Evidence Summary 15-14

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario

Colorectal Cancer Screening in Average Risk Populations: Evidence Summary

J. Tinmouth, E. Vella, N.N. Baxter, C. Dubé, M. Gould, A. Hey, N. Ismaila, B.R. McCurdy, L. Paszat

Report Date: November 11, 2015

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ES 15-14 is comprised of 3 sections. You can access the summary and full report here:
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Section 1:	**Executive Summary and Conclusions**
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PEBC Evidence summary citation (Vancouver style): Tinmouth J, Vella E, Baxter NN, Dubé C, Gould M, Hey A, et al. Colorectal cancer screening in average risk populations: Evidence summary. Toronto (ON): CCO; 2015 November 11. Program in Evidence-based Care Evidence Summary No.: 15-14.

Publication related to this report: Jill Tinmouth, Emily T. Vella, Nancy N. Baxter, et al., "Colorectal Cancer Screening in Average Risk Populations: Evidence Summary," Canadian Journal of Gastroenterology and Hepatology, vol. 2016, Article ID 2878149, 18 pages, 2016. doi:10.1155/2016/2878149.

Evidence Summary 15-14: Section 1

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Colorectal Cancer Screening in Average Risk Populations: Conclusions

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EXECUTIVE SUMMARY

Cancer Care Ontario's Prevention and Cancer Control portfolio and the Program in Evidence-Based Care (PEBC) developed this evidentiary base to help inform program policy and the quality assurance program for colorectal cancer (CRC) screening in Ontario.

The purpose of this systematic review was to evaluate the existing evidence concerning screening of adults at average risk for CRC in the context of an organized, population-based screening program. The main objectives were to identify the benefits and harms of screening in this population, the optimal primary CRC screening test(s) for this population, the appropriate ages for screening initiation and cessation in this population, and the intervals at which people at average risk should be recalled for CRC screening.

A systematic review of the evidence was performed and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method was used to evaluate the quality of the evidence for each of the outcomes. There was strong agreement among the members of the Working Group that CRC-related mortality and complications from screening tests were critical outcomes for recommendation development. All-cause mortality, CRC incidence, participation rate and diagnostic outcomes were considered important outcomes of interest.

CONCLUSIONS

The following were the conclusions developed by the working group. When discussing the effects of various screening tests, the outcomes vary by test. Please see Section 2 of the evidence summary for more details.

Fecal Tests for Occult Blood

There was strong evidence to support the use of fecal tests for occult blood to screen people at average risk for CRC.

Guaiac Fecal Occult Blood Test (gFOBT) Versus No Screening

- The overall certainty of the evidence was high, suggesting a definite reduction in CRC-related mortality. The magnitude of the effect was small (relative risk [RR], 0.87; 95% confidence interval [CI], 0.82 to 0.92); it was comparable to the disease-specific reduction in mortality from mammography for breast cancer screening (RR, 0.79; 95% CI, 0.68 to 0.90) [1], but was less than that from the human papillomavirus (HPV) test for cervical cancer screening (hazard ratio [HR], 0.52; 95% CI, 0.33 to 0.83) [2]. The

anticipated harms associated with gFOBT (including follow-up colonoscopy for people with positive tests) are small and outweighed by the benefits.

Fecal Immunochemical Test (FIT) Versus gFOBT

- The overall certainty of the evidence was moderate. The magnitude of the desirable anticipated effects was at least equivalent to gFOBT, and it is likely that the desirable effects of FIT are greater than for gFOBT. The anticipated undesirable effects associated with FIT (including follow-up colonoscopy for people with positive tests) are small and outweighed by the benefits.
- While there were well-designed randomized controlled trials (RCTs) comparing FIT with gFOBT, the outcomes of these trials (participation, detection rates) were considered to be of lesser importance than CRC-related mortality. However, it was anticipated that the reduction in CRC-related mortality and the complications resulting from screening with FIT would be at least equivalent to those observed from screening with gFOBT. FIT's greater sensitivity for detection of CRC and advanced adenomas compared with gFOBT suggest that the reduction in CRC incidence with FIT could be greater than for gFOBT; however, the magnitude and significance of any additional benefit of FIT over gFOBT is unknown. It is important to highlight that the FIT positivity threshold selected would be an important determinant of the magnitude of the benefits and harms of FIT relative to gFOBT.

Lower Bowel Endoscopy

There was strong evidence to support the use of flexible sigmoidoscopy (FS) to screen people at average risk for CRC. There was no direct evidence to support the use of colonoscopy to screen people at average risk for CRC, but evidence from FS informed the assessment of the benefits and harms of colonoscopy in screening people at average risk for CRC.

FS Versus No Screening

- The overall certainty of the evidence was high, suggesting that FS has a definite effect on CRC-related mortality and incidence when compared with no screening. The magnitude of the effect on CRC mortality was modest (RR, 0.72; 95% CI, 0.65 to 0.80); it exceeds the anticipated disease-specific reduction in mortality from gFOBT for CRC screening (RR, 0.87; 95% CI, 0.82 to 0.92), and is similar to the effects of mammography on breast cancer mortality (RR, 0.79; 95% CI, 0.68 to 0.90) [1] and of the HPV test on cervical cancer mortality (HR, 0.52; 95% CI, 0.33 to 0.83) [2]. The effect on survival with FS was also comparable to the benefit achieved with the current standard of care for patients with completely resected stage III CRC (5-fluorouracil/leucovorin plus oxaliplatin [FOLFOX or FLOX] versus 5-fluorouracil/leucovorin alone, HR for overall survival at six years, 0.80; 95% CI, 0.65 to 0.97) [3]. The anticipated harms associated with FS (including follow-up colonoscopy for people with positive tests) were small and outweighed by the benefits.

Colonoscopy versus no screening

- The overall certainty of direct evidence supporting the use of colonoscopy to screen people at average risk for CRC was very low when compared with no screening. The desirable and undesirable anticipated effects were uncertain.
- It is anticipated that the benefit of screening with colonoscopy would be at least equivalent to that observed for screening with FS; however, the magnitude of

additional benefit over FS, if any, is unknown. The magnitude of additional undesirable effects of colonoscopy relative to FS is also unknown.

Fecal Tests for Occult Blood Versus Lower Bowel Endoscopy

There was insufficient evidence to determine how fecal tests for occult blood perform compared with lower bowel endoscopy to screen people at average risk for CRC.

- The studies that compared one-time fecal tests for occult blood to lower bowel endoscopy were heterogeneous, with few comparisons where data could be pooled. However, in general, the evidence suggested that participation was higher and detection rate was lower with fecal-based tests compared with endoscopic tests.
- The overall certainty of the evidence was low. CRC-related mortality was not evaluated and the design of the studies favoured endoscopic tests because the comparison was to one-time fecal-based testing (rather than repeated testing over time, which is how these tests are used in usual practice). There was significant heterogeneity in participation. The undesirable anticipated effects of endoscopy (including follow-up endoscopy for people with positive fecal tests) are probably small. It is uncertain whether the desirable effects are large relative to the undesirable effects.

Radiological Tests

Computed Tomography Colonography Versus Colonoscopy

There was insufficient evidence to determine how computed tomography colonography performs compared with colonoscopy to screen people at average risk for CRC.

- The overall certainty of the evidence was low. The desirable and undesirable anticipated effects were uncertain.

Capsule Colonoscopy Versus Colonoscopy

There was insufficient evidence to determine how capsule colonoscopy performs compared with colonoscopy to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Double-Contrast Barium Enema (DCBE)

There was no evidence to support the use of DCBE to screen people at average risk for CRC.

- Since 2006, there has been no new published evidence on this topic. Most recent CRC guidelines except for a 2008 guideline by the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology [4] have not endorsed the use of DCBE for screening [5-9].

DNA Tests

Stool DNA versus fecal occult blood tests (gFOBT or FIT)

There was insufficient evidence to determine how stool DNA performs compared with gFOBT or FIT to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Other DNA Tests

There was insufficient evidence to support the use of mSEPT9 to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Metabolomic Tests

Fecal M2-PK

There was insufficient evidence to support the use of fecal M2-PK to screen people at average risk for CRC.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

Other Metabolomic Tests

There was no evidence to support the use of other metabolomic tests (e.g., low levels of hydroxylated polyunsaturated long chain fatty acids [Cologic®]) to screen people at average risk for CRC.

Age of Initiation/Cessation

Age of Initiation/Cessation With gFOBT

Currently, the Ontario CRC screening program recommends that average-risk individuals initiate screening with gFOBT beginning at 50 years of age and ending at age 74. There was insufficient evidence to support changing the ages of initiation and cessation for CRC screening with gFOBT in Ontario.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in reduction of CRC mortality using gFOBT across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.

Age of initiation/cessation with FS

There was insufficient evidence to recommend ages of initiation or cessation when screening with FS in people at average risk for CRC.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in reduction of CRC mortality or incidence using FS across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.
- Of the four large FS RCTs, three examined “once in a lifetime” FS between the ages of 55 and 64, while the fourth RCT examined baseline FS between the ages of 55 and 74 with a second FS after three or five years.

Age of Initiation/Cessation with Colonoscopy

There was insufficient evidence to recommend an age of initiation or cessation to screen with colonoscopy in people at average risk for CRC.

- The overall certainty of the evidence was very low. There was insufficient evidence to demonstrate differences in CRC detection using colonoscopy across age groups. The desirable and undesirable anticipated effects across age groups were uncertain.
- Currently, the Ontario CRC screening program does not recommend colonoscopy to screen persons at average risk for CRC. The program does recommend colonoscopy in people at increased risk (one or more first-degree relatives with CRC) starting at 50 years of age or 10 years younger than the age at which the relative was diagnosed, whichever occurred first.

Age of Initiation/Cessation with FIT

There were no studies that met our inclusion criteria for age of initiation/cessation for FIT.

Screening Intervals

gFOBT Intervals

There was evidence to suggest that either annual or biennial screening using gFOBT in people at average risk for CRC reduces CRC-related mortality.

- The overall certainty of the evidence was moderate. The desirable anticipated effects on CRC mortality were small and similar for annual or biennial screening. The undesirable anticipated effects were not reported for each interval group. Anticipated harms associated with gFOBT (including follow-up colonoscopy for people with positive tests) were small for biennial screening and were likely to be greater for annual screening. In addition, annual screening is anticipated to increase burden to the participant.

FIT Intervals

There was insufficient evidence to recommend an interval to screen people at average risk for CRC using FIT.

- The overall certainty of the evidence was very low. The desirable and undesirable anticipated effects were uncertain.

FS and Colonoscopy Intervals

There were no studies that met our inclusion criteria for screening intervals for FS or colonoscopy.

NEXT STEPS

This evidence summary reports what is known about the clinical effectiveness and safety of CRC tests and is central to the ongoing development of Ontario's colorectal cancer screening program. However, the evidence summary is necessary but not sufficient to guide program development as other context-specific criteria such as cost-effectiveness, existing program design, public acceptability and feasibility (from an organizational and economic perspective) must be considered. In addition, the program must also consider the balance between choice and informed decision making and issues not well addressed by the evidence such as how best to implement colorectal cancer screening when there is more than one colorectal cancer screening test supported by high-quality evidence. An expert panel which included members from national and international screening programs, primary care physicians, general surgeons, gastroenterologists, pathologists and laboratory medicine professionals, nurse endoscopists and members of the public was convened to provide guidance on how to incorporate the evidence in light of the other issues listed above. Their level of agreement with the conclusions and their comments are reflected in Section Three. The CCC program will use findings from the evidence summary as well as expert panel recommendations to guide its ongoing development.