Physical harm of screening for colorectal cancer

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Physical harm of screening for colorectal cancer: a systematic review

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Citation

Frederik Martiny, Sigrid Brisson Nielsen, Or Rahbek, Christian Jauernik, Anne Katrine Lykke Bie, John Brodersen. Physical harm of screening for colorectal cancer: a systematic review. PROSPERO 2017 CRD42017058844 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017058844

Review question

What is the evidence for the physical harms of colorectal cancer screening?

Objectives: to report the number and types of studies investigating any type of physical harm of colorectal cancer screening;

to report the types of physical harms of colorectal cancer screening including the risk, magnitude and consequences of these harms;

to assess and report whether studies have investigated if any factors modify the physical harm of colorectal cancer screening;

to assess and report the overall quality of the evidence as well as the risk of bias and the adequacy of harm measurements in studies.

Searches

The search strategy was developed and conducted in cooperation with an information specialist at the Copenhagen University Library. To maximise the amount of relevant literature retrieved a combination of index words and keywords was searched. We searched the databases PubMed, MEDLINE, Embase, CINAHL, PsycINFO and Cochrane Library. All databases were searched from the date from which the databases have literature coverage until the 12-04-2017.
We initially developed the search strategy for MEDLINE and subsequently adapted it to the other databases. We applied no restrictions concerning date, language or study design. The database search will be supplemented by a targeted grey literature search in Google Scholar. Ongoing trials will be obtained by searching WHO's ICTRP Search Portal.
A preliminary search strategy for MEDLINE is presented in the attached document. We will report the final literature searches for all databases in the final publication. All studies identified will be compiled in the reference programme Endnote where duplicates will be removed.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/58844_STRATEGY_20170505.pdf

Types of study to be included

We will include all types of study designs to promote identification of different types of harms and especially rare adverse events. The Cochrane Collaboration also recommends this practice, when reviewing studies of adverse events [3]. Both qualitative and quantitative studies will be included. Articles identified in the search strategy that do not represent original studies and hence do not report original data like journalism, editorials etc. will be excluded on title/abstract level. Likewise, systematic reviews will be excluded as they report data from other studies. We will scrutinize reference lists of systematic reviews deemed relevant to the research question to identify studies that might be missed in the database searches.

3. Loke YK, Price D, and Herxheimer A., Chapter 14: Adverse effects. In: Higgins JPT, Green S (editors). in Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochranehandbook.org.

Condition or domain being studied

Colorectal cancer screening is restricted to conventional screening methods as defined under the text box "Interventions".
The term "screening" covers all aspects of the screening cascade from invitation, primary testing to downstream diagnostic workup. Harms might occur at any step during the screening cascade [1]. We define harm as recommended in the PRISMA harms checklist [2]: Harm is the totality of adverse consequences of screening, being the direct opposite of benefits. Harm, as a term, thereby comprises both complications, safety issues, adverse events, adverse effects and side effects occurring in relation to screening for colorectal cancer.

1. Harris, R.P., et al., The harms of screening: a proposed taxonomy and application to lung cancer screening. JAMA Intern Med, 2014. 174(2): p. 281-5.
2. Zorzela, L., et al., PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ, 2016. 352: p. i157.

Participants/population

Inclusion: 40 < Age < 80 years, at average risk of colorectal cancer and asymptomatic regarding signs of colorectal cancer.
Exclusion: People at higher than average risk of colorectal cancer, including people recruited because of personal or family history of colorectal cancer, people with known genetic susceptibility, people with earlier or current diagnosis of colorectal cancer, people with increased risk of colorectal cancer because of illness, for example inflammatory bowel disorder.
We will include studies with mixed populations if data and analyses are divided so that data regarding our target group is available and not mixed in with the data for i.e. symptomatic individuals, colorectal cancer patients etc.

Intervention(s), exposure(s)

Inclusion: Conventional colorectal cancer screening tools, including any type and combination of the following: Faecal occult blood test, sigmoidoscopy and colonoscopy.
Exclusion: Stool testing using in-office digital rectal exam, genetic testing, blood tests, stool DNA tests, capsule endoscopy or CT colonography.

Comparator(s)/control

Included studies do not need to have a comparator/control group.

Context

We will exclude studies taking place in settings that diverge from the normal screening setting to an extent that comparison with other studies is not meaningful. This exclusion will be on full text level with reasons noted.

Primary outcome(s)

Physical harm. We define harms as any bodily injury or condition. Physical harms are often divided in major adverse events and other adverse events. We include both types of physical harm. Major adverse events require medical assistance such as perforation or bleeding due to colonoscopy, anaesthesia complications, infections, cardiopulmonary complications etc. Other adverse events do not necessarily result in medical assistance such as discomfort, loss of sleep, physical symptoms due to diagnostic procedures, bloating, water-electrolyte disturbances etc.

Timing and effect measures

We only include harms which the screening participant experiences. We will exclude studies that report expected/potential harm to the screening participant. Such studies are excluded on abstract/title level. We accept any definition of physical harm and any measurement method and timing that does not conflict with the above-described definition of the physical harm of screening.

Secondary outcome(s)

We will assess the adequacy of measurement of harms in studies. We will extract any data or analyses in studies investigating factors which modify the risk, magnitude or consequences of physical harm.

Data extraction (selection and coding)

Study selection process: according to the eligibility criteria defined above two review authors will independently assess all titles and abstracts of studies identified in the literature searches to identify potentially eligible studies. Subsequently the full-text of potentially eligible studies will be retrieved. If full text studies of potentially eligible papers are not available, authors of the studies will be contacted. All full-text studies retrieved will be independently assessed by two review authors for eligibility.
Multiple reports of the same study will be linked together when necessary. Disagreements will be resolved by discussion and if consensus is not reached, a third review author will be consulted to reach agreement. The main author will assess reference lists of included studies to identify studies relevant to the research questions that were not identified in the database search. Any study deemed relevant in the reference list assessment will also be independently assessed by a second review author to ensure objective inclusion/exclusion.
Once the total number of studies included for review is reached, we will perform a preliminary data extraction of study details. From the preliminary data extraction we will decide which types of studies to include for detailed data extraction as described below. The data extraction is divided in this two-step approach to ensure that studies are comparable so that data can be compared across studies.
The data extraction strategy has been developed using the recommendations in the PRISMA harm checklist and using a data collection template by the Cochrane Collaboration [4].
Data extraction strategy: The data extraction strategy is divided in five categories:
1. Study characteristics
2. Definition of harm(s)
3. Adequacy of the measurements of harms
4. Estimate(s) of harm(s)
5. Potential modifying factors on harms
A standardised pre-defined form will be developed and used to extract data from the included studies. As non-randomized studies are also included, we expect it will be necessary to revise the data extraction form during data extraction. All data are extracted by the main author and double-checked by co-authors. Any disagreements will be discussed until consensus, possibly involving a third review author to reach agreement.
Data extraction from studies will include:
1. Study characteristics: - Author, journal, year of publication, funding, study period, study design, information regarding population, setting and intervention.
2. Definition of harm(s): - How the harm domain(s) is defined; which types of harm constitute the harm domain(s).
3. Adequacy of the measurements of harms
- Who assesses/reports the harm?
- How is the harm measured? Are the measurements performed systematically?
- When is the harm evaluated? Prospectively or retrospectively? Measurements at different time points?
- How are the harms analysed, coded or grouped? Are any simplifications made?
3. Estimate(s) of harm(s)
- Any estimate of harm. Both qualitative and quantitative data are accepted
Potential modifying factors on harms:
- Are any factors identified as potentially modifying the magnitude, risk or consequence of the physical harm?
- How are those factors modifying the harm estimates assessed?

If any of the above data is not reported it will be designated as not reported (NR) in data extraction tables. Reviewers will not be blinded regarding authors and studies when extracting data as this has not been proved to affect data extraction [5].
We will prioritize to include comparative studies and RCTs of colorectal cancer screening. We prioritize these types of studies because they are the focus of two former Cochrane reviews regarding the benefit and harm of colorectal cancer screening [6, 7]. The United States Preventive Services Task Force also recently updated their review about colorectal cancer screening, which also assesses harms of different screening interventions to some extent [8]. In addition, a third review from the Cochrane Collaboration including harms of colorectal cancer screening is in the protocol stage. This review focuses on comparing the mortality reduction of sigmoidoscopy versus colonoscopy [9]. In summary, we have prioritized to include comparative studies to allow for comparison with existing reviews and to facilitate comparison of harm and harm assessment to benefit.

4. The Cochrane Collaboration. Good practice data extraction form. 21-09-2017]; Available from: http://epoc.cochrane.org/resources/epoc-resources-review-authors.

5. Higgins JPT Deeks JJ (editors), Chapter 7: Selecting studies and collecting data In: Higgins JPT, Green S (editors),, in Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochranehandbook.org.
6. Hewitson, P., et al., Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol, 2008. 103(6): p. 1541-9.
7. Holme, Ø., et al., Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. Cochrane Database of Systematic Reviews, 2013(9).
8. Bibbins-Domingo, K., et al., Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. Jama, 2016. 315(23): p. 2564-2575.
9. Phillips, J., C. Ridd, and K. Thomas, Screening sigmoidoscopy and colonoscopy for reducing colorectal cancer mortality in asymptomatic persons. Cochrane Database of Systematic Reviews, 2013(9).

Risk of bias (quality) assessment

We will assess the risk of bias regarding harm estimates in studies using the Cochrane Collaborations ROBINS-I tool [10]. We will perform the risk of bias assessment on the study outcome level and not according to study design. This decision stems from the fact that the definition, measurement and reporting of harms is heterogeneous and often of poor quality in many clinical studies [3, 11]. In an attempt to account for the heterogeneity in studies regarding physical harm, we will expand the ROBINS-I tool to include other types of bias deemed relevant to the review question. The ROBINS-I tool will be altered using reporting guidelines from the Equator Network and various study quality checklists. We plan to report the altered ROBINS-I checklist in the final publication.
The risk of bias assessment will be performed independently by two review authors. Any disagreements will be discussed until consensus, possibly involving a third review author to reach agreement.

3. Loke YK, Price D, and Herxheimer A., Chapter 14: Adverse effects. In: Higgins JPT, Green S (editors). in Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochranehandbook.org.
10. Sterne, J.A.C., et al., ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ, 2016. 355
11. Ioannidis, J.P., et al., Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med, 2004. 141(10): p. 781-8.

Strategy for data synthesis

For quantitative data we will calculate summed estimates of harms across studies. These pooled estimates will be presented via meta analyses using random effect models. Summed estimates will not be calculated in instances where heterogeneity between studies is deemed too great to allow for meaningful comparisons. In

these instances harms will be presented by narrative syntheses.
Using the risk of bias assessment of studies, we expect to perform sensitivity analyses to test how the quality of studies might affect the aggregate harm estimates.
The harm domain “physical harm” is comprised of different types of harms, i.e. perforation, bleeding, pain etc. Wherever possible, we will present estimates of the magnitude of each type of harm alongside a GRADE evaluation of the quality of the evidence. GRADE evaluation of the evidence is performed by the main review author and double-checked by co-authors. Any disagreements will be discussed until consensus, possibly involving a third review author to reach agreement.
Zero events: Studies that do not report harms they have assessed or planned to assess are deemed selective in reporting. Reporting of zero occurrences of a type of harm is noted as a zero event in data extraction tables.

Analysis of subgroups or subsets
Please view above.

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Anticipated or actual start date
02 January 2017

Anticipated completion date
29 December 2017

Funding sources/sponsors
The Danish Cancer Society Scientific Committee has granted a scholarship of 120.000 DKK to finance the salary of the main author Frederik Martiny for the year 2017. Grant number R165-A10525-16-S7. The funding source has no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Conflicts of interest
None known

Language
English

Country
Denmark

Stage of review
Review_Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Colorectal Neoplasms; Humans; Occult Blood

Date of registration in PROSPERO
03 November 2017

Date of publication of this version
22 September 2017

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
22 September 2017