**Colonoscopy related adverse events in a colon screening program – a population-based study**

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**Abstract**

Background

Colorectal cancer screening is recommended for Canadians between 50 and 74 years of age. The British Columbia Colon Screening Program (BCCSP) is a population-based program, screening average risk individuals with a biennial fecal immunochemical test (FIT) and colonoscopy to follow-up an abnormal FIT or for screening higher risk individuals. The risks of colonoscopy in a FIT-based screening program are not well understood. The objective was to determine the rate of colonoscopy related serious adverse events (SAEs) within the BCCSP.

Methods

This is a population-based study with prospective data collection of all participants undergoing colonoscopy in BCCSP from November 1, 2013 to December 31, 2017. BCCSP contacts screening participants 14 days following colonoscopy to determine if any unplanned medical events occurred. Unplanned events underwent review and were defined as a SAE if they resulted in death, hospital admission or intervention, and sub-classified as probably, possibly, or unlikely related to the colonoscopy.

Results

A total of 106,282 colonoscopies were performed by 308 physicians at 50 sites. SAEs were observed in 409 colonoscopies (47/10,000), of which 389 (95.1%) were probably or possibly related to colonoscopy. The perforation rate was 6 per 10,000, bleeding rate 27 per 10,000 and the mortality rate 3 per 100,000 colonoscopies.

Interpretation

The BCCSP has a colonoscopy SAE rate in keeping with previous publications and meeting accepted benchmarks. The findings are generalizable to other jurisdictions and will help inform FIT-based screening program stakeholders of the risks of colonoscopy.

## Introduction

In Canada, colorectal cancer (CRC) is the second most common cause of cancer related death in men and third in women (1). While the incidence of CRC has declined slightly over time, it remains the second most commonly diagnosed cancer in Canada and 1 in 16 individuals will be diagnosed with CRC during their lifetime (1). Screening has been shown to decrease CRC related mortality and incidence (2) and to be cost effective when compared to not screening (3). Hence, the Canadian Task Force on Preventative Health has recommended colon screening for individuals 50 to 74 years of age with either a fecal occult blood test (FOBT) every two years or flexible sigmoidoscopy every 10 years (2). All Canadian provinces and one territory have commenced or intend to commence provincial colon screening programs using FOBT (4). Apart from one province, all are using a fecal immunochemical test (FIT) as the primary screening test. The FIT is a type of FOBT that detects human hemoglobin in stool using an immunoassay. It has been shown superior to traditional guaiac FOBT in terms of screening participation rates and detection of CRC and high-risk pre-cancerous polyps at follow-up colonoscopy (5). By 2025, there will be an estimated 12 million Canadians in the eligible age range for screening. Depending on participation with screening, colonoscopy to follow-up an abnormal FIT or a history of pre-cancerous polyps will become the most common indication for colonoscopy.

There are risks associated with undergoing colonoscopy, primarily bleeding following removal of a pre-cancerous polyp and perforation, but there is also a risk of dying following colonoscopy. Population-based screening targets asymptomatic healthy individuals and, therefore, any benefits derived through future prevention of CRC and CRC related mortality must account for the immediate harms of a colonoscopy related adverse event.

The risks of colonoscopy in Canada were described in a landmark population-based study by Rabeneck et al (6) who assessed all outpatient colonoscopies in 50 to 75 year old individuals living in four Canadian provinces and reported a risk of colonoscopy-related perforation of 9 per 10,000 colonoscopies, bleeding of 16 per 10,000 colonoscopies and death of 7 per 100,000 colonoscopies. A recent systematic review and meta-analysis, including three Canadian studies (6-8), reported the risk of perforation and bleeding to be approximately 6 per 10,000 colonoscopies and 24 per 10,000 colonoscopies, respectively and the risk of colonoscopy-related mortality to be 3 per 100,000 colonoscopies (9). The risk of bleeding (6, 9) and perforation (6) is higher in patients undergoing polyp removal. Monitoring and reviewing post-colonoscopy adverse events has become standard of care to identify performance gaps and continuously improve the safety of colonoscopy (10-12).

FIT-based screening programs consist of an enriched patient population with a high prevalence of pre-cancerous polyps. The risks of colonoscopy in this population are not well understood and may differ from the published risks that have been the basis for the widely accepted expert consensus benchmarks: less than 1 perforation per 500 colonoscopies performed for any indication, less than 1 perforation per 1000 screening colonoscopies, and less than 1 episode of bleeding per 100 colonoscopies (11).

The British Columbia Colon Screening Program (BCCSP) is a population-based program enrolling 50 to 74-year-old average-risk adults for biennial FIT with follow-up colonoscopy for an abnormal FIT and primary colonoscopy for individuals at higher than average risk of CRC. The BCCSP colonoscopy serious adverse event rate is an important quality metric of the program and, once established, will allow a more accurate informed consent discussion with screening

participants undergoing colonoscopy. The objective of this study is to determine the overall serious adverse event rate related to colonoscopy as well as the specific rates of death, perforation and bleeding following colonoscopy.

## Methods

### *Study Design*

This is a population-based study with prospective data collection of all participants referred for colonoscopy in the BCCSP from November 1, 2013 to December 31, 2017. A pRoject Ethics Community Consensus Initiative (ARECCI) screening tool determined the project fell within the category of Quality Improvement and Evaluation projects. As a result, the BC Cancer Research Ethics Board waived review (reference H19-02975).

### *BC Colon Screening Program*

The BCCSP is a provincial CRC screening program available province-wide until 2015 at which time the Northern Health Authority, in which resides 5.5% of the age eligible population, ceased participating. Potential participants are initially risk-stratified by their primary care provider. High risk participants, defined as having either a first-degree relative diagnosed with CRC under the age of 60 years, 2 or more first-degree relatives diagnosed with CRC at any age, or a personal history of pre-cancerous polyps, undergo primary colonoscopy within the program. Participants aged 50-74 years are otherwise classified as average-risk and undergo biennial FIT with a test cut-off of ≥10 microgram hemoglobin/gram feces (NS-Plus® Alfresa Pharma Corporation, Japan). If FIT is abnormal or patient is at higher than average risk of CRC, the

participant is referred by the BCCSP to local Health Authority staff who complete the pre-colonoscopy assessment with the patient and determine whether they are eligible for colonoscopy. Exclusion criteria are participant refusal, a personal history of CRC, a personal history of ulcerative colitis or Crohn's disease and significant medical co-morbidities contraindicating colonoscopy. Colonoscopy is performed by a local physician in the participant's community. Physicians performing BCCSP colonoscopies are general surgeons, gastroenterologists, and internists and general or family practitioners with additional training in colonoscopy. Trainees do not perform program colonoscopies.

Unplanned events are defined as those leading a participant to seek or receive additional medical care. Unplanned events occurring during the colonoscopy are recorded by the colonoscopist on a standardized Colonoscopy Report Form that is shared with BCCSP. BCCSP contacts screening participants 14 days following the colonoscopy to determine whether an unplanned event occurred the day prior (during bowel preparation) or in the 14 days following the colonoscopy.



*Unplanned Event Review*

Unplanned events met criteria for review if the event was a perforation, cardiovascular/respiratory event, or resulted in death, hospital admission, or significant intervention including repeat colonoscopy, interventional radiology, surgery, blood transfusion, or cardioversion. A review was conducted by the Colonoscopy Leads for each Health Authority (SC, RE, PM, CN, DP) and the Medical Director (JT) and the Operations Director (LG) for the Colon Screening Program. Unplanned events were defined as serious adverse events (SAE) if they

resulted in death, hospitalization or significant intervention and sub-classified as probably, possibly, or unlikely related to the colonoscopy.

The primary outcome was the overall rate of SAEs. Secondary outcomes included 14-day post-colonoscopy rates of perforation, bleeding and death per colonoscopy performed.

## Results

*British Columbia Colon Screening Program: Participant and Colonoscopist Description*

106,282 colonoscopies were performed at 50 sites by 308 physicians. Of these, 63% were surgeons, 20% gastroenterologists, 14% internists, and 3% general or family practitioners. The median age of the participants was 67.0 years (57, 76 years; 10th, 90th percentile) and 56% were male. Of the 106,282 colonoscopies included, 71,655 (66%) had a polyp removed.

*British Columbia Colon Screening Program: Serious Adverse Events*

87,007 (82%) of the participants were successfully contacted following colonoscopy (Figure 1). SAEs were observed in 409 (0.47%) colonoscopies, or 47 per 10,000 colonoscopies. Of these, 389 (95%) were probably or possibly related to the colonoscopy (Table 1). Perforation occurred in 56 colonoscopies (6/10,000 colonoscopies) and bleeding was recorded in 239 colonoscopies (27/10,000 colonoscopies). Less frequent SAEs included cardiovascular events (20 events), post-polypectomy syndrome (17 events), events related to bowel preparation (13 events), and splenic injury (four events) (Table 1).

Three deaths were noted within 14 days of colonoscopy (3/100,000 colonoscopies). Two deaths occurred following perforation. One death occurred at home three days following

colonoscopy in a patient with significant co-morbid medical conditions was determined to be possibly related to colonoscopy.

**Interpretation**

The rate of colonoscopy-related SAEs was determined in the BCCSP using prospective data collection and formal review of unplanned events. The risk of a SAE occurring 14 days following colonoscopy was 47 per 10,000 colonoscopies including a 6 per 10,000 risk of perforation, a 27 per 10,000 risk of bleeding and a 3 per 100,000 risk of death. The BCCSP has a colonoscopy-related rate of SAEs meeting accepted benchmarks (11), particularly in the context of the high proportion of colonoscopies with polyp removal, which is a known risk factor for perforation and bleeding (6, 13).

Kothari et al performed a recent systematic review and meta-analysis, including three Canadian studies, assessing colonoscopy SAE rates amongst 21 population-level studies (9). The pooled rate of perforation amongst 10,328,360 colonoscopies was 6 per 10,000 colonoscopies with significant heterogeneity between studies due to inclusion of all patient ages and indications for colonoscopy. After adjusting for age and gender between different studies, polypectomy was not significantly associated with a risk of perforation. In contrast, Rabeneck et al. retrospectively assessed 97,091 outpatient colonoscopies performed for various indications in 50 to 75-year old Canadians and reported a perforation rate of 9 per 10,000 colonoscopies with a 3-fold higher risk of perforation when a polyp was removed (6). Similarly, within the BCCSP, the majority (81%) of perforations were attributed to polypectomy. Colonoscopy-related bleeding occurred in 27 per 10,000 colonoscopies, a rate in keeping with the systematic review which reported a 24 per

10,000 risk of bleeding based on over 5 million colonoscopies (9). Bleeding was strongly associated with polypectomy (6, 9). The rate of mortality directly attributable to colonoscopy in the current study was 3 per 100,000 colonoscopies. This is identical to the pooled rate by Kothari et al, who also found that cardiopulmonary events or sequelae of bowel perforation were the most commonly reported causes of death, consistent with our findings (9).

There are few studies evaluating colonoscopy-related complications in FIT-based screening programs and it is difficult to interpret the findings relative to other programs due to different processes and timing of data collection (Table 2). The Danish and Basque screening programs reported serious adverse event rates that were higher than the current study (14, 15) perhaps, in part, due to a longer window of data collection following colonoscopy. In addition, both these studies used administrative databases rather than contacting the participant directly. In the Basque study, which did not perform chart review, it is possible that some hospital admissions were misclassified as a colonoscopy related complication. Alternatively, participant self-reported unplanned events may result in underestimating colonoscopy risk. However, the process of participant contact to ascertain adverse events has been validated by the English National Bowel Screening Program (16). Finally, the Slovenian FIT-based screening program reported very low rates of adverse events (17). Data on adverse events was collected via a standard form initiated by physicians or patients and it is unlikely that such methodology captured all adverse events. There are higher quality publications on colonoscopy-related complications in screening programs using guaiac based FOBTs (Table 2) but the rates of adverse events continue to vary widely (18-20).

The strengths of this study include the large number of colonoscopies included and population-based design. Systematic, prospective data gathering, event reporting and assessment enhance the quality of the results. Furthermore, the indication for all the colonoscopies was screening, the majority in follow-up of an abnormal FIT. Physicians performing colonoscopy in BCCSP have varied training backgrounds and practice settings. As a result, the data should be generalizable to other population-based screening programs with a similar mixture of physicians, as is the case in other Canadian provinces (8).

This study may be limited by the duration of follow up post-colonoscopy. Fourteen day unplanned hospitalization following colonoscopy is a quality indicator for Canadian colon screening programs as established by the Canadian Partnership Against Cancer (12). However, a recent study has included follow up for 30 days post-colonoscopy and demonstrated that SAEs may occur between 14 and 30 days (21). Second, it was not possible to contact all patients who underwent a BCCSP colonoscopy. These factors could have led to an underestimate of the SAE rate. In future studies, data linkage to hospital administrative databases could further validate our findings.

In conclusion, the BCCSP colonoscopy-related SAE rate is in keeping with previous publications and meets accepted benchmarks. This study will help BCCSP, and other provincial screening programs, inform screening participants about the risks of colonoscopy in a FIT-based colon screening program.

## Tables and Figures

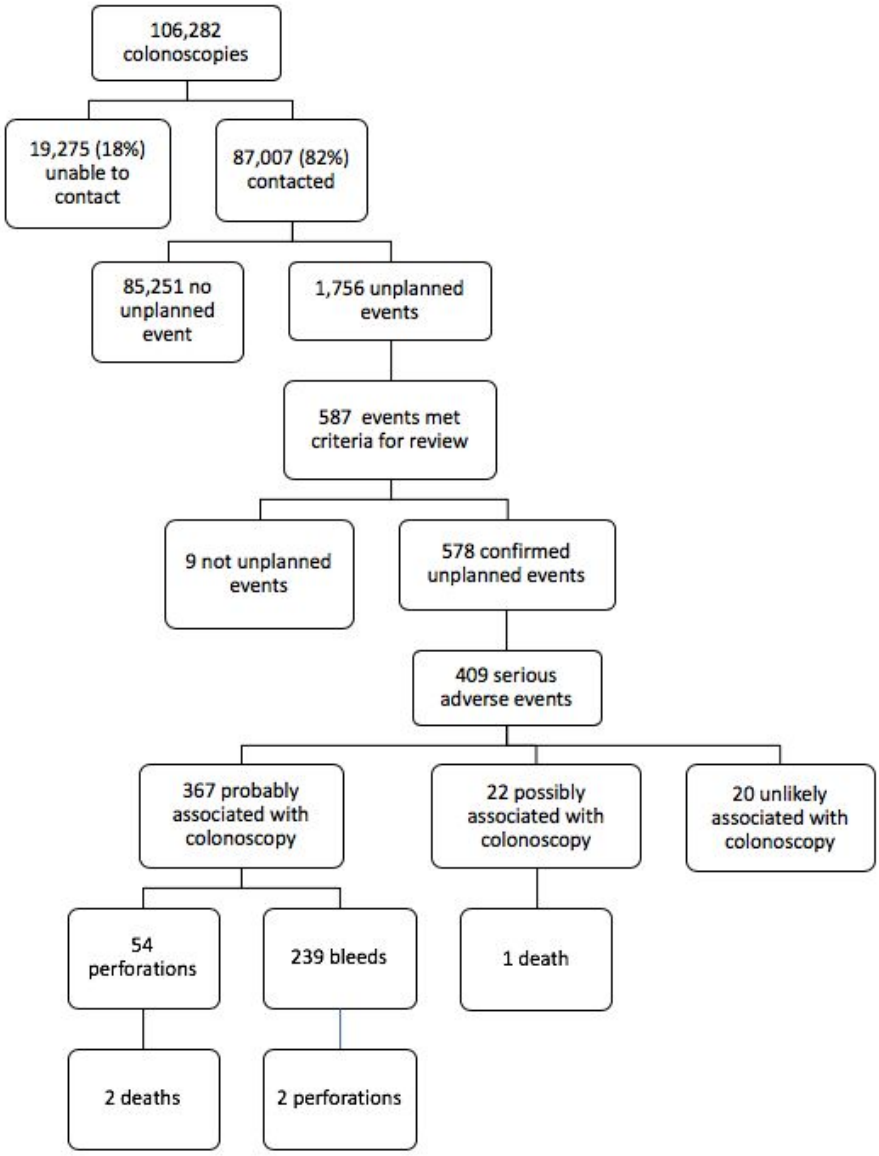


Figure 1. Serious adverse events of the British Columbia Colon Screening Program

| SAE | N | Repeat colonoscopy | Surgery | Blood Transfusion | Death |
|---|---|---|---|---|---|
| Perforation* | 56 | 2* (3.6) | 44 (78.6) | 1 (1.8) | 2 (3.6) |
| Bleeding | 239 | 123 (51.5) | 4 (1.7) | 57 (23.8) | 0 |
| Post-polypectomy syndrome | 17 | 0 | 0 | 0 | 0 |
| Bowel preparation | 13 | 2 (15.4) | 1 (7.7) | 0 | 0 |
| Splenic injury | 4 | 0 | 1 (25.0) | 1 (25.0) | 0 |
| Cardiovascular | 20 | 1 (5.0) | 4 (20.0) | 1 (5.0) | 1 (5.0) |
| Respiratory | 3 | 1 (33.3) | 0 | 0 | 0 |
| Other | 37 | 0 | 13 (35.1) | 3 (8.1) | 0 |
| Total | 389 | 129 (33.2) | 67 (17.2) | 63 (16.2) | 3 (0.8) |

Table 1. Outcome of SAEs probably or possibly related to colonoscopy N (%)

Legend: *2 patients with post-polypectomy bleeding who sustained a perforation as a complication of endoscopic therapy.

| Study | Number of colonoscopies | Data Collection | FOBT | Polyp Removed (%) | Follow-up | Total | Perforation | Bleeding | Death |
|---|---|---|---|---|---|---|---|---|---|
| British Columbia | 106,282 | Phone call | FIT | 66% | 14 days | 47/10,000 | 6/10,000 | 27/10,00 | 3/100,000 |
| Basque, Spain (14) | 39,254 | Hospital admission data | FIT | NR | 30 days | 100/10,000 | 27/10,000 | 62/10,000 | NR |
| Denmark (15) | 14,671 | Chart review of cases identified through hospital admission data | FIT | 55% | 14 days bleeding 30 days for other SAEs 90 days death | 61/10,000 | 10/10,000 | 41/10,000 | 7/100,000 |
| Slovenia (17) | 13,919 | Physician and/or patients had the option of mailing a standardized form to the program | FIT | NR | NR | 8/10,000 | 8/10,000 | 3/10,000 | NR |
| England (19) | 130,831 | Phone call 1 day following and mailed questionnaire 30 days following | Guaiac FOBT | 53% | 30 days | 142/10,000 | 6/10,000 | 65/10,000 | 0 |
| Alsace, France (18) | 10,277 | Phone call 1 day following and mailed questionnaire 30 days following | Guaiac FOBT | 49% | 30 days | 243/10,000 | 10/10,000 | 30/10,000 | 0 |
| Gotland, Sweden (20) | 2,984 | Hospital admission data | Guaiac FOBT | 40% | 30 days | 100/10,000 | 10/10,000 | 140/10,000 | 0 |

Table 2 Risks of colonoscopy in FOBT-based CRC screening programs
Legend: FOBT, fecal occult blood test; FIT, fecal immunochemical test; *NR,* not reported

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