coded according to the 9th revision of the Clinical Modification of the International Classification of Diseases (ICD-9-CM).

3. Linked VA-Centers for Medicare and Medicaid Services (CMS) data were used to identify Veterans who had colonoscopies performed in non-VA facilities for which CMS was the primary payer. Similar to the VA Medical SAS datasets, the VA-CMS data contain inpatient and outpatient data, including diagnoses, procedure dates, and other healthcare utilization information.

4. Department of Defense (DoD) Suicide Data Registry (SDR) was used to identify patients with CRC who died of their cancer (cases). The registry contains date of death and cause of death information for all VA health system users, which is based on information from the National Death Index (NDI), the "gold standard" for death ascertainment. At the time of the study, cause of death information was available through 2010.

5. Pharmacy Benefits Management Services (PBM) contains information about all outpatient prescriptions dispensed within the VHA since FY 1999. The PBM was accessed to obtain information regarding exposure to aspirin, other NSAIDs, and statin medications, from 1999 to the day prior to the index date.

Statistical Analysis

Descriptive statistics for demographic and clinical variables were calculated for cases and controls. We used chi-square or Fishers exact test to compare proportions and t-tests to compare continuous variables. The primary analysis was based on the matched quintuplets (1 case, 4 controls). We performed conditional logistic regression, adjusting for potential confounders, to calculate the odds ratio (OR) with 95% confidence intervals for death from CRC by exposure to colonoscopy. This calculation was performed using colonoscopy as the exposure, and then repeated for screening colonoscopy as the exposure (based on the El-Serag algorithm[11]). To investigate the association between exposure to colonoscopy and the

anatomic location of cancer (right-sided or left-sided), we recalculated odds ratios for death from CRC based on the location of cancer. To assess the effect of varying control definitions, we performed a sensitivity analysis in which the CRC diagnosis restriction was removed; in other words, controls could have been diagnosed with CRC *prior* to the index date. Sensitivity analysis was also performed to determine the effect of varying the 6-month time window between CRC diagnosis (and corresponding index date in controls) and exposure to colonoscopy, using a window of 3, 12, and 24 months. All analyses were performed using SAS v9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 4,964 cases and 19,856 controls were identified; mean age (± SD) was 70.7 ± 10.0 years, and 99.3 % were male. Clinical characteristics of cases and controls are shown in Table 1. Cases had higher comorbidity burden, as reflected by higher mean Charlson comorbidity score. The proportion of patients exposed to colonoscopy was significantly lower for cases than controls (13.5 % vs 26.4 %, $p<0.0001$). There were 668 cases and 5,250 controls exposed to colonoscopy; the indication was diagnostic in 68.7 % and 60.9 %, screening in 15.3 % and 21.3 %, and surveillance in 16.0 % and 17.8 %, respectively ($p = 0.0002$). Median time between colonoscopy and CRC diagnosis was 43.5 months (range 6 to141) in the cases. The proportions of patients who underwent colonoscopy for a screening indication were 8.0% for 1997-2001, 32.2% for 2001-2006, and 32.6% for 2007 and later.

Unadjusted and adjusted odds ratios for the association between colonoscopy and CRC death are presented in Figures 2 and 3. Cases were significantly less likely than controls to have undergone any colonoscopy (adjusted OR=0.39; 95% CI, 0.35-0.43). Colonoscopy was associated with reduced odds for left-sided cancer (aOR=0.28; 95% CI, 0.24-0.38) and right-sided cancer (aOR=0.54; 95% CI, 0.47-0.63). Among cases and controls exposed to screening

colonoscopy, the adjusted ORs were 0.30 (95% CI, 0.24 -0.38) overall, 0.20 (95% CI, 0.14 - 0.27) for left-sided cancer, and 0.48 (95% CI, 0.35-0.66) for right-sided cancer.

In sensitivity analyses, varying the time interval between CRC diagnosis date for cases (and corresponding index date for controls) and exposure to colonoscopy did not significantly change the main results when the exclusionary period was set at 3 months (adjusted OR 0.39, 95% CI 0.36-0.43), 12 months (adjusted OR 0.40, 95% CI 0.36-0.44) or 24 months (adjusted OR=0.41, 95% CI 0.36-0.45). In addition, the results were not affected by varying the definition of controls to allow CRC diagnoses prior to the index date. Finally, the odds of exposure to colonoscopy were not significantly changed based on time period [adjusted OR 0.40 (95% CI 0.35-0.45) for 1997-2002, 0.38 (95% CI 0.34-0.43) for 2002-2008].

DISCUSSION

In this national VA-Medicare study, colonoscopy was associated with a 61 % reduction in CRC mortality among Veterans. This mortality reduction was observed for left-sided and right-sided CRC, although the association was weaker for right-sided cancer (46 % versus 72 % mortality reduction). These trends were maintained in the screening colonoscopy subgroup.

Several studies have assessed the association of colonoscopy with CRC incidence and mortality[4-9,18-25]. Population-based case-control studies from Ontario[4] and Manitoba[5], Canada, initially reported that colonoscopy was associated with a 47% to 67% reduction in distal CRC mortality risk, but afforded no protection against proximal colon cancer. These findings have been partly attributed to characteristics of the Canadian system, where colonoscopy is performed predominantly by non-gastroenterologists[10]. Several studies[26-28] have shown that physician specialty is associated with colonoscopy quality, with gastroenterologists outperforming physicians from other disciplines. Subsequent case-control studies from Germany and the United States, where gastroenterologists perform most colonoscopies, have shown that colonoscopy was associated with decreased proximal colon cancer incidence[6] and mortality[8,9,25]. To our knowledge, this is the first study to assess whether colonoscopy is

associated with CRC mortality reduction in the Veterans Affairs system, the largest integrated healthcare system in the United States.

Our study can be most directly compared to that of Baxter and colleagues[9] which used SEER-Medicare data, as both studies employed a similar design and are US-based. In the Baxter study, cases who had died of CRC were less likely than matched controls to have undergone colonoscopy (OR, 0.40; 95% CI, 0.37 to 0.43); the association was stronger for distal (OR, 0.24; 95% CI, 0.21 to 0.27) than proximal (OR, 0.58; 95% CI, 0.53 to 0.64) cancer. The odds ratios reported in our study are comparable, despite a shorter observation time than in the Baxter study (median 46 months versus 113 months). The similar findings of the two studies add support to the effectiveness of colonoscopy to prevent CRC deaths in a US health care setting, and is aligned with evidence that the quality of care in the VHA system, reflected by risk-adjusted mortality, is comparable to non-VHA settings[29]. Our findings extend those of Baxter and colleagues, because we were able to demonstrate that exposure to screening colonoscopy was also associated with significant reductions in CRC mortality. However, our subgroup analysis by colonoscopy indication was limited by the relatively small proportion (20.6%) of procedures performed for screening. This was expected given the timeframe of the study; most of the colonoscopies in our study occurred before 2007, prior to the VHA's endorsing colonoscopy as a CRC screening option. There may be variability within the VHA system based on geographic location and resource availability not captured by our findings; this is being actively investigated by our group.

Similar to other studies, we observed that the reduction in right-sided colon cancer deaths was less than that for left-sided cancers. Several factors have been proposed to explain the lower protection for the proximal colon. These include potentially reversible factors such as bowel preparation quality, patient factors (diet, cigarette smoking), operator-dependent factors (cecal intubation, withdrawal time and technique, adenoma detection, detection of nonpolypoid neoplasms, detection of serrated lesions, completeness of polypectomy), system-related factors

(financial incentives or disincentives, organizational pressures, adequacy of equipment), and irreversible factors such as altered tumor biology with accelerated progression to invasive cancer.

Similar to health care organizations in other countries[30], the VHA has recently issued directives emphasizing the importance of high-quality CRC screening, and requiring measurement and reporting of colonoscopy quality metrics[31]. Knowledge of the effect of colonoscopy on patient outcomes is a fundamental component of such an initiative, and is required for a health care system that provides preventive care to a large number of patients. Our findings do not answer the question of whether colonoscopy is the best CRC screening test. From the standpoint of any large integrated health care system, this issue not only requires comparison of effectiveness at the patient level, but also considerations of cost, cost-effectiveness, resource availability and allocation, and patient adherence. There are currently 4 ongoing randomized controlled trials[32-35] comparing fecal immunochemical test (FIT)- to colonoscopy-based screening, one of which is a VA Cooperative study (CSP 577, CONFIRM)[35]. These trials will provide more definitive information regarding which test should be the front-line option for CRC screening in the VHA.

Our rate of colonoscopy utilization was consistent with prior publications, although the proportion of controls who underwent colonoscopy (26.4 %) was relatively high. This is important to consider, because in such settings systematic differences between those who underwent colonoscopy and those who did not may affect CRC risk[9]. Patients undergoing colonoscopy may differ in important ways, such as health-seeking behaviors and healthier lifestyles, than those not undergoing colonoscopy, leading to overestimation of the association between colonoscopy and CRC death reduction. However, our study included mostly male patients with higher prevalence of colon neoplasia risk factors (such as cigarette smoking), greater comorbidity as reflected by the Charlson comorbidity scores, and higher CRC prevalence than non-Veteran populations[14]. Thus, the benefit of colonoscopy and polypectomy

may be more apparent, particularly in the proximal colon. As with all observational studies, unmeasured bias and confounding may threaten the validity of our findings. We attempted to further address this possibility by determining the number of PSA measurements (in men) during the study time frame, to assess health-care utilization propensity. Our findings suggest that cases and controls may not necessarily have differences in lifestyles, opportunity to undergo other healthcare interventions or screening, or health-seeking behavior, that are important enough to bias the results.

Our methodological approach anticipates and addresses concerns for bias and confounding in several ways: First, we matched cases and controls by VA facility—this was partly intended to "level the playing field" for geographic accessibility to health care. Second, we selected cases and controls who were VA health care users (at least 2 PCP visits in the 3 years before the index date). This approach would reduce the chance of having missed exposure to colonoscopy that was performed outside the VA for Veterans less than 65 years of age (and that would not be captured through Medicare data). Third, we adjusted our analyses for several factors which are relevant to the subjects' health status and propensity to seek health care, including comorbidity burden and socioeconomic status. Despite these measures, some limitations remain. We could not, for example, measure potentially confounding factors such as body mass index or physical exercise. The adjudication algorithm[11] we utilized has about 70% sensitivity and 72% specificity, hence some misclassification according to indication may have occurred. We could not ascertain non-prescription use of aspirin and other NSAIDs; however, we expect this to be uncommon, given that our case and control selection strategy was "VA-centric". In addition, most cases and controls were eligible for "free care" due to disability or low-income; thus, they are more likely to obtain medications, including aspirin and NSAIDs from a VA pharmacy. Finally, information on procedure quality (as measured by bowel preparation adequacy, adenoma detection and cecal intubation rates) was not available. Nevertheless, our

estimates of CRC death reductions are comparable to those from different health care settings[9], supporting the validity of our findings.

In conclusion, our study shows that colonoscopy is associated with approximately 60 % CRC mortality reduction in the VHA system, although the reduction is less pronounced in the proximal colon. Reducing variability in colonoscopy effectiveness, particularly against proximal colon cancer, is critical to improve the effectiveness of colonoscopy.

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