PROTECTION FROM COLORECTAL CANCER
FOLLOWING NEGATIVE COLONOSCOPY IN PATIENTS WITH FAMILY HISTORY OF COLORECTAL CANCER: A SYSTEMATIC REVIEW

By

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for any proprietary material contained therein
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedication</td>
<td>7</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>8</td>
</tr>
<tr>
<td>Abstract</td>
<td>9</td>
</tr>
<tr>
<td>Introduction</td>
<td>10</td>
</tr>
<tr>
<td>Methods</td>
<td>11</td>
</tr>
<tr>
<td>Search Strategy</td>
<td>12</td>
</tr>
<tr>
<td> Eligibility</td>
<td>12</td>
</tr>
<tr>
<td> Literature Search</td>
<td>12</td>
</tr>
<tr>
<td> Selection Process</td>
<td>13</td>
</tr>
<tr>
<td> Data Extraction</td>
<td>13</td>
</tr>
<tr>
<td>Results</td>
<td>14</td>
</tr>
<tr>
<td>Discussion</td>
<td>18</td>
</tr>
<tr>
<td>Conclusion</td>
<td>19</td>
</tr>
</tbody>
</table>
LIST OF APPENDICES

Appendix I Search Strategy ........................................................................................................20

Appendix II CRC Screening Form ..............................................................................................22
LIST OF TABLES

Table 1 – Characteristics of Included Studies -----------------------------------24

Table 2 – Second Colonoscopy Findings for Patients with Normal Index Colonoscopy 25

Table 3: Second Colonoscopy Findings for Patients with Abnormal Index Colonoscopy26
LIST OF FIGURES

Figure 1 – The Study Flow Diagram ..........................................................23
DEDICATION

I dedicate this work to the memory of my father Abu Khaled and my brother Khaled, who taught me that nothing is impossible. You will forever be my role models and greatest inspiration.

To my mother Im Khaled for teaching me that failure is not an option.

To Bassima, Ghada, Rajaa, Jihan, Bilal, Fatima, Ibrahim, and Mohamad Sadek for their love, affections and encouragement.

To my friends “Karl, Nour, Youssef, Danijella, Rob, Johnny, Tim …” for their enormous support. I am blessed to have you in my life.
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My sincere gratitude goes to my mentors Dr. Gregory Cooper, Dr. Douglas Einstadter and Dr. James Spilsbury who guided me throughout conducting and finishing the research.

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Protection From Colorectal Cancer Following Negative Colonoscopy In Patients With Family History Of Colorectal Cancer: A Systematic Review

Abstract

By

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Objective: My aim is to detect if there are any data in the literature supporting the current guidelines for screening for colorectal cancer (CRC) for individuals with at least one first-degree relative (FDR) with CRC and a negative index colonoscopy.

Methods: Three reviewers following specific inclusion and exclusion criteria performed a literature search in MEDLINE, Embase, and Cochrane (CENTRAL).

Results: Out of the 911 studies identified, five studies met inclusion criteria. Accurate screening intervals were impossible to identify based on the available data. Four of the five studies leaned toward increasing screening interval to more than five years.

Conclusion: The reviewed studies suggest that an increased risk of CRC compared to the general population persists despite negative colonoscopy. Increased screening frequency is likely indicated for these patients. However, further research is needed to determine optimum screening intervals.
Introduction

Colorectal cancer (CRC) is the second most common cancer in women and third most common cancer in men worldwide[1]. In the United States, CRC is the third most frequent cause of death attributed to cancer[2]. Around 4-10% of general population has family history of CRC[3-5]. One meta-analysis published in 2006 investigating the risk for individuals with family history of CRC found that the risk increases with the number of affected first-degree relatives (FDR). The lifetime risk for a 50-year-old individual with one FDR with CRC is 3.4% compared to 6.9% if 2 FDRs are affected[3]. Furthermore, the lifetime risk of CRC increases if the affected FDR is diagnosed at a younger age[4]. One study showed that the lifetime relative risk increases from 2.25 if the individual has one FDR with CRC to 3.87 if the FDR is diagnosed before the age of 45[6]. Multiple screening programs are available for early detection and prevention of CRC. These programs depend upon protocols that directly reflect the risk of CRC in order to increase cost-effectiveness, as well as patient adherence[7-9].

Colonoscopy is the most used modality for screening in the United States[10] and colonoscopy with polypectomy decreases CRC incidence and its related mortality[11, 12]. Multiple guidelines have been developed for screening and surveillance for people with a family history of colorectal cancer. The two major guidelines in United States for CRC screening, the Multi-Society Task Force and the US Preventive Services Task Force, do not address screening for individuals with family history. Current practice is based on guidelines from both The American College of Gastroenterology and the American
Cancer Society. Both guidelines recommend screening with colonoscopy for primary prevention of CRC beginning at the age of 50 if a patient has one FDR diagnosed after the age of 60 with CRC or advanced adenoma (defined as adenoma $\geq 1$ cm in size, or with high-grade dysplasia or has villous histology) and should be performed every 10 years. If the family member was diagnosed before age of 60, or 2 or more family members were diagnosed at any age with CRC or advanced adenoma, then screening should be done every 5 years starting at age 40 or 10 years earlier than the diagnosis of the youngest affected relative [11, 13-15].

These recommendations are primarily based on the estimated lifetime risk of CRC rather than observational studies of patients undergoing screening or surveillance programs. They do not account for adjustments in estimated risk based on a negative colonoscopy [16].

The focus of my review is on clinical studies that provide data concerning the risk of CRC or advanced adenoma after a negative colonoscopy in persons at increased lifetime risk based on a family history of CRC. Such data ultimately will inform optimum screening intervals for CRC in patients with elevated risk.

**Methods**

We published the research protocol of this systematic review online on PROSPERO, which is an international database of prospectively registered systematic reviews in health and social care. The database aims to prevent duplicate research worldwide. The PROSPERO registration number is CRD42014014193. Reference URL for published
protocol:
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014193

No similar systematic review was listed in PROSPERO, indicating that our study is the first of its kind in the database.

**Search strategy**

*Eligibility:*

Inclusion criteria were as follows: studies that included individuals with normal index colonoscopy with at least one first-degree family member with CRC, who had a repeat colonoscopy within a specific interval of time. The primary outcome was to detect the interval of time for a second colonoscopy in this population. The study’s secondary outcome was to detect adenoma rate on the second colonoscopy.

Exclusion criteria were: patients with family history of Lynch syndrome, or Familial adenomatous polyposis, or a personal history of IBD. These patients are at higher risk for CRC and, therefore, require different screening guidelines compared to our population of interest.

*Literature search:*

We conducted a literature search in MEDLINE, Embase.com, and Cochrane (CENTRAL) on Feb/02/2014. We did not apply publication type filters to the search strategy. We used a balanced combination of MeSH terms and keywords utilizing the various search options of the searched databases as shown in Appendix 1. MeSH terms included “Colorectal Neoplasm”, “colonoscopy”, and “Adenoma”. Examples of Keywords used are, “family history”, ”cancer”, ”colon”, ”surveillance”, “initial”, and
“repeat”. We also searched for ongoing research trials about the topic in http://www.controlled-trials.com/isrctn/ and http://www.clinicaltrials.gov. The detailed search strategy is summarized in Appendix 1. We developed the search strategy in compliance with the guidelines of peer review of electronic searches set by Sampson et al.\cite{17}

**Selection process:**

Three reviewers (ME, AB, AB) independently screened the titles and abstracts of identified citations. The full texts for citations that were judged by at least one of the two reviewers as potentially eligible were subsequently retrieved and screened independently. The results of the screening process were compared, and any disagreement was resolved by discussion. Standardized screening forms (Appendix II) based on the eligibility criteria were used to ensure each reviewer included or excluded the studies correctly.

**Data extraction:**

The three reviewers independently extracted data from eligible studies using standardized forms. The data collected included: type of study design, characteristics of the population, control, and outcomes.

We reviewed studies relevant to the question does family history affect the rate of adenoma recurrence / CRC that would impact surveillance intervals given a patient has a negative screening colonoscopy.
Results

Selected Studies

A total of 911 articles and abstracts were obtained based on our search strategy and post removal of duplicates. Of these, 831 articles/abstracts were excluded based on title review. The abstracts of the remaining articles were screened for eligibility (Figure 1). Only 3 articles and 2 abstracts met our inclusion criteria and were therefore included in our final review. We documented basic characteristics of each article, year of publication, study design, how many FDR were affected, the adenoma rate, and the interval time until second colonoscopy (Tables 1-3). There was no comparison or control group to compare to, given that none of the studies was a randomized control study. Each of these studies is described in detail below.

In 2001, Fossi et al. [18] enrolled 436 asymptomatic Italian patients in a colonoscopy surveillance study to estimate cumulative adenoma incidence over a 3-year interval after baseline-screening colonoscopy. One-hundred-ninety patients underwent surveillance colonoscopy within 3 years of initial colonoscopy and were included in the study. Patients were stratified based on family history of CRC: 69/190 with one first-degree relative with CRC and 121/190 without family history. Findings at the baseline examination were also stratified by the presence (134/190) or absence (56/190) of adenomatous polyps and further classified by adenoma number, size, and histology (presence of villous features and degree of dysplasia). The cumulative 3-year incidence
of adenoma during follow-up colonoscopy was higher in patients with family history (one FDR) regardless of whether or not they had polyps at initial colonoscopy. For patients with no polyps at initial colonoscopy and no family history, 6.7% had polyps at follow-up. In contrast, 26.9% of patients with no polyps at initial colonoscopy and a positive family history, had polyps at follow-up (OR 8.95 95% CI 1.29–62.22). The polyps found during surveillance were low risk, small with mild to moderate dysplasia. The authors did not differentiate recurrent polyps found at surveillance based on high-risk features. Based on the results presented by the authors, it is unclear whether the increased incidence of low risk adenomas in patients with family history of CRC during follow-up of only 3 years would necessitate more intensive screening compared with average risk patients. The small sample size, reflected in the wide confidence intervals, and the short follow-up intervals limit generalization of the results. Furthermore, quality indicators of the colonoscopy procedure were not discussed.

The study by Schoenfeld et al. [19], a prospective observational study, included 100 asymptomatic military personnel with negative first screening colonoscopy and a single FDR with positive family history of CRC. Results of surveillance colonoscopy after 5 years showed 33% (33/100) had advanced adenoma, 7% (7/100) had tubular adenoma more than 10 mm in size, and one patient 1% had a villous adenoma. The risk of adenomas of any size showed a trend towards association with multiple relatives with CRC or younger age of the affected relative (<60 years old), but did not reach statistical significance (OR=1.35 CI 95% 0.56-3.23). While the sample size was small, the rate of 8% advanced adenomas in this population would support more frequent screening for
patients with first-degree relatives with CRC compared to the general population. The study results are difficult to generalize for several reasons: the small sample size, absence of control patients, Caucasian predominance of the study participants (91% of the patients were Caucasian), and the “military-personnel” composition of the study population. Also, specialists from multiple fields performed the colonoscopies in this study, which could have resulted in different adenoma detection rates.

In order to assess the risk reduction from colonoscopy in patients with strong family history of CRC (one or more 1st-degree relatives with CRC) Dove-Edwin et al.\[20\] enrolled 1,143 patients from 740 families in a prospective observational study over a 16-year period at a family cancer clinic in London. In the families with moderately increased risk, the authors estimated that repeat screening colonoscopy after a negative initial colonoscopy conferred an 80% reduction in CRC risk. Advanced neoplasia and CRC were uncommon under age 45 (1.1% and 0%) and at follow-up colonoscopy if initial screening colonoscopy was negative (1.7% and 0.1%). The incidence of advanced neoplasia at follow-up was most strongly associated with the findings at initial colonoscopy. Advanced neoplasia was discovered at a rate of 26.7/1000 patient-years if baseline colonoscopy was positive and 1.95/1000 patient-years if negative. The incidence of advanced neoplasia after a negative screening colonoscopy varied with the degree of family history and with age. This study indicates (1) a risk reduction from colonoscopy screening and surveillance in patients with family history of CRC; and (2) a negative screening colonoscopy predicts a relatively low risk of future high-risk neoplasia. Based on their findings, they concluded that more than 5 years’ screening is
indicated. However, study limitations temper support for this conclusion: there is no separate control group in the study, and the authors use best estimates of CRC incidence from the literature. Additionally, there was no comparison to estimates of rates of advanced adenoma, which may have excluded analysis of important predictive factors of future CRC incidence in the study population.

The study by Walshe, a cohort conducted in 2008, included patients with a moderate family history of CRC\textsuperscript{[21]}. Walshe compared adenoma yield at second screening colonoscopy between patients with or without adenoma at index colonoscopy. A total of 97 patients had negative first screening colonoscopy. Out of these 97 individuals, 1% had advanced adenoma and 10% had simple adenoma on the surveillance colonoscopy with mean interval of 4.6 years. In contrast, of 30 patients who had adenoma on index colonoscopy, 13% of them had advanced adenoma, and 23% had a simple adenoma with a mean interval of 3.62 years on the second colonoscopy. Walshe concluded that patients who have a negative first screening colonoscopy have a low risk of having adenoma on the follow-up colonoscopy compared to those with adenoma on the index colonoscopy.

The study by Moran reported adenoma detection rate in patients with a family history of CRC\textsuperscript{[22]}. The study was conducted from 1997 to 2010 in a tertiary referring center. They followed up patients over a period of 3-5 years. Out of 50 individuals who had normal index colonoscopy, 5 (10%) had simple adenoma with a mean interval of 4.54 years, and no patients had advanced adenoma. The percentage was less if the patient has adenoma on index colonoscopy. Moran’s study suggested that interval screening could be increased to more than five years.
Discussion

Unfortunately, the data on the incidence of adenoma after the first normal screening colonoscopy in patients with a family history of CRC is very limited. The available guidelines extrapolated from data on the average-risk population instead of evidence-based studies. Because of the small number of available studies, lack of randomized control groups, and differences in study design (e.g., length of follow-up intervals, sample composition), it was not possible to conduct advanced meta-analytic statistics on the pooled data.

Four of the five reviewed studies recommended increasing screening intervals following a normal index colonoscopy for patients with moderate risk due to family history of CRC: One FDR diagnosed before the age of 60, or 2 or more FDRs diagnosed at any age with CRC or advanced adenoma. All of them had at least one FDR diagnosed with CRC below age of 60, except for the Fossi study, which did not specify the age of the FDR with CRC. Adopting an extended interval for screening may be a more effective approach than is currently employed from a cost / benefit standpoint. For example, increasing the number of colonoscopies performed for one individual will increase the risk of the procedure itself: There is 1 in 1000 risk of perforation by colonoscopy in the general population. The sedation given during colonoscopy also poses risks of harm. Moreover, a patient may experience anxiety or psychological stress with each repeat colonoscopy.
An additional limitation common to all of the reviewed studies is that the adenoma miss rate was not taken into account. It is well known that the colonoscopy miss rate for adenoma greater than 1 cm is between 6-12 % and the miss rate for cancer is 5 % [28] [29]. Adenoma detection is dependent on the performance of the endoscopist; interval cancer is less likely to occur with a high-performance endoscopist vs. a low-performance endoscopist, or with a gastroenterologist vs. non- gastroenterologist [30, 31]. Therefore, a positive finding on the second colonoscopy might be in fact a missed lesion on the first procedure, and this is difficult to compare across studies.

**Conclusion**

In summary, while negative screening indicates reduced risk of future colonic neoplasia, the reviewed studies suggest that persons with a family history of CRC have an increased risk of CRC compared to the general population despite negative colonoscopy. Therefore, current recommendations should continue to reflect the patient’s inherent increased risk for CRC, similar to the shortened intervals currently recommended for patients with autosomal dominant familial syndromes. However, the optimum screening interval is not currently known due to an absence of adequate data. Though challenging given the long latency of the disease, future studies should be directed toward assessing the appropriateness of current recommendations, to more accurately estimate the risk of CRC and thereby determine optimum screening interval by conducting randomized control trial stratifying patient to different screening intervals.
Appendix I

Search Strategy

- Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present>
- Search Strategy:
-  
- 1 exp Colorectal Neoplasms/ (156088)
- 2 (colo* adj3 (canc* or tum* or neoplas* or carcino*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (167021)
- 3 (famil* adj3 histor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (51554)
- 4 exp Colonoscopy/ (22753)
- 5 colonoscop*.mp. (29365)
- 6 (initial* or repeat* or screening* or surveillance* or second*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2794703)
• 7 exp Adenoma/ (86317)
• 8 adenoma*.mp. (96886)
• 9 (1 or 2) and 3 and (6 and (4 or 5)) and (7 or 8) (338)
Appendix II

CRC Screening Form-

1- Type of the Study----

2- Family history documented
   Yes --- No----

3- how many first Degree relatives (FDR) are affected with CRC
   ----

4- Age of FDR upon diagnosis
   ----

5- Does the individual has
   A- lynch syndrome yes--- No----
   B- FAP yes--- No---
   C- Personal History Of CRC yes--- No---

6- Index Colonoscopy is normal
   Yes--- No----

7- Repeat Colonoscopy is documented
   Yes---- No----

8- Interval time is documented
   Yes---- No----

9- Results of repeat Colonoscopy is Documented
   Yes---- NO----
Figure 1 - Study Flow Diagram

- Medline: 338
- Cochrane: 0
- Embase: 906
- Final (after duplicate removal): 911

- 80 studies included and underwent abstract review

- 831 articles were excluded based on the title review

- 1 study excluded based on language

- 2 studies were reviews

- 14 studies had no data on family history

- 58 studies had no data on repeat colonoscopies

- 3 articles and 2 abstracts included*
<table>
<thead>
<tr>
<th>Study</th>
<th>Year of Publication</th>
<th>Study design</th>
<th>Population</th>
<th>Family history</th>
<th>Year Enrolled</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fossi et al</td>
<td>2001</td>
<td>Prospective</td>
<td>Italy</td>
<td>One FDR affected with CRC</td>
<td>1990 - 1992</td>
<td>3 yrs.</td>
</tr>
<tr>
<td>Schoenfeld</td>
<td>2003</td>
<td>Prospective</td>
<td>US</td>
<td>One or more FDR affected CRC</td>
<td>(-)</td>
<td>5 yrs.</td>
</tr>
<tr>
<td>Dove-Edwin</td>
<td>2005</td>
<td>Prospective</td>
<td>UK</td>
<td>One or more FDR affected CRC</td>
<td>March 1987-Decemb er 2003</td>
<td>5.1yrs</td>
</tr>
<tr>
<td>Walshe</td>
<td>2012</td>
<td>Prospective</td>
<td>Ireland</td>
<td>One or more FDR affected CRC</td>
<td>(-)</td>
<td>Mean 4.6 years</td>
</tr>
<tr>
<td>Moran</td>
<td>2011</td>
<td>Retrospective</td>
<td>(-)</td>
<td>One or more FDR affected CRC</td>
<td>1997-2010</td>
<td>3 yearly until 2003, 5 yearly after 2003, mean 4.44</td>
</tr>
</tbody>
</table>
Table 2: Second Colonoscopy Findings for Patients with Normal Index Colonoscopy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients with the defined family history and normal first screening CNSPY who underwent a repeat CNSPY</th>
<th>Normal Repeat CNSPY</th>
<th>Abnormal Repeat CNSPY</th>
<th>Low risk: &lt;1cm, Frequently tubular, Mild to moderate Dysplasia</th>
<th>High risk: Advanced adenoma (&gt;1cm, High Grade Dysplasia or villous component), or &gt;3 tubular adenoma</th>
<th>CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fossi et al</td>
<td>26</td>
<td>19/26 (73%)</td>
<td>7/26 (26.9%)</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schoenfeld</td>
<td>100</td>
<td>67/100</td>
<td>33/100</td>
<td>17</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Dove-Edwin</td>
<td>545</td>
<td>406</td>
<td>86</td>
<td>78</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Walshe</td>
<td>97</td>
<td>86/97</td>
<td>11/97</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Moran</td>
<td>50</td>
<td>45/50</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: CNSPY = colonoscopy
Table 3: Second Colonoscopy Findings for Patients with Abnormal Index Colonoscopy

<table>
<thead>
<tr>
<th>Study</th>
<th>Adenoma on index CNSPY</th>
<th>Adenoma on repeat CNSPY given positive index CNSPY</th>
<th>Low risk adenoma on repeat CNSPY if index CNSPY was positive</th>
<th>High risk adenoma on repeat CNSPY if index CNSPY was positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fossi et al</td>
<td>43</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schoenfeld</td>
<td>no data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dove-Edwin</td>
<td>147</td>
<td>66</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>Walshe</td>
<td>30</td>
<td>11</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Moran</td>
<td>21</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: CNSPY = colonoscopy
References:


21 Walshe

22 Moran


Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based