Performance of a quantitative Fecal Immunochemical Test in a Colorectal Cancer Screening Pilot Program

Abstract

Background:
Colorectal cancer (CRC) is a major public health issue in Canada and all ten provinces have commenced or are planning CRC screening programs. British Columbia (BC) undertook a CRC screening pilot program, Colon Check, in three communities using a fecal immunochemical test (FIT) from January 1, 2009 to March 31, 2013. There are limited North American data on CRC screening program outcomes using FIT. Our objective was to assess the performance of a quantitative FIT in the detection of colorectal neoplasia in a population-based screening program.

Methods:
Data was collected prospectively into a central database in a cohort of asymptomatic, average risk 50 to 74 year old men and women participating in Colon Check. The primary screening test was biennial two specimen quantitative FIT with a cut-off of 100 ng/mL buffer with follow-up colonoscopy if either test was positive. Participant demographics, FIT results, colonoscopy quality indicators, and pathology results were reviewed. Pathology per participant was classified by the most significant lesion detected. Non-screen detected CRC was assessed through the BC Cancer Registry.

Results:
16,234 individuals completed a first round of FIT with a positivity rate of 8.6% and 5305 (86.0% of eligible) completed a second round of FIT with a positivity rate of 6.7%. Of the 1756 with a positive FIT, 1555 underwent colonoscopy (88.6%). The detection rate of FIT for CRC was 3.5 per 1000 participants. The positive predictive value of FIT for CRC, high risk polyps and all neoplasia was 5.0% (95% CI 3.8-6.0%), 34.8% (95%CI 32.5-37.2%) and 62.0% (95%CI 59.6-64.4%), respectively. The number needed to screen to detect one CRC was 283, to detect one high risk polyp was 40 and to detect any neoplasia was 22.

Interpretation:
Biennial screening with a two sample quantitative FIT surpassed current benchmarks for neoplasia detection in population-based CRC screening.

Background

Colorectal cancer (CRC) is the second leading cause of cancer and cancer death in Canadian men and the third in Canadian women (1). Randomized, controlled trials have demonstrated that colon screening with the guaiac fecal occult blood test can decrease CRC incidence(2) and mortality(3). Analyses show that screening average risk individuals for CRC is cost-effective at acceptable levels of 3rd party payers willingness to pay (4). The Canadian Task Force on Preventative Health Care has recommended that screening be offered to individuals 50-74 years of age using a fecal occult blood test biennially, preferably in an organized screening program(5).

The fecal immunochemical test (FIT) is an immunologic test consisting of monoclonal or polyclonal antibodies directed against human globin. The FIT is more sensitive and specific than the guaiac fecal occult blood test and participation rates are higher for FIT than for guaiac fecal occult blood test(6), flexible sigmoidoscopy(7) or colonoscopy(8). It is the primary screening test for eight of the provincial programs.

From January 2009 to April 2013, the BC Cancer Agency oversaw a CRC screening program pilot in three communities using a quantitative biennial FIT. Our objective is to evaluate the performance of a 2-specimen quantitative FIT at a cut-off of 100 ng/mL buffer in the detection of CRC and pre-cancerous polyps in an average risk Canadian population.

Methods

Participants

Three BC communities participated in Colon Check: Penticton from January 2009, Powell River from October 2009 and downtown Vancouver from April 2010. The Colon Check program completed screening on March 31, 2013. Eligible participants were mailed invitations using the BC Medical Services Plan database and recruited by family doctors or through local publicity. Participants were then registered by a central call center.

Inclusion Criteria:

1) Age 50-74 years
2) Asymptomatic
3) Resident and/or primary care provider in a Colon Check community

Exclusion Criteria:

1) Rectal bleeding
2) Personal history of CRC
3) Personal history of inflammatory bowel disease
4) Colonoscopy or sigmoidoscopy within the last 5 years

Individuals with one or more first degree relatives ~~a family history of~~with ~~colorectal cancer~~CRC were identified at the time of registration ~~offered primary screening colonoscopy~~ and their results will be reported separately.

Screening Test

The primary screening test was a semi-automated FIT, OC-Auto Micro 80 (Polymedco Inc., New York, USA). Participants received two FIT kits in the mail and were instructed to take one sample each from two consecutive bowel movements. Once complete, participants returned the kits to a local laboratory for transport to the central Vancouver lab for analysis. The ~~FIT~~ screening episode was considered abnormal if either test was ≥ 100 ng/mL buffer (20 micrograms/mL feces). If the ~~FIT~~ episode was abnormal, then colonoscopy was recommended.

Colonoscopy and Pathology

A trained Registered Nurse Navigator assessed all patients prior to colonoscopy for medical fitness, to provide patient education, and to relay bowel preparation instructions. Colonoscopy was performed in the usual manner by community colonoscopists. A standard reporting form was used to collect colonoscopy quality indicators, polyp morphology and mode of polypectomy. Tissue specimens were assessed by BC Cancer Agency pathologists and reported in a standardized format.

High-risk polyps (HRP) were defined as tubular adenomas ≥10 mm in size, tubulovillous or villous adenomas, adenomas with high grade dysplasia, sessile serrated adenomas, traditional serrated adenomas, and multiple (≥ 3) tubular adenomas less than 10 mm in size. Low risk pre-cancerous polyps (LRP) were defined as one or two tubular adenomas less than 10 mm in size. Non-screen detected CRC was defined as cancers diagnosed before or within six months ~~of~~ following ~~following(?)~~ the next recommended screening or surveillance interval.

The colonoscopy and pathology results were communicated to the participant's family physician, the colonoscopist, the patient Navigator, and Colon Check. The Navigator conducted a telephone interview 2 to 4 weeks following the colonoscopy to assess for delayed adverse events, to inform the participant of the pathology results and re-screening or surveillance interval. Participants in whom a neoplastic lesion was detected at colonoscopy were recalled for colonoscopy in five years for LRP(s) and three years for HRPs. If CRC or inflammatory bowel disease was identified, then the participant was discharged from Colon Check for ongoing management under the care of their colonoscopist. Participants with a positive FIT and a negative colonoscopy were recalled for FIT in two years. All adverse events were reviewed by the quality assurance committee and labeled serious or not serious as well as probably, possibly or unlikely related to the colonoscopy. A serious adverse event was defined as an adverse event resulting in a repeat colonoscopy, surgery, hospital admission or death.

Data Collection and Analysis

All data was collected prospectively from participants, colonoscopists and pathologists and entered into a central database at the BC Cancer Agency including: participant demographics, FIT results, colonoscopy results, pathology results and adverse events. There is mandatory reporting of all cancers diagnosed in BC to the British Columbia Cancer Registry. The Cancer Registry was reviewed in April 2015 to assess for the development of interval CRC in Colon Check participants.

The primary objective of this study is to determine the positive predictive value of a 2-sample FIT with a cut-off of 100 ng/mL for colorectal neoplasia in a Canadian population. The secondary objectives are to compare the incidence and stage of colorectal cancer in Colon Check compared to the general population in BC.

The BC Cancer Agency Research Ethics Board approved this study.

Results

Of approximately 95,000 eligible individuals, 16,234 (17.1%) successfully completed a first round of screening with FIT (Figure 1). FIT was unsatisfactory for analysis in 1.3% of individuals. The mean age of the screening participants was 62 years (SD 7) and 51% were female. The FIT was positive in 1395 (8.6%) participants. The positivity rate was higher with increasing age and for male gender (Figure 2~~1~~). Of the 6,255 participants who underwent screening prior to April 1, 2011, and were eligible to complete a second round of screening in the Colon Check program, 5,378 (86%) completed the second round and the positivity rate for the second round of screening was 6.7% (n=361).

Of those 1756 participants with a positive FIT, 1555 (88.6%) underwent 1597 colonoscopies. The overall cecal intubation rate was 96% (95% CI: 95%, 97%) and the overall bowel preparation adequacy was 97.4% (95% CI: 96.6%, 98.1%). Of the 1597 colonoscopies performed, 47(2.9%) resulted in a serious adverse event probably or possibly related to the procedure. There were 3 (0.19%) colon perforations (1 immediate and 2 delayed) and 26 (1.6%) post-polypectomy hemorrhages. There were no deaths in the 30 days following colonoscopy.

Of the 1597 colonoscopies performed, 1156 (72.5%) had at least one specimen with a total of 2,855 specimens submitted to pathology. There were 2040 colorectal neoplasms detected in 1555 participants undergoing colonoscopy including 76 colorectal adenocarcinomas. The pathology results, classified by the most significant finding per colonoscopy are shown in the Table. The number needed to screen with FIT to detect one CRC is 283, to detect one HRP is 40 and to detect any neoplasm is 22. The number needed to colonoscope is 21 to detect one CRC, 3 to detect one HRP and 2 to detect any neoplastic lesion amongst individuals with a positive FIT.

Colon Check participant follow-up in the BC Cancer Registry was conducted on June 9, 2015. The median follow-up from the last screening episode (FIT or colonoscopy)

was 47 months (range 23-76 months). There were nine non-screen detected cancers identified in Colon Check participants. One patient had CRC diagnosed at the site of a previous polypectomy of a high-risk polyp two months prior to scheduled colonoscopy surveillance. The remaining eight participants had a negative FIT test within the 30 months preceding cancer diagnosis. The median FIT value of the 18 FITs performed in the nine participants with interval cancer was 8.5 ng/mL buffer (range 0-71). The TMN stage was: stage I in two, stage II in two, stage III in three and stage IV in two.

The stage distribution of the CRCs diagnosed in Colon Check, including screen detected and interval cancers, compared to the general BC population is shown in Figure 3~~2~~.

Interpretation:

The first FIT was approved in 2008 by Health Canada and reimbursed by the BC Medical Services Plan beginning April 1, 2013. There are several brands available, both quantitative and qualitative, which may have different test performance characteristics. The sensitivity and specificity of the FIT may depend on the brand used (9)(10), the underlying cancer risk in the population being tested, the number of stool specimens tested in each screening round (11), the cut-off chosen for positivity(12), the screening interval, and the quality of the follow-up colonoscopy. The results from randomized controlled trials demonstrating that screening with guaiac fecal occult blood tests decreases the mortality and incidence of CRC are often extrapolated to FIT; however, FIT has not been evaluated in this manner. There are surrogate data demonstrating that participating in a FIT screening program will result in CRC diagnosis at an earlier stage of disease as compared to the non-participants(13), that participants of a FIT-based CRC screening program will have a lower CRC associated mortality as compared to the general population (9), and that participants in subsequent rounds of FIT screening have a lower incidence of CRC than earlier rounds(14). An important advantage of the FIT is that participation is higher than with the guaiac fecal occult blood test, (6)(7) flexible sigmoidoscopy, (7) or colonoscopy(8).

In the current study, we assessed the performance of a two specimen quantitative FIT with a cut-off of 100 ng/mL in the detection of colorectal neoplasia. The positive predictive value for pre-cancerous polyps was 57% surpassing the national benchmark of 50% derived through expert consensus by the Canadian Partnership Against Cancer (CPAC). Major et al published results (including preliminary Colon Check data) from five of the provincial CRC screening programs reporting an adenoma detection rate of 16.9 per 1000 screened and a CRC detection rate of 1.8 per 1000 screened (15). The detection rate for Colon Check was 3.5 cancers per 1000 screened and 41.2 adenomas per 1000 screened. The lower rates observed in the national report are due to the use of different fecal tests by other provinces, some with a lower sensitivity. The CRC screening program in Tuscany reported a detection rate of 4.5 per 1000 screened with a FIT(16).

In Colon Check, the manufacturer's recommended cut-off of 100 ng/mL buffer was used; however, a jurisdiction may chose a different cut-off for positivity which will alter the sensitivity of the test. For instance, the French CRC screening program also used two specimens per screening round with the same brand of FIT as Colon Check but at a higher cut-off of 150 ng/mL buffer(10). As expected, the positivity rate was lower at 4% compared to 8.7% in Colon Check and the positive predictive value for CRC was higher at 6.2% compared to 5.0%. The number needed to screen to detect one CRC was 450 and the number needed to colonoscope to detect one CRC was 16 compared to 283 and 21 in Colon Check.

Non-screen detected CRC were discovered 0.55/1000 Colon Check participants; in eight participants following a negative FIT and in one participant following polypectomy of an advanced adenoma. Our results are similar to the Tuscan screening program which reported non-screen detected CRC in 0.54/1000 screened(16). This study is the first report of non-screen detected CRC in a North American screening program and, to our knowledge, only the second report world-wide.

There was a shift in CRC stage distribution between the general BC population and Colon Check participants. The Canadian Community Health Survey of 2012 estimated 49.6% of British Columbians are up to date with CRC screening (17). In the general BC population over the same time period as Colon Check, 36.1% of the cancers diagnosed were Stage I or II while 68% of the cancers diagnosed in Colon Check participants were Stage I or II. This high rate of localized CRC will translate into a future decrease in CRC mortality and is in keeping with data from other Canadian provincial screening programs(15).

Other positive outcomes observed in Colon Check were the low proportion of unsatisfactory FITs and the high participant satisfaction with FIT. Participant compliance with follow-up colonoscopy was 88.6%, which compares favorably with other programs and is due, in part, to the patient navigation incorporated into Colon Check. The provision of additional colonoscopy resources specifically for Colon Check participants avoided usual colonoscopy wait-times and we believe contributed to the high rate of follow-up colonoscopy and high participant satisfaction.

There are several limitations to this study. We were unable to accurately determine participation in Colon Check as individuals who lived outside of the target communities were eligible to participate if their primary care provider practiced within a target community. Using BC census data, we roughly estimate participation in Colon Check at 17%. As individuals with a negative FIT did not undergo colonoscopy, we are unable to measure the false negative rate of FIT in the detection of colorectal neoplasia. Using a two-year follow-up period to determine false negative results for CRC, the FIT sensitivity and specificity for CRC is 91% and 92%, respectively. Limitations of this method include the unknown asymptomatic dwell

time of CRC and lag time for cancer reporting into the BC Cancer Registry which could underestimate the number of interval CRCs. Using follow-up to ascertain FIT true and false negatives has been shown to yield a higher sensitivity than when colonoscopy is performed on all subjects (12).

In conclusion, programmatic CRC screening of average risk British Columbians with biennial FIT resulted in a CRC detection rate of approximately 1 in 200 with a favorable CRC stage shift compared to the general BC population. The participants of Colon Check will continue CRC screening in the BC Colon Screening Program launched province-wide on November 15, 2013. Long-term monitoring is ongoing to assess for the effect of population-based screening on CRC mortality and incidence.

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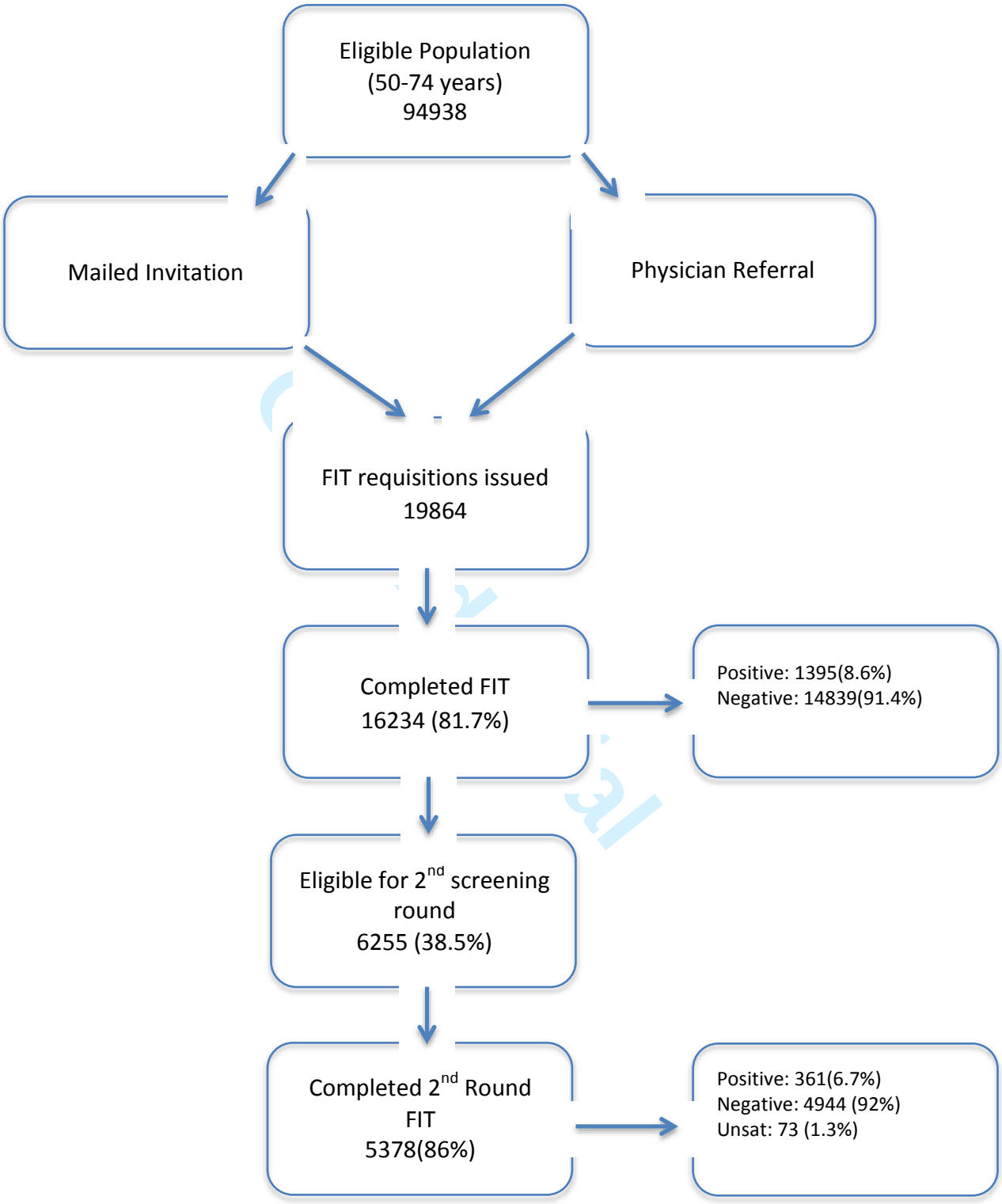
Table. Pathology findings classified by most significant lesion in 1555 participants undergoing colonoscopy for a positive FIT

Pathology*	**Number**	**Positive Predictive Value (95% CI)**	**Detection Rate per 1000 screened**
CRC	76	5% (3.8-6.0%)	3.5
Pre-cancerous polyp	888	57.0% (54.7-59.6%)	41.2
High-risk polyp	543	35.0% (32.5-37.2%)	25.2
Low-risk polyp	345	22.2% (20.1-24.3%)	16.0
Any neoplasia	964	62.0% (59.6-64.4%)	44.8

*Pre-cancerous polyp: adenoma, sessile serrated adenoma/polyp, traditional serrated adenoma. High-risk polyp: tubular adenomas ≥10 mm in size, tubulovillous or villous adenomas, adenomas with high grade dysplasia, sessile serrated

Figure 1: Participation in Colon Check



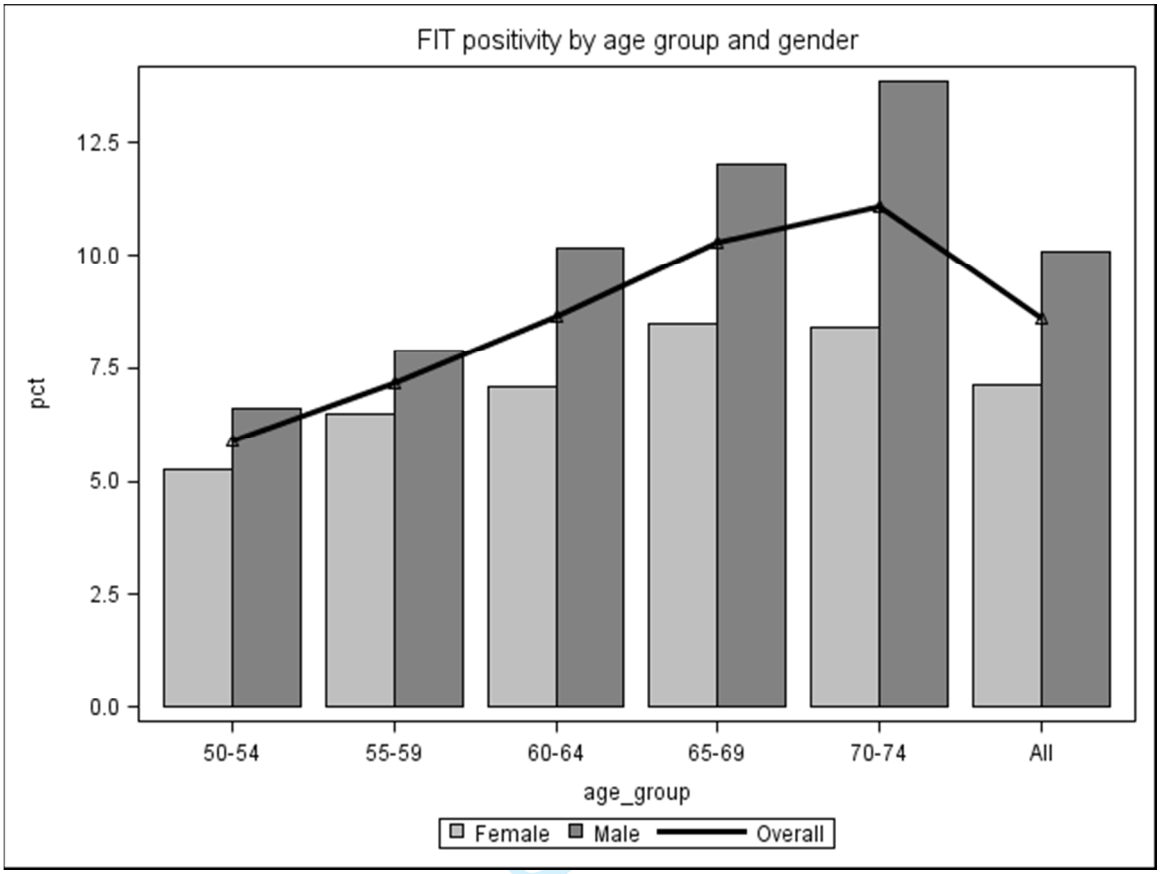


Figure 2. FIT positivity by age and gender

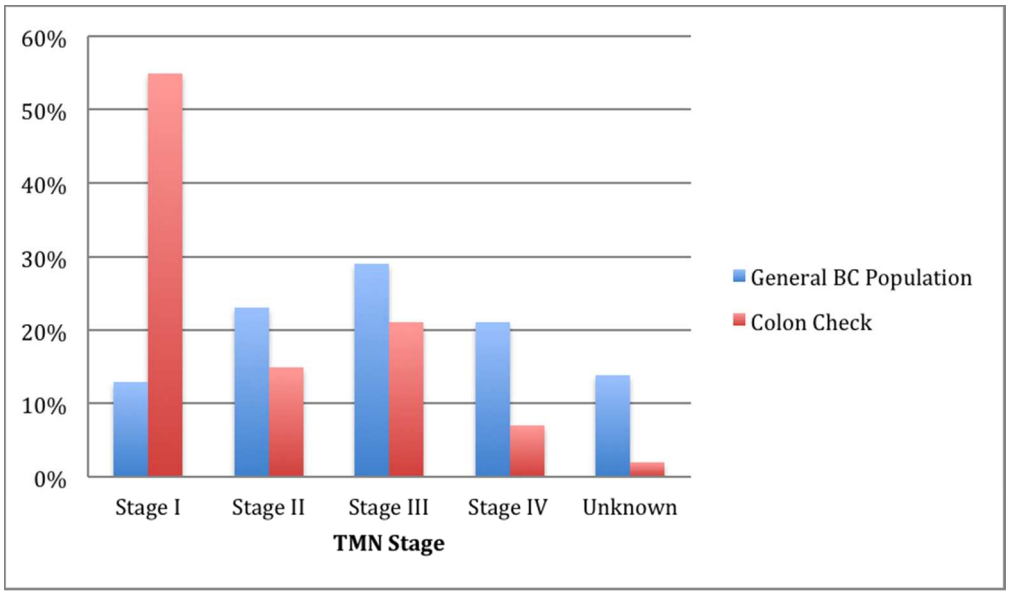


Figure 3. CRC stage distribution for Colon Check and the BC population